NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Truvelog (insulin aspart) 100 units/mL solution for injection in a 3 mL cartridge

Truvelog SoloStar® (insulin aspart) 100 units/ mL solution for injection in a 3 mL pre-filled pen.

Truvelog (insulin aspart) 100 units/mL solution for injection in a 10 mL vial

Truvelog is a biosimilar medicine to NovoRapid®, NovoRapid® Penfill® and NovoRapid® FlexPen®. The comparability of Truvelog with NovoRapid® has been demonstrated with regard to physicochemical characteristics and pharmacology, efficacy and safety outcomes.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of the solution contains 100 units (equivalent to 3.5 mg) insulin aspart.

Truvelog (insulin aspart) 100 units/mL solution for injection in a 3 mL cartridge – equivalent to 300 units.

Truvelog SoloStar® (insulin aspart) 100 units/ mL solution for injection in a 3 mL pre-filled pen – equivalent to 300 units.

Truvelog (insulin aspart) 100 units/mL solution for injection in a 10 mL vial – equivalent to 1000 units.

For further information regarding the biosimilarity of Truvelog to Novorapid, see Section 5.1. The prescribing physician should be involved in any decision regarding interchangeability. For further information see: www.medsafe.govt.nz/profs/RIss/Biosimilars.asp

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Truvelog is a clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of diabetes mellitus.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Truvelog has a faster onset and a shorter duration of action than soluble human insulin. Due to the faster onset of action, Truvelog should generally be given immediately before a meal or when necessary, soon after the start of a meal.

The dosage of insulin aspart is determined by the physician according to the patient's individual needs. The individual insulin requirement is usually between 0.5 and 1.0 units/kg/day in adults and children. In a meal-related treatment 50-70% of this requirement may be provided by Truvelog and the remainder provided by an intermediate-acting or long acting insulin given at least once a day.

The daily insulin requirement may be higher in patients with insulin resistance (e.g. due to obesity), and lower in patients with residual endogenous insulin production. Adjustment of dosage may also be necessary if patients undertake increased physical activity, change their usual diet, or during concomitant illness. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

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

As with all insulins, in elderly patients and patients with hepatic or renal impairment glucose monitoring should be intensified and dosage adjusted on an individual basis.

Method of Administration

Truvelog 10mL vial may be used for continuous subcutaneous insulin infusion ('CSII') in pump systems suitable for insulin infusion (see 'Clinical Trials'). When used in external insulin infusion pumps the initial programming of the pump should be based on the total daily insulin dose on the previous regimen. Approximately 50% of the total dose is to be given as the basal rate, and the remainder is to be divided between breakfast, lunch, dinner and snacks. The usual individual daily insulin requirement of between 0.5 and 1.0 U/kg/day also applies when Truvelog is used in CSII.

When used in an insulin infusion pump Truvelog should not be mixed with any other medicinal products. Patients using CSII should be comprehensively instructed in the use of the pump system. The infusion and reservoir set should be changed every 48 hours using aseptic technique. Patients administering Truvelog by CSII must always carry a spare vial of Truvelog and a U100 syringe, or an alternative insulin delivery system, in case of pump system failure.

Truvelog is administered by subcutaneous injection in the abdominal wall, the thigh, the deltoid region or the gluteal region. Truvelog may also be administered by subcutaneous infusion in the abdominal wall. Injection and infusion sites should be rotated within the same region in order to reduce the risk of lipodystrophy. When injected subcutaneously into the abdominal wall, the onset of action for Truvelog will occur within 10-20 minutes of injection. For Truvelog, the maximum effect is exerted between 1 and 3 hours after the injection, and the duration of action is 3 to 5 hours. As with all insulins the duration of action will vary according to the dose, injection site, blood flow, temperature and level of physical activity. Based on

studies of soluble insulin aspart and soluble human insulin, subcutaneous injection in the abdominal wall is expected to result in a faster absorption than from other injection sites. However, the faster onset of action of insulin aspart products compared to their respective human insulin products is expected to be maintained regardless of injection site. Formal studies on the bioavailability of insulin aspart administered by subcutaneous injection in the gluteal region have not been conducted.

Insulin aspart may be administered intravenously under medical supervision. For emergency use with insulin aspart must first be withdrawn into a syringe. Discard after emergency use. Insulin aspart has been used intravenously (see Clinical Trials). No studies have been conducted in critically ill people with diabetes who are likely to require intravenous administration. There is no pharmacokinetic or pharmacodynamic advantage in using insulin aspart over soluble human insulin when these insulins are given intravenously.

Transfer of patients to insulin aspart products

Truvelog differs from human insulin by its rapid onset and shorter duration of action. Because of the rapid onset of action, the injection of Truvelog should immediately be followed by a meal.

Truvelog is equipotent to its respective human insulin products, in regards to hypoglycaemic effect, receptor affinity and effect on lipogenesis. Patients currently treated with human insulin can be transferred to Truvelog products on a unit for unit basis when administered just before a meal. Although no change in dose is anticipated other than the routine adjustments made in order to maintain stable diabetic control, any change to insulin therapy should be made under medical supervision and blood glucose should be monitored.

