

AUSTRALIAN PRODUCT INFORMATION - TRUVELOG (INSULIN ASPART (RBE) SOLUTION FOR INJECTION)

1 NAME OF THE MEDICINE

Insulin aspart (rbe)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

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

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 is produced by recombinant DNA technology using *Escherichia coli*.

For the full list of excipients, see section 6.1 List of excipients.

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

Insulin aspart has a faster onset and a shorter duration of action than soluble human insulin. Due to the faster onset of action, insulin aspart 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.

Method of Administration

Truvelog is administered by subcutaneous injection in the abdominal wall, the thigh, the deltoid region or the gluteal region. Injection sites should be rotated within the same region in order to reduce the risk of lipodystrophy. 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 compared to their respective human insulin products is expected to be maintained regardless of injection site. Formal studies on the bioavailability of Truvelog administered by subcutaneous injection in the gluteal region have not been conducted.

Dosage Adjustment

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.

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 insulin aspart should immediately be followed by a meal.

Insulin aspart is equipotent to human insulin, in regards to hypoglycaemic effect, receptor affinity and effect on lipogenesis. Patients currently treated with human insulin can be transferred to Truvelog 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.

Instructions for use and handling

Truvelog 3mL cartridge:

The carton contains a Consumer Medicine Information package leaflet with instructions for using and handling the cartridge. The leaflet refers to the instructions for using the accompanying Sanofi insulin delivery system.

Truvelog cartridges are for use by one person only. The cartridges must not be refilled.

Truvelog cartridges are designed to be used with Sanofi insulin delivery systems with compatible sterile needles.

Failure to change the needle may result in needle blockage. The patient should be advised to discard the needle after each injection.

Truvelog SoloStar[®] 3mL pre-filled pen:

The carton contains a Consumer Medicine Information and instructions for using the SoloStar pen package leaflet.

Truvelog SoloStar pre-filled pen is for use by one person only. The cartridge inside the pen must not be refilled. A new sterile needle must be attached before each injection.

Failure to change the needle may result in needle blockage. The patient should be advised to discard the needle after each injection.

4.3 CONTRAINDICATIONS

- Hypoglycaemia
- Hypersensitivity to insulin aspart or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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 Section 4.8 Adverse Effects (Undesirable effects) and Section 4.9 Overdose).

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.

Insulin aspart 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.

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 levels in order to minimise the risk of hypoglycaemia.

Injection site reactions

As with any insulin therapy, injection site reactions may occur and include pain, redness, itching, hives, bruising, swelling 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 insulin aspart.

Insulin aspart contains metacresol which on rare occasions may cause allergic reactions.

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.

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 insulin aspart 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.

Use in the elderly

No data available

Paediatric use

No data available

Effects on laboratory tests

No data available

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 sulfonamides.

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 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 insulin aspart during lactation, there are no restrictions on treatment with these medicines during lactation. Insulin treatment of the nursing mother should not affect the baby. However, the dosage of insulin aspart 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 to avoid hypoglycaemia while 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety profile of insulin aspart 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 ($\geq 1/10$), 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

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.

Lipodystrophy

Lipodystrophy (including lipohypertrophy, lipoatrophy) may occur at the injection site. Continuous rotation of the injection site within the particular area reduces the risk of developing these reactions.

Antibody production

In a Phase III study of insulin aspart, the level of antibodies cross-reactive to human insulin and insulin aspart showed an increase during the first 3 months which persisted at a lower level after 12 and 24 months. After 24 months of treatment a correlation was found between absolute antibody level and absolute insulin dose; no correlation, however, was found between the increase in antibody formation and the increase in insulin dose. There was no significant correlation with glycaemic control attained or adverse event reporting. The long- term clinical significance of insulin antibodies is uncertain.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or <https://nzphvc.otago.ac.nz/reporting/> (New Zealand).

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 general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes insulins and analogues for injection, fast-acting, ATC code: A10AB05

Mechanism of action

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

As with all insulins in clinical practice, 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.

