NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Apidra 100 IU/mL solution for injection in 10 mL vials.

Apidra 100 IU/mL solution for injection in 3 mL cartridges.

Apidra SoloStar 100 IU/mL solution for injection in a 3 mL pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Apidra contains 100 IU/mL (3.49 mg/mL) insulin glulisine.

Apidra 100 IU/mL solution for injection in 10 mL vials - equivalent to 1000 IU.

Apidra 100 IU/mL solution for injection in 3 mL cartridges - equivalent to 300 IU.

Apidra SoloStar 100 IU/mL solution for injection in a 3 mL pre-filled pen – equivalent to 300 IU.

Insulin glulisine is produced by recombinant DNA technology in Escherichia coli.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Apidra is a sterile clear, colourless solution of insulin glulisine in vials and cartridges for use as an injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Apidra is indicated for the treatment of type 1 and type 2 diabetes mellitus in adults and children of 4 years or above who require insulin for the control of hyperglycaemia.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Apidra is a recombinant human insulin analogue that has been shown to be equipotent to human insulin. After subcutaneous administration it has a more rapid onset and a shorter duration of action than regular human insulin.

Apidra is for single patient use only.

Apidra should be given by injection within 15 minutes before a meal or within 20 minutes after starting a meal.

The dosage of Apidra should be individualised and determined based on the physician's advice in accordance with the needs of the patient. Apidra should normally be used in regimens that include a longer-acting insulin or basal insulin analogue.

Paediatric population

There is insufficient clinical information on the use of Apidra in children younger than the age of 4 years.

Method of administration

Apidra should be administered by subcutaneous injection in the abdominal wall, the thigh or deltoid. As with all insulins, injection sites within an injection area (abdomen, thigh, deltoid) should be rotated from one injection to the next in order to reduce the risk of lipodystrophy and localised cutaneous amyloidosis. Do not inject into areas of lipodystrophy and localised cutaneous amyloidosis. (see Section 4.4 Special warnings and precautions for use and 4.8 Adverse Effects (Undesirable Effects).

As for all insulins, the rate of absorption, and consequently the onset and duration of action, may be affected by injection site, exercise and other variables. Blood glucose monitoring is recommended for all patients with diabetes.

Mixing of insulins for subcutaneous injection

Apidra can be mixed with NPH human insulin. If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Pens to be used with Apidra cartridges

Apidra cartridges should only be used with the following pens:

- AllStar and AllStar Pro which deliver Apidra in 1 unit dose increments; or
- JuniorSTAR which delivers Apidra in 0.5 unit dose increments from 1 unit; or
- ClikSTAR which delivers Apidra in 1 unit dose increments.

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

4.3 CONTRAINDICATION

Apidra is contraindicated in patients hypersensitive to insulin glulisine or any of its excipients. For the full list of excipients, see section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Because of the short duration of action of Apidra, patients with diabetes also require a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

As with all insulins, the time course of action of Apidra may vary in different individuals or at different times in the same individual and the rate of absorption is dependent on blood supply, temperature and physical activity.

Adjustment of dosage of any insulin may be necessary if patients change their physical activity or their usual meal plan.

Insulin requirements may be altered during intercurrent conditions such as illness, emotional disturbances or stress.

Any change of insulin should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type (e.g. regular, NPH, analogues), species (animal, human), or method of manufacture (rDNA versus animal-source insulin) may result in the need for a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

Glucose monitoring is recommended for all patients with diabetes.

Patients must be instructed to perform continuous rotation of the injection site to reduce the risk of developing lipodystrophy and localised 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, and dose adjustment of antidiabetic medications may be considered (See Section 4.8 Undesirable Effects).

Medication errors have been reported in which other insulins, particularly long-acting insulins, have been accidentally administered instead of Apidra.

Hypoglycaemia

Hypoglycaemia is the most common adverse effect of insulins and may occur if the insulin dose is too high in relation to the insulin requirement. The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, differ among various different insulin formulations.

As with all insulins, the warning symptoms of hypoglycaemia may be changed, less pronounced or absent, in certain risk groups, as for example, in patients whose glycaemic control is markedly improved or in whom hypoglycaemia is developing gradually; in elderly patients; where an autonomic neuropathy is present; in patients with a long history of diabetes; in patients receiving concurrent treatment with certain drugs. (See section 4.5).

Such situations may result in severe hypoglycaemia (and possibly, loss of consciousness) prior to the patient's awareness of hypoglycaemia.