When patients are transferred between different types of insulin products, the early warning symptoms of hypoglycaemia may change or become less pronounced than those experienced with their previous insulin.

4.3 CONTRAINDICATIONS

- Hypoglycaemia
- Hypersensitivity to insulin aspart

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperglycaemia

Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, may lead to hyperglycaemia and diabetic ketoacidosis. The first symptoms of hyperglycaemia usually develop gradually, over a period of hours or days. They include nausea, vomiting, drowsiness, flushed dry skin, dry mouth, increased frequency of urination, thirst and loss of appetite as well as acetone breath. Untreated hyperglycaemic events may be life threatening.

Hypoglycaemia

Omission of a meal or unplanned, strenuous physical exercise may lead to hypoglycaemia (see 'Undesirable Effects' and 'Overdosage').

Patients whose blood glucose control is greatly improved, e.g. by intensified insulin therapy, may experience a change in their usual warning symptoms of hypoglycaemia, and should be advised accordingly. Usual warning symptoms may disappear in patients with longstanding diabetes.

Truvelog should be administered immediately before a meal or, when necessary, after the start of a meal. The rapid onset of action should therefore be considered in patients with concomitant diseases or medication where a delayed absorption of food might be expected.

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

Renal or hepatic impairment, or concomitant diseases in the kidney or liver or affecting the adrenal, pituitary or thyroid gland, can require changes in the insulin dose.

Skin and subcutaneous tissue disorders

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

Truvelog contains metacresol which on rare occasions may cause allergic reactions.

Transfer of patients between insulin types

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type, origin (human insulin, insulin analogue) and/or method of manufacture may result in the need for a change in dosage. Patients transferred to Truvelog from another type of insulin may require an increased number of daily injections or a change in dosage from that used with their usual insulin products. If an adjustment is needed, it may occur with the first dose or during the first few weeks or months.

Combination of thiazolidinediones and insulin

Cases of congestive heart failure have been reported when thiazolidinediones were used in combination with insulin, especially in patients with risk factors for development of congestive heart failure. This should be kept in mind if treatment with the combination of thiazolidinediones and insulin medicinal products is considered. If the combination is used, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema. Thiazolidinediones should be discontinued if any deterioration in cardiac symptoms occurs.

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 Truvelog and other insulins.

Insulin antibodies

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 hypoglycaemia.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

A number of drugs are known to interact with glucose metabolism. Possible interactions must therefore be taken into account by the physician.

The following substances may reduce the patient's insulin requirements:

Oral hypoglycaemic agents (OHAs), monoamine oxidase inhibitors (MAOIs), non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, anabolic steroids (except danazol and oxymetholone), alpha-adrenergic blocking agents, quinine, quinidine and sulphonamides.

The following substances may increase the patient's insulin requirements:

Oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid, oxymetholone and danazol.

Beta blockers may mask the symptoms of hypoglycaemia and delay recovery from hypoglycaemia.

Octreotide and lanreotide may either increase or decrease the insulin requirement.

Alcohol may intensify and prolong or reduce the hypoglycaemic effect of insulin.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In reproductive toxicity studies, insulin aspart did not affect the fertility of male and female rats but caused a slight increase in pre-implantation loss at subcutaneous doses greater than 10U/kg/day. Similar effects were seen with human insulin.

Use in pregnancy

Pregnancy Category: A

Insulin aspart can be used in pregnancy. Data from two randomised controlled clinical trials with insulin aspart (157 + 14 insulin aspart-exposed pregnancies, respectively) did not indicate

any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn when compared to human insulin (see Section 5.1 Pharmacodynamic Properties – 'Clinical Trials').

Intensified blood glucose control and monitoring of pregnant women with diabetes (type 1 diabetes, type 2 diabetes or gestational diabetes) are recommended throughout pregnancy and when contemplating pregnancy. Insulin requirements usually fall in the first trimester and increase subsequently during the second and third trimesters. After delivery, insulin requirements return rapidly to pre-pregnancy levels.

Use in lactation

Although no clinical trial data are available with Truvelog during lactation, there are no restrictions on treatment with this medicine during lactation. Insulin treatment of the nursing mother should not affect the baby. However, the dosage of Truvelog may need to be adjusted.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia. 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 in order to avoid hypoglycaemia whilst driving or operating a machine. This is particularly important in those who have reduced or absent awareness of the warning signs of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving or operating a machine should be considered in these circumstances

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The safety profile of insulin aspart products observed in clinical trials is similar to the safety profile reported for the respective human insulin products.

Adverse drug reactions observed in patients using insulin aspart are mainly dose-dependent and due to the pharmacological effect of insulin. As for other insulin products, hypoglycaemia in general is the most frequently occurring undesirable effect. In clinical trials and during marketed use the frequency varies with patient population, dose regimens and level of glycaemic control. Therefore, no specific frequency can be presented.

Refraction anomalies, oedema and injection site reactions (pain, redness, hives, inflammation, bruising, swelling and itching at the injection site) may occur upon initiation of insulin therapy. These reactions are usually of a transitory nature. Fast improvement in blood glucose control may be associated with acute painful neuropathy, which is usually reversible. Intensification of insulin therapy with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy. Long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.