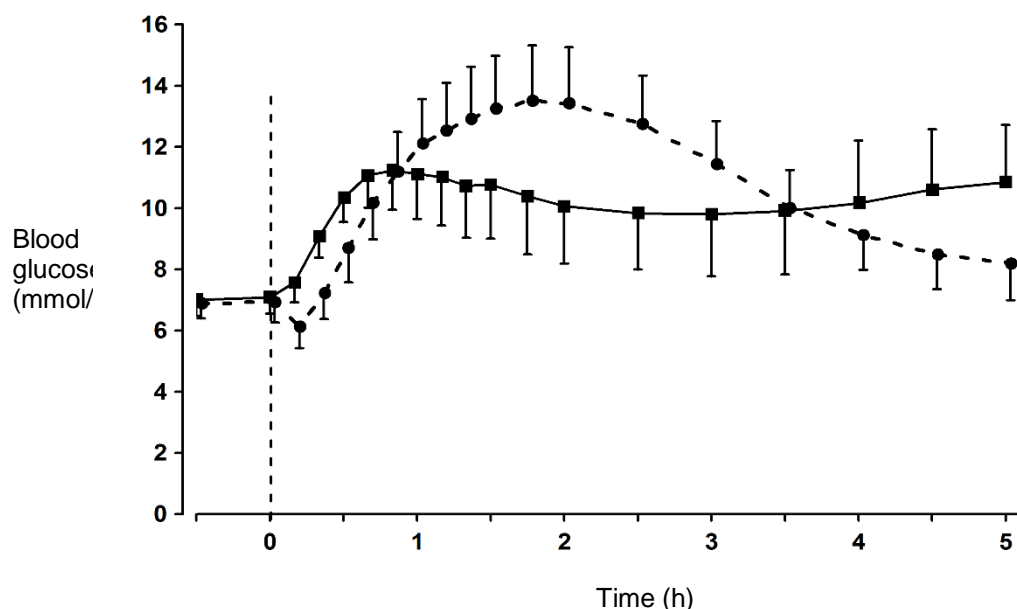
Insulin aspart produces a more rapid and pronounced blood glucose lowering effect than soluble human insulin, due to the faster onset of action.

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 \pm 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 aspartglar Trial 024/UK, a randomised, double-blind, crossover trial involving 24 subjects

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 subjects 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.

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 HbA_{1c} in patients with type 1 diabetes. A similar improvement in HbA_{1c} was observed in type 2 patients, but was not significant due to the lower number of patients (Table 2).

Table 1 - HbA_{1c} 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
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/DCD/066

This phase IIIb, double-blind, randomized, 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 HbA_{1c} 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.

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. The pharmacokinetics of biphasic insulin aspart have not been investigated in the elderly.

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. The pharmacokinetics of biphasic insulin aspart have not been investigated in this population.

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. The pharmacokinetics of biphasic insulin aspart have not been investigated in this population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Phenol
Metacresol
Zinc chloride
Polysorbate 20
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 INCOMPATIBILITIES

In general, insulin aspart products should only be added to compounds with which they have 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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Before first use

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the cartridge and pre-filled pen in the outer carton in order to protect from light.

After first use

Store below 30°C. Do not refrigerate. Do not freeze. Keep the cartridge and pre-filled pen 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.

6.5 NATURE AND CONTENTS OF CONTAINER

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 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.

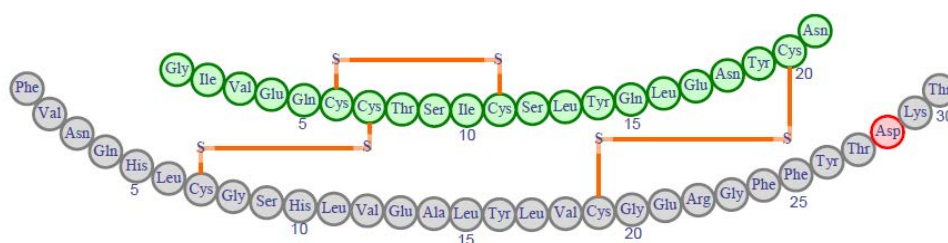
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

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



Attachment 1: Product information for AusPAR –Truvelog– insulin aspart – Sanofi-Aventis Australia Pty Ltd - PM-2019-04815-1-5 final – 1 March 2021. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

CAS number

116094-23-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

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9 DATE OF FIRST APPROVAL

15 October 2020

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information

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