Renal impairment

The pharmacokinetic properties of Apidra were generally maintained in subjects with renal impairment. However, as with all insulins, the requirements for Apidra may be reduced in patients with renal impairment (See section 5.2). In the elderly, progressive deterioration of renal function may lead to a steady decrease in insulin requirements.

Hepatic impairment

In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Injection site and allergic reactions

As with any insulin therapy, lipodystrophy may occur at the injection site and delay insulin absorption. Local allergy in patients occasionally occurs as redness, swelling and itching at the site of insulin injection. These reactions usually resolve in a few days to a few weeks. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic allergic reactions to insulin (including Apidra), may be associated with rash (including pruritis) over the whole body, shortness of breath, wheezing, reduction in blood pressure, rapid pulse or sweating. Severe cases of generalised allergy, including anaphylactic reaction, may be life-threatening.

Localised reactions and generalised myalgias have been reported with the use of cresol as an injectable excipient.

Information for patients

Patients should be instructed on self-management procedures including glucose monitoring, proper injection technique, and hypoglycaemia and hyperglycaemia management. Patients must be instructed on handling of special situations such as intercurrent conditions (illness, stress, or emotional disturbances), an inadequate food intake or skipped meals, and missed doses.

Accidental mix-ups between insulin glulisine and other insulins, particularly long-acting insulins, have been reported. To avoid medication errors between insulin glulisine and other insulins, patients should be instructed to always check the insulin label before each injection.

As with all patients who have diabetes, the ability to concentrate and/or react may be impaired as a result of hypoglycaemia or hyperglycaemia, or, for example, as a result of visual impairment. 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 whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. It should be considered whether it is advisable to drive or operate machinery in these circumstances.

Women with diabetes should be advised to inform their doctor if they are pregnant or are contemplating becoming pregnant

Paediatric population

The relative differences in pharmacokinetic and pharmacodynamic properties of Apidra compared with regular human insulin observed in healthy adult subjects and adults with type 1 diabetes are similar in paediatric patients with type 1 diabetes (7-16 years) (See section 5.2). Apidra can be administered to children ≥ 4 years of age. Administration to children < 4 years has not been studied.

Geriatric use

In phase 3 clinical trials (n=1617), Apidra was administered to 147 patients ≥65 years of age and 27 patients ≥75 years of age. The majority of these were patients with type 2 diabetes. The change in A1C values and hypoglycaemia frequencies did not differ by age, but greater sensitivity of

some older individuals cannot be ruled out. Hypoglycaemia may be difficult to recognise in the elderly.

Interference with Laboratory or Diagnostic Tests

None known.

Abuse and dependence

No risk of abuse or dependence is likely to occur with Apidra.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

A number of substances affect glucose metabolism and may require dose adjustment of human insulin.

Substances that may enhance the blood-glucose-lowering effect and increase susceptibility to hypoglycaemia include: oral antidiabetic agents, ACE inhibitors, disopyramide, fibrates, fluoxetine, MAO inhibitors, pentoxifylline, propoxyphene, salicylates, sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering effect include: atypical antipsychotic medications (e.g. olanzapine, clozapine), corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in oral contraceptives), phenothiazine derivatives, protease inhibitors, somatotropin, sympathomimetic agents (e.g. adrenaline (epinephrine), salbutamol, terbutaline), thyroid hormones.

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation induced by hypoglycaemia may be reduced or absent.

Mixing of insulins

A clinical study in healthy volunteers (n=32) showed that mixing of Apidra with NPH human insulin immediately before injection did not affect the time to peak and that the total bioavailability was similar. There was some attenuation in peak concentration.

Mixtures should not be administered intravenously.

No data are available on mixing Apidra with insulin preparations other than NPH. (See section 5.2). Apidra should not be mixed with insulin preparations other than NPH.

4.6 FERTILITY, PREGNANCY AND LACTATION

Carcinogenicity, Mutagenicity and Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with Apidra. Results from a 12 month toxicity study in normal (non-diabetic) rats, and from other control studies, did not show any effect of treatment on incidences of mammary gland tumours. Subcutaneous doses tested were up to 50 IU/kg twice daily (plasma AUC approximately 150-fold that expected in patients). Insulin glulisine did not show any genotoxicity in tests for bacterial gene mutation and V79 cell chromosomal aberrations in vitro, or in an in vivo rat micronucleus test for clastogenicity.