Tabulated list of adverse reactions

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

Immune system disorders	Uncommon - Urticaria, rash, eruptions Very rare - Generalised hypersensitivity reactions
Metabolism and nutrition disorders	Very common – Hypoglycaemia*
Nervous system disorders	Rare - Peripheral neuropathy
Eye disorders	Uncommon - Refraction disorders Uncommon - Diabetic retinopathy
Skin and subcutaneous tissue disorders	Uncommon - Lipodystrophy
General disorders and administration site conditions	Uncommon - Injection site reactions Uncommon - Oedema

see 'Description of selected adverse reactions'

Adverse reactions listed below are based on post-marketing source data and classified according to MedDRA System Organ Class.

Skin and subcutaneous tissue disorders	Not known – Cutaneous amyloidosis*

*see 'Description of selected adverse reactions'

Description of selected adverse reactions

Generalised hypersensitivity reactions

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

Hypoglycaemia

The most frequently reported adverse reaction is hypoglycaemia. It may occur if the insulin dose is too high in relation to the insulin requirement. Severe hypoglycaemia may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death. The symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, 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.

During clinical trials the overall rates of hypoglycaemia did not differ between patients treated with insulin aspart compared with human insulin

Skin and subcutaneous tissue disorders

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the particular area may help to reduce the risk of developing these reactions (see section 4.4 Special Warnings and Precautions for Use).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

A specific overdose for insulin cannot be defined, however hypoglycaemia may develop over sequential stages if doses are administered which are too high relative to the patient's requirements:

- Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the person with diabetes always carry products containing sugar with them.
- Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated with glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a trained person or with glucose given intravenously by a medical professional. Glucose must be given intravenously if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, oral administration of carbohydrate is recommended for the patient in order to prevent relapse

For advice on the management of overdose, please contact the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Insulin aspart (rbe) has the empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and a molecular weight of 5825.8.

Mechanism of action

Insulin aspart is a rapid-acting analogue of human insulin that rapidly lowers blood glucose. Insulin aspart is homologous with human insulin with the exception of a substitution of the amino acid proline by aspartic acid at position 28 on the B-chain. The unique structure of insulin aspart increases the rate of absorption from a subcutaneous injection site, giving a faster onset of action, an earlier peak effect and a shorter duration of action than soluble human insulin. Insulin aspart should be given immediately before a meal or, when necessary, after the start of a meal.

Insulin aspart is produced by recombinant DNA technology using *Escherichia coli.* One unit of insulin aspart corresponds to 6 nmol, 0.035 mg salt-free anhydrous insulin aspart.

Insulin lowers blood glucose levels by binding to insulin receptors to increase glucose uptake and inhibit hepatic glucose output.

The duration of action of insulin aspart will vary according to the dose, injection site, blood flow, temperature and level of physical activity.

Insulin aspart is equipotent to soluble human insulin on a molar basis.

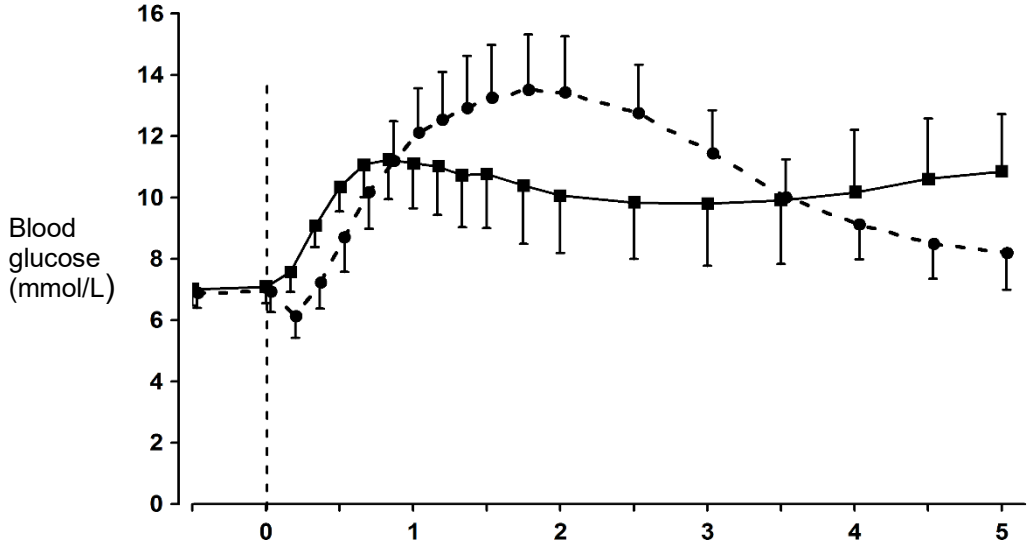
Insulin aspart produces a more rapid and pronounced blood glucose lowering effect than soluble human insulin, due to the faster onset of action.

Insulin aspart has a shorter duration of action compared to soluble human insulin after subcutaneous injection (Figure 1).

When administered immediately before a meal, the effect of insulin aspart more closely mimics normal physiological postprandial insulin release than soluble human insulin.

The onset of action of insulin aspart occurs within 10-20 minutes of subcutaneous injection. The maximum effect is exerted between 1 and 3 hours after injection. The duration of action is 3 to 5 hours. Insulin aspart has a more predictable time to peak effect within subjects than soluble human insulin.

Figure 1 - Blood glucose concentrations* (mean +/- 2SEM) following a single pre-meal dose (0.15 U/kg) of insulin aspart injected immediately before a meal (solid curve) or soluble human insulin administered 30 minutes before a meal (dashed curve) in patients with type 1 diabetes mellitus



*Data from insulin aspart Trial024/UK, a randomised, double-blind, crossover trial involving 24 subjects

Comparability Study (Truvelog versus NovoRapid)

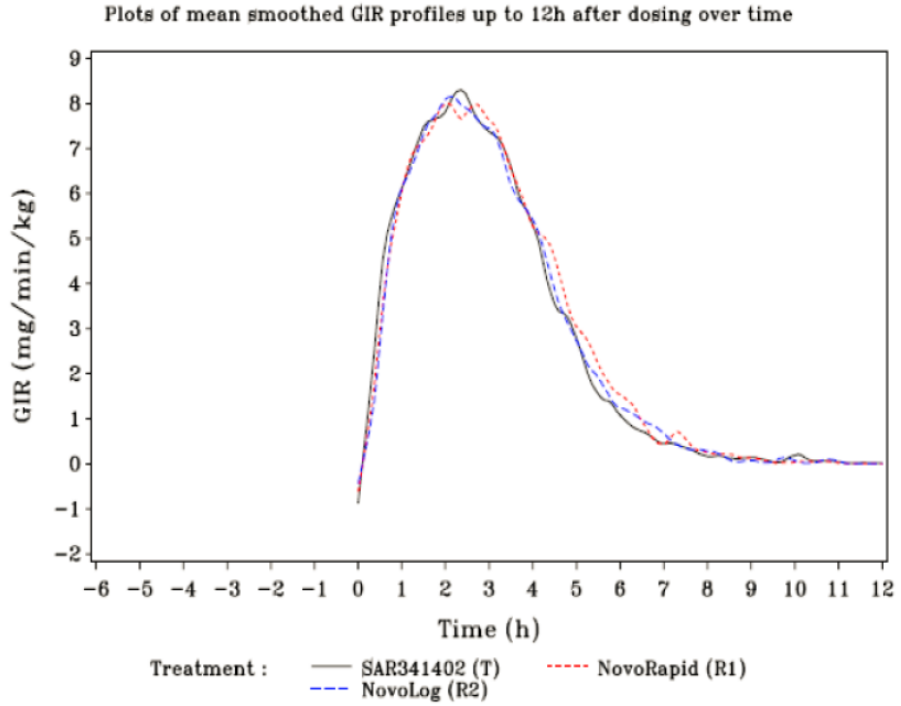
The pharmacodynamic profile (PD) of a single 0.3 unit/kg dose of Truvelog administered subcutaneously was compared to the pharmacodynamics of a single 0.3 unit/kg dose of NovoLog and NovoRapid administered subcutaneously in a crossover, double-blind, euglycemic clamp study enrolling 30 patients with type 1 diabetes. Patients were administered subcutaneous single dose injections of 0.3 unit/kg insulin aspart under fasting conditions. The pharmacodynamic parameters are summarised in Table 1. Figure 2 shows the pharmacodynamic profiles of Truvelog and the reference products. Truvelog was determined to have similar pharmacodynamic properties compared to the reference products and displayed a short acting profile.

Table 1 - Comparative PD data for Truvelog versus reference products in patients with T1DM after single dose administration

Parameter	Truvelog	NovoRapid	NovoLog
GIR-AUC$_{0-12}$ (mg/kg)			
Mean (SD)	1916.37 (524.28)	1966.71 (403.18)	1901.71 (332.48)
Point estimates of treatment ratio for Truvelog vs NovoRapid or NovoLog		0.96	0.99
90% confidence interval		0.89 to 1.04	0.91 to 1.07
95% confidence interval		0.88 to 1.05	0.90 to 1.08
GIR$_{max}$ (mg/kg/min)			
Mean (SD)	9.34 (2.01)	9.23 (1.98)	9.00 (1.67)
Point estimates of treatment ratio for Truvelog vs NovoRapid or NovoLog		1.02	1.03
90% confidence interval		0.95 to 1.09	0.96 to 1.10

Parameter	Truvelog	NovoRapid	NovoLog
95% confidence interval		0.94 to 1.10	0.95 to 1.12
GIR-t_{max} (hours)			
Mean (SD)	2.41 (0.85)	2.70 (0.92)	2.46 (0.64)
Point estimates of treatment difference for Truvelog vs NovoRapid or NovoLog		-0.29	-0.05
90% confidence interval		-0.58 to -0.04	-0.38 to 0.37

Figure 2 - Mean activity profile in patients with T1DM after administration of a single dose (0.3 unit/kg) of Truvelog or the reference product (smoothing factor 0.06)



Smoothing factor is 0.06.