Subcutaneous treatment of normal (non-diabetic) male and female rats with Apidra doses of up to 10 IU/kg/day had no effect on fertility (plasma AUC approximately 5-fold that expected in patients).

Pregnancy (Category B3)

Embryofoetal toxicity studies in normal (non-diabetic) pregnant rats did not show any effects specific to Apidra. A subcutaneous dose of 10 IU/kg/day did not affect embryofoetal development in rats (plasma AUC approximately 5-fold that expected in patients). Increased post-implantation losses were seen in rabbits treated with doses of 0.5 and 1.5 IU/kg/day (plasma AUC approximately 0.5-fold and 3-fold that expected in patients, respectively). Foetal skeletal defects (including scoliosis) seen in rabbits treated with 1.5 IU/kg/day also occurred with human insulin treatment, and were associated with maternal hypoglycaemia.

There are no well-controlled clinical studies of the use of Apidra in pregnant women. As animal reproduction studies are not always predictive of human response, insulin glulisine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters and rapidly decline after delivery. Careful monitoring of glucose control is essential in such patients. Patients with diabetes should be advised to inform their doctor if they are pregnant or are contemplating pregnancy.

Breast-feeding

Offspring development was unaffected after subcutaneous treatment of rats from early gestation and through the lactation period with doses of up to 8 IU/kg/day (plasma AUC approximately 4-fold that expected in patients). It is not known whether insulin glulisine is excreted in human milk. Many drugs, including insulin, are excreted in human milk. For this reason, caution should be exercised when Apidra is administered to a nursing mother. Lactating women may require adjustments in insulin dose and diet.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

a. Summary of the safety profile

The adverse events observed are those known in this pharmacological class and consequently common to insulins. Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

Overall, clinical studies comparing Apidra with rapid-acting insulins in adults or children and adolescents did not demonstrate a difference in frequency of adverse events.

Medication errors have been reported in which other insulins have been accidentally administered instead of insulin glulisine.

b. Tabulated summary of adverse reactions

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence:

very common: >1/10;
common >1/100, <1/10;
uncommon: >1/1,000, <1/100;
rare: >1/10,000, <1/1,000;
very rare: <1/10,000.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Frequency and symptom
Metabolism and nutrition disorders	**Very Common** Hypoglycaemia**.**
Skin and subcutaneous tissue disorders	**Common** Injection site reactions and local hypersensitivity reactions. **Rare** Lipodystrophy.
General disorders and administration site conditions	**Uncommon** Systemic hypersensitivity.

c. Description of selected adverse reactions

Metabolism and nutrition disorders

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. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders

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.

As with any insulin therapy, lipodystrophy may occur at the injection site and delay local insulin absorption.

Localised cutaneous amyloidosis at the injection site has occurred with insulins. Hyperglycaemia has been reported with repeated insulin injections into areas of cutaneous amyloidosis; hypoglycaemia has been reported with a sudden change to an unaffected injection site.

Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions. (see section 4.4 Special warnings and precautions for use).

General disorders and administration site conditions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritis. Severe cases of generalised allergy, including anaphylactic reaction, may be life-threatening.

Reporting suspected adverse events

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 https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms

Hypoglycaemia (see section 4.8) may occur as a result of an excess of insulin relative to food intake energy expenditure or both.

Management

Mild/moderate episodes of hypoglycaemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns or exercise may be needed.

More severe episodes with coma, seizure or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycaemia may recur after apparent clinical recovery.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

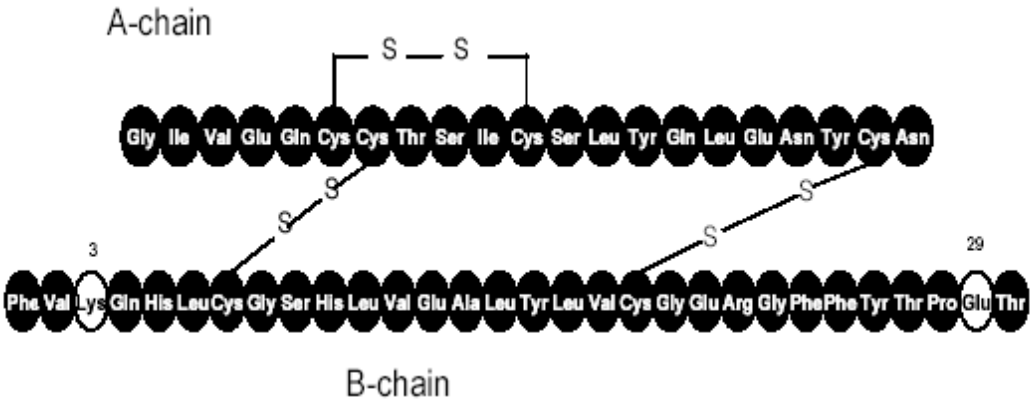
5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Drugs used in diabetes, insulins and analogues for injection, fast-acting, ATC code: A10AB06