EFC15081

The efficacy and safety of Truvelog was compared to that of the reference product in a 26-week, open label, randomised, active-controlled, 2-arm parallel-group study including 597 patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). There were no relevant differences between Truvelog and the reference product.

Patients with HbA1c in the range of 7% to 10% on rapid-acting mealtime insulin (100 units/mL) for at least 6 months in combination with insulin glargine (100 units/mL) for at least 6 months or insulin detemir for at least 12 months were eligible for the study. 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 Truvelog and the reference product.

Patients with type 1 or type 2 diabetes participated in a phase 3 study to compare the glucose lowering effect of Truvelog to that of administration of the reference product, both in combination with insulin glargine 100 units/mL. Prior to randomisation, 41.7%, 55.5% and 2.9% of the patients were taking insulin lispro 100 units/mL, the reference product and both, respectively. These patients were switched to Truvelog 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 randomisation. Truvelog or reference product was administered by subcutaneous injection immediately (within 5 to 10 minutes) prior to the start of a meal.

Among the 597 randomised 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/1.73m^2.

At week 26, treatment with Truvelog 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 Truvelog and reference product, as well as the incidence of severe hypoglycaemia, were similar in the two treatment groups. There were no episodes of diabetic ketoacidosis reported as SAEs in the reference product and 2 episodes in the Truvelog group. Results from the study comparing Truvelog and the reference product showed similarity in terms of development of anti-insulin antibodies. No effect of anti-insulin aspart antibodies on efficacy, safety or dose of insulin was observed.

Table 2 - T1DM and T2DM adults (Truvelog plus insulin glargine 100 units/mL versus reference product plus insulin glargine 100 units/mL)

	Truvelog (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	- 0.08	
[95% CI]	[- 0.192 to 0.039]	
Proportion of patients achieving HbA1c < 7%	16.6%	14.5%
FPG mmol/L		
Baseline mean	9.87	9.97
Adjusted mean change from baseline	- 0.49	- 0.17
Adjusted mean difference	- 0.31	
[95% CI]	[- 0.997 to 0.368]	
Daily rapid-acting insulin dose (U/kg/day)		
Baseline mean	0.398	0.394

	Truvelog (n = 301)	Reference product (n = 296)
End of study (week 26) (mean)	0.391	0.413
Mean change from baseline	- 0.011	0.011
Body weight (kg)		
Baseline mean	81.7	81.6
Mean change from baseline	1.5	1.1
Patients with any hypoglycaemia	291 (96.7)	285 (96.3)
Patients with severe hypoglycaemia		
N, incidence (%)	12 (4.0)	10 (3.4)
Documented symptomatic hypoglycaemia		
≤ 3.9 mmol/L (70 mg/dL)	264 (87.7)	251 (84.8)
< 3.0 mmol/L (54 mg/dL)	206 (68.4)	193 (65.2)

Clinical Trials

Adults: Clinical trials with insulin aspart have demonstrated an improved postprandial blood glucose control compared to soluble human insulin. In long-term trials, insulin aspart has shown a small but statistically significant improvement in glycosylated haemoglobin with no increase in hypoglycaemic events compared to soluble human insulin. In the pivotal trials, insulin aspart has shown a statistically significant reduction in the number of patients experiencing major nocturnal hypoglycaemia compared to soluble human insulin. Hypoglycaemic events with insulin aspart were seen at 2-4 hours post dose compared to 2-7 hours with soluble human insulin. There were no safety issues with insulin aspart and no evidence of increased immunogenicity with insulin aspart compared with soluble human insulin.

There were four adequate and well-controlled clinical trials in the insulin aspart clinical development program: one phase II trial in men with type I diabetes (025/UK), and three phase III trials - two in adults with type 1 diabetes (035/EU and 036/USA), and one in adults with type 2 diabetes (037/USA). In all pivotal efficacy trials, insulin aspart was administered immediately before meals, and soluble human insulin was dosed 30 minutes before meals. The phase III trials involved a wide variety of people (aged 18 - 77 years) with type 1 and 2 diabetes.

Elderly: A randomised, double-blind cross-over PK/PD (ANA-1416) trial comparing insulin aspart with soluble human insulin 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 soluble human insulin in elderly were consistent with those seen in healthy subjects and in younger subjects with diabetes. 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: Limited data suggest that when given to children insulin aspart showed similar glucose control compared to soluble human insulin. A clinical trial (ANA-1415) comparing preprandial soluble human insulin with postprandial insulin aspart was

performed in small children (26 patients aged 2 to 6 years), and a single dose PK/PD trial (043/UK) was performed in children (6-12 years) and adolescents (13-17 years). The pharmacodynamic profile of insulin aspart in children was similar to that seen in adults. Long term data in children, including the effects on growth and development, are not available.

Continuous subcutaneous insulin infusion ('CSII'):

Compatibility with insulin aspart was investigated in MiniMed 506 and Disetronic H-TRON pIus V-100 infusion pumps, and in MiniMed Polyfin (MMT-106) and Sof-set (MMT-111) and Disetronic Classic and Tender infusion sets. Two clinical trials (ANA-2018/US and ANA-2024/US) were conducted to evaluate the safety and efficacy of insulin aspart when administered by continuous subcutaneous insulin infusion (`CSII'). Clinical use was investigated in MiniMed 506, 507, 507c and Disetronic H-TRON plus V-100 insulin infusion pumps.