Insulin glulisine injection {rDNA origin} is a recombinant human insulin analogue produced by recombinant DNA technology. Insulin glulisine differs from human insulin in that the amino acid asparagine at position B3 is replaced by lysine and the lysine in position B29 is replaced by glutamic acid. The chemical name is 3^{B}-Lys-29^{B}-Glu-human insulin. The empirical formula is

$C_{258}H_{384}N_{64}O_{78}S_6$, the molecular weight is 5823 and the CAS number is 207748-29-6. The structural formula is shown below:



Mechanism of action

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit proteolysis and enhance protein synthesis.

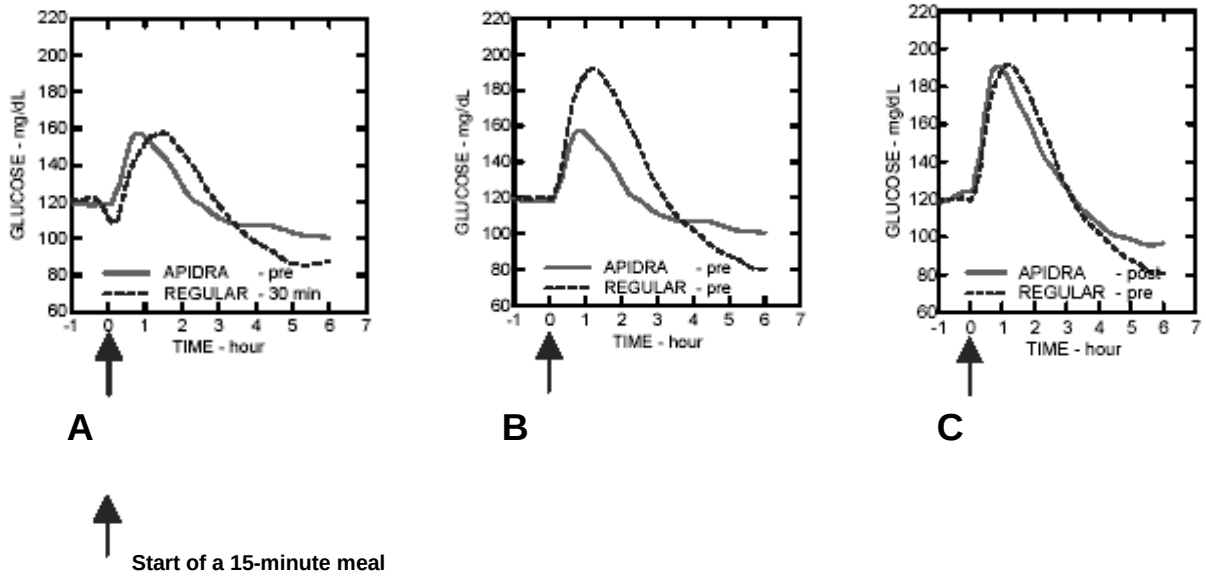
Pharmacodynamic effects

The glucose lowering activities of Apidra and of regular human insulin are equipotent when administered by the intravenous route.

Studies in healthy volunteers and patients with diabetes demonstrated that Apidra has a more rapid onset of action and a shorter duration of activity than regular human insulin when given subcutaneously.

In a study in patients with type 1 diabetes (n=20), the glucose-lowering profiles of Apidra and regular human insulin were assessed at various times in relation to a standard meal at a dose of 0.15 IU/kg.

Time-action profiles of Apidra and regular human insulin



Glucose-lowering effect over 6 hours. Apidra given 2 minutes (APIDRA - pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR - 30 min) before start of the meal (**A**) and compared to regular human insulin (REGULAR - pre) given 2 minutes before a meal (**B**). Apidra given 15 minutes (APIDRA - post) after start of a meal compared to regular human insulin (REGULAR - pre) given 2 minutes before a meal (**C**). On the x-axis zero (0) is the start of a 15-minute meal.