In a randomised, 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 Truvelog-treated patients and reference product-treated patients was evaluated. Infusion set occlusions were defined as failure to correct hyperglycaemia (plasma glucose ≥ 13.9 mmol/L) by insulin bolus via the insulin pump. The results of the study do not suggest a difference in the risk of infusion set occlusion with Truvelog and the reference product when used in CSII.

025/UK, 035/EU, 036/USA and 037/USA

The pivotal phase II and III trials, were multi-centre, randomised, active-controlled studies of 1 month (025/UK) or 6 months (035/EU, 036/USA and 037/USA) duration, designed to evaluate short- and long-term efficacy and safety of insulin aspart compared to soluble human insulin in type 1 and type 2 diabetes.

In the short-term study, the insulin aspart glucose profiles were lower after meals and higher during the night than soluble human insulin. Overall, 24-hour glucose control, as assessed by the excursion of glucose level outside the range 4.0 – 7.0 mmol/l, was significantly improved with insulin aspart. The number of major hypoglycaemic events was significantly lower with insulin aspart than soluble human insulin. The minor hypoglycaemic event rate with insulin aspart was the same as, if not lower than, the soluble human insulin but with fewer events during the night.

In the 6 month phase III studies, treatment with insulin aspart significantly improved HbA1c in patients with type 1 diabetes. A similar improvement in HbA1c was observed in type 2 patients, but was not significant due to the lower number of patients (Table 3).

Table 3 - HbA1c after 6 Months Treatment - Phase III Trials (ITT Population)

	Insulin aspart		**Soluble human insulin**				
Trial	n	Mean (SEM)	n	Mean (SEM)	Difference in Mean	95% C.I.	P
Type 1 Diabetes							
036/USA	585	7.78(0.03)	278	7.93(0.05)	-0.15	[-0.26 to -0.05]	0.0048
035/EU	694	7.88(0.03)	346	8.00(0.04)	-0.12	[-0.22 to -0.03]	0.0137

	Insulin aspart		Soluble human insulin				
Type 2 Diabetes							
037/USA	90	7.70(0.09)	86	7.82(0.10)	-0.12	[-0.38 to 0.14]	0.3684

Postprandial glucose levels and mean prandial glucose increments were significantly lower in the insulin aspart treated than in the soluble human insulin treated type 1 patients.

Overall, the relative risk of major hypoglycaemic events was 19% lower with insulin aspart compared to soluble human insulin. The number of mild hypoglycaemic events was similar between insulin groups. Treatment with insulin aspart led to higher glucose levels at night compared to human insulin, resulting in a lower incidence of nocturnal, major hypoglycaemic events. Specifically, compared to soluble human insulin, there was a 50% lower risk of experiencing a major nocturnal hypoglycaemic event with insulin aspart ($p = 0.013$) in the 036/USA trial and, similarly, a 30% lower risk with insulin aspart ($p = 0.076$) in the 035/EU trial.

ANA-2024/US

This was a multi-centre, open-label, parallel-group, phase IIIb study in which 146 adults with type 1 diabetes were randomised 2:2:1 to receive insulin aspart, buffered regular insulin or insulin lispro by CSII over a 4-week dose adjustment period and 12-week maintenance periods. All subjects had been on other forms of CSII for at least 3 months prior to study entry. The primary efficacy outcome measure was a comparison against baseline of HbAlc values at 16 weeks. The major endpoints for the safety analysis were comparisons of the numbers of adverse events and hypoglycaemic episodes.

Change-from-baseline values of HbAlc, blood glucose variability, average daily insulin use or body weight were not significantly different between treatment groups at any time point. The adverse event profile of insulin aspart was similar to that of buffered regular insulin and insulin lispro, and the three treatment groups had similar rates of hypoglycaemia. When administered as continuous subcutaneous insulin infusion in a pump, insulin aspart was shown to be as safe and effective as buffered regular human insulin.

ANA/DCD/066

This phase IIIb, double-blind, randomised, cross-over, multi-centre trial compared the frequency of major hypoglycaemic episodes after 16 weeks treatment with insulin aspart versus 16 weeks treatment with soluble human insulin in 139 adults with well-controlled type 1 diabetes treated on a basal bolus regimen. Frequency of major hypoglycaemic episodes during the treatment periods was the primary endpoint.

A statistically non-significant ($p = 0.119$) insulin aspart/soluble human insulin relative risk for major hypoglycaemia of 0.72 (95% CI: 0.47-1.09) was found. A secondary finding was that subjects treated with insulin aspart experienced a significantly ($p = 0.001$) lower rate of major hypoglycaemic episodes during the night (midnight-6am). The estimated insulin aspart/soluble human insulin relative risk was 0.28 (95% CI: 0.13-0.59). This was not a predefined endpoint

in the study protocol and this result represents a post hoc analysis. A statistically significant (p = 0.048) reduction in the frequency of minor hypoglycaemic episodes was found with insulin aspart treatment (N = 1590) compared to human soluble insulin (N = 1752), with the estimated insulin aspart/soluble human insulin relative risk being 0.93 (95% CI: 0.87-1.00). No significant differences between insulin aspart and human soluble insulin were found for the investigated glycaemic control parameters or in the domain scores of the Quality of Life questionnaires. The statistical testing was not adjusted for the multiple variables examined.

028/UK

This phase II trial was conducted in 16 subjects with well controlled type 1 diabetes who did not require intravenous therapy. Both insulin aspart and human soluble insulin were given intravenously to determine the blood glucose threshold for autonomic activation during hypoglycaemia. There were no statistically significant differences between insulin aspart and soluble human insulin. No advantage is expected in giving insulin aspart intravenously over soluble human insulin intravenously.

ANA-1415

A clinical trial investigated the safety and efficacy of insulin aspart (N = 26) vs. soluble human insulin (N = 26) in children with type 1 diabetes aged 2 – 6 years. Human NPH insulin was used as the basal insulin in both groups. Similar results for the two primary safety and efficacy endpoints (frequency of hypoglycaemic episodes and postprandial glucose increment, respectively), as well as the secondary endpoints, were observed with both regimens.

ANA-1474 and -2067

A clinical trial comparing safety and efficacy of insulin aspart vs. soluble human insulin in the treatment of pregnant women with type 1 diabetes (322 exposed pregnancies: insulin aspart, N = 157; human insulin, N = 165) did not detect any adverse effect of insulin aspart on pregnancy or on the health of the foetus/newborn. Efficacy when measured by HbA1c was observed to be comparable to insulin aspart versus soluble human insulin, whilst mean prandial glucose increments were significantly improved for insulin aspart during the first and third trimesters. In addition, the data from a clinical trial including 27 women with gestational diabetes randomised to treatment with insulin aspart vs. soluble human insulin (insulin aspart, N = 14; soluble human insulin, N = 13) showed similar safety profiles between treatments.

5.2 PHARMACOKINETIC PROPERTIES

Human insulin molecules self-associate to form hexamers. The substitution of proline by aspartic acid at position B28 in insulin aspart produces an intermolecular repulsion which reduces the tendency of the insulin molecules to self-associate. This increases the rate of dissociation of hexamers into dimers and monomers in the subcutaneous layer.

Insulin aspart is more rapidly absorbed from the subcutaneous layer than soluble human insulin. The t_{max} is on average half of that for soluble human insulin. In different studies, the t_{max} was reached after 40-50 minutes with insulin aspart compared to 80-120 minutes for soluble human insulin. The intra-individual variability in t_{max} is significantly less for insulin aspart than for soluble human insulin.

The C_{max} is on average at least twice as high with insulin aspart than with soluble human insulin. In one study in subjects with type 1 diabetes, the mean C_{max} was 492 pmol/L with insulin aspart and 216 pmol/L with soluble human insulin (administered at a dose of 0.15 U/kg bodyweight). The return to baseline insulin levels is faster with insulin aspart than soluble human insulin.

In a clinical study in healthy subjects, the pharmacokinetic differences between insulin aspart and soluble human insulin were maintained independent of the injection site (abdomen, thigh or deltoid).

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

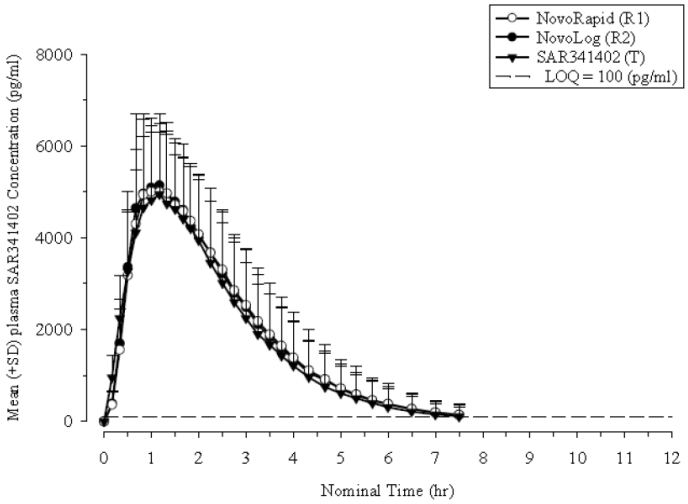
Comparability Study (Truvelog versus NovoRapid)

The pharmacokinetic profile (PK) of a single 0.3 unit/kg dose of Truvelog administered subcutaneously was compared to the pharmacokinetics of a single 0.3 unit/kg dose of NovoLog and NovoRapid administered subcutaneously in a crossover, double-blind, euglycemic clamp study enrolling 30 patients with type 1 diabetes. Patients were administered subcutaneous single dose injections of 0.3 unit/kg insulin aspart under fasting conditions. The pharmacodynamic parameters are summarised in Table 4. Table 4 shows the pharmacokinetic profiles of Truvelog and the reference products. Truvelog was determined to have similar pharmacokinetic properties compared to the reference products.

Table 4 - Comparative PK data for Truvelog versus reference products in patients with T1DM after single dose administration

Parameter	Truvelog (n = 29)	NovoRapid (n = 30)	NovoLog (n = 29)
INS-C_{max} (pg/kg)			
Mean (SD)	5320 (1510)	5490 (1460)	5760 (1780)
Point estimates of treatment ratio (90% confidence intervals) Truvelog vs NovoRapid or NovoLog		0.97 (0.90 to 1.05)	0.93 (0.87 to 1.01)
INS-AUC_{last} (pg.h/mL)			
Mean (SD)	14000 (5150)	14800 (4960)	14900 (4760)
Point estimates of treatment ratio (90% confidence interval) Truvelog vs NovoRapid or NovoLog		0.93 (0.88 to 0.97)	0.93 (0.89 to 0.98)
INS-AUC (pg.h/mL)			
Mean (SD)	13900 (5040)	15000 (5000)	15100 (4830)
Point estimates of treatment ratio (90% confidence interval) Truvelog vs NovoRapid or NovoLog		0.92 (0.88 to 0.96)	0.92 (0.88 to 0.96)

Figure 3 - Mean (±SD) plasma concentration versus time profiles for Truvelog and NovoRapid and NovoLog



Special patient populations

Children

The pharmacokinetic and pharmacodynamic properties of soluble insulin aspart were investigated in children (6-12 years) and adolescents (13-17 years) with type 1 diabetes. The relative difference in pharmacokinetics and pharmacodynamics in children and adolescents with type 1 diabetes between soluble insulin aspart and soluble human insulin correlated well with those in healthy adult subjects and adults with type 1 diabetes.

Elderly

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

Hepatic impairment

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

Renal impairment

A single dose pharmacokinetic study of soluble insulin aspart in 18 subjects with renal function ranging from normal to severely impaired was performed. No apparent effect of creatinine

clearance values on AUC, C_{max} and CL of soluble insulin aspart was found. The PK in subjects with renal failure necessitating dialysis treatment was not investigated. Special precautions should be taken in these patients as insulin clearance may be reduced.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

Lifetime carcinogenicity studies of insulin aspart have not been performed in animals. In 52-week repeat dose toxicity studies in Sprague-Dawley rats at doses up to 50 U/kg/d SC, the only significant toxicity findings were related to hypoglycaemia. At a higher dose of 200 U/kg/d SC in female Sprague-Dawley rats, insulin aspart, like human insulin, caused induction of mammary tumours. The clinical relevance of these findings is not known. Neither clinical nor epidemiological studies conducted to date have shown an association between insulin use and carcinogenesis but the available evidence is considered too limited to be conclusive at this time. *In vitro* studies showed that the mitogenic activity of insulin aspart does not differ from that observed with human insulin.

Genotoxicity

Insulin aspart did not cause gene mutations, chromosomal damage or DNA damage in a range of genotoxicity tests.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Phenol (as preservative)

Metacresol (as preservative)

Zinc chloride

Polysorbate 20

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 INCOMPATIBILITIES

In general, Truvelog should only be added to compounds with which it has known compatibility. Drugs added to the insulin may cause degradation of the insulin, e.g. if the drugs contain thiols or sulphites.

6.3 SHELF LIFE

The shelf-life of the cartridge, pre-filled pen and vial is 30 months when stored between 2°C and 8°C.

After first opening or carried as a spare: a maximum of 28 days (4 weeks), any remainder must then be discarded.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before first use

Cartridge, pre-filled pen and vial: store in a refrigerator (2°C - 8°C). Do not freeze. Keep in the outer carton in order to protect from light.

After first use

Cartridge, pre-filled pen and vial: store below 30°C. Do not refrigerate. Do not freeze. Keep in the outer carton in order to protect from light. Discard after 28 days (4 weeks) from the first use.

The pen should not be stored with the needle attached. Keep the pen cap on.

6.5 NATURE AND CONTENTS OF CONTAINER

Truvelog 100 units/ml solution for injection in vial:

Type 1 colourless multi-dose glass vial closed with a flanged cap (aluminium) with tear-off lid (polypropylene) and laminated disk (laminate of isoprene and bromobutyl rubber). Each vial contains 10 ml of solution.

Pack sizes: 1 or 5 vials.

Truvelog 100 units/mL solution for injection in cartridge

Type I colourless glass cartridge with a grey plunger (bromobutyl rubber) and a flanged cap (aluminium) with a sealing disk (laminate of isoprene and bromobutyl rubber). Each cartridge contains 3 mL of solution.

Pack sizes: 5 or 10 cartridges.

Truvelog SoloStar®100 units/mL solution for injection in a pre-filled pen

Type I colourless glass cartridge with a grey plunger (bromobutyl rubber) and a flanged cap (aluminium) with a sealing disk (laminate of isoprene and bromobutyl rubber) sealed in a disposable pen injector (SoloStar). Each pre-filled pen contains 3 mL of solution.

Pack sizes: 1, 5 or 10 pre-filled pens.

Needles are not included in the pack.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
PO Box 62027
Sylvia Park Auckland 1644
Freecall: 0800 283 684

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

15 December 2022

10 DATE OF REVISION

15 December 2022

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New document