Clinical efficacy and safety

The safety and efficacy of Apidra was studied in adult patients with type 1 and type 2 diabetes (n=1617) and in children and adolescents with type 1 diabetes (n=572). The primary efficacy parameter was glycaemic control, as measured by glycated haemoglobin (GHb), and expressed as either GHb or haemoglobin A1c equivalents (A1C).

Type 1 Diabetes in Adults

A 26-week, randomised, open-label, active-control study (Study 3001, n=672) was conducted in patients with type 1 diabetes to assess the safety and efficacy of Apidra compared to insulin lispro when administered subcutaneously within 15 minutes prior to a meal. Lantus® (insulin glargine) was administered once daily in the evening as the basal insulin. Before start of the study there was a 4-week run-in period combining insulin lispro and Lantus followed by randomisation. Glycaemic control and the rates of hypoglycaemia requiring intervention from a third party, were comparable for the two treatment regimens. The number of daily insulin injections and the total daily doses of Apidra and insulin lispro were similar. The decrease in A1C was observed in patients treated with Apidra without an increase in the basal insulin dose. (See Table 1). The change in basal insulin dose (p=0.0001) and total insulin dose (p=0.0123) at endpoint was statistically significantly different between the two groups. The clinical value of this difference was not assessed in this study.

Table 1: Type 1 Diabetes Mellitus - Adult

Treatment duration	**26 weeks**	
Treatment in combination with:	**Lantus®**	
	Apidra	**Insulin lispro**
Number of subjects treated	339	333
A1C (%)		
Endstudy mean	7.46	7.45
Adj. mean change from baseline	-0.14	-0.14
APIDRA - Insulin lispro	0.00	
95% CI for treatment difference	(-0.09; 0.10)	
Basal insulin dose (IU/day)		
Endstudy mean	24.16	26.43
Adj. mean change from baseline	0.12[a]	1.82
Rapid-acting insulin dose (IU/day)		
Endstudy mean	29.03	30.12
Adj. mean change from baseline	-1.07	-0.81
Hypoglycaemia (events/month/patient)[b]	0.02	0.02
Mean number of rapid-acting insulin injections per day	3.36	3.42

[a] p=0.0001 for Apidra compared with insulin lispro

[b] events requiring assistance from a third party during the last 3 months of the study

Type 1 Diabetes in Children and Adolescents

In a 26-week phase 3 clinical study (Study D3001, n=572) comparing Apidra with insulin lispro, both injected subcutaneously shortly (0-15 minutes) before a meal in children and adolescents with type 1 diabetes mellitus (4-17 years of age, inclusive), using Lantus or NPH human insulin as basal insulin, Apidra was comparable to insulin lispro for glycaemic control, as reflected by changes in GHb from baseline to endpoint. (See Table 2). Comparable self-monitored blood glucose values were observed. To achieve similar glycaemic control, subjects in the Apidra group required significantly less increase in basal (p=0.0084), rapid-acting (p=0.0465) and total (p=0.0074) insulin doses as compared to subjects treated with insulin lispro. (See Table 2). The majority of subjects had an average number of rapid-acting insulin injections between 3 and 4, in both groups, and this number remained stable throughout the study.

Table 2: Type 1 Diabetes Mellitus - Children and Adolescents

Treatment duration	**26 weeks**	
	Apidra	**Insulin lispro**

Treatment duration	**26 weeks**	
	Apidra	**Insulin lispro**
Number of subjects treated	277	295
GHb (%)[a]		
Endstudy mean	8.31	8.37
Adj. mean change from baseline	0.10	0.16
APIDRA - Insulin lispro	-0.06	
95% CI for treatment difference	(-0.24; 0.12)	
Basal insulin dose (IU/day)[a]		
Endstudy mean	28.44	28.86
Adj. mean change from baseline	1.09[b]	2.22
Rapid-acting insulin dose (IU/day)[a]		
Endstudy mean	25.48	26.97
Adj. mean change from baseline	1.36[c]	2.71
Total insulin dose (IU/day)[a]		
Endstudy mean	53.85	55.80
Adj. mean change from baseline	2.53[d]	4.91
Hypoglycaemia (events/month/patient)[e]	3.45	3.02

[a] Efficacy analyses were performed on a modified intent-to-treat (mITT) population, defined as all randomised and treated subjects with a baseline and at least one efficacy evaluation on treatment; for GHb (%), Apidra (n=271), Insulin lispro (n=291); for basal and total insulin dose, Apidra (n=275), NPH insulin (n=294); for rapid-acting insulin dose, Apidra (n=274), NPH insulin (n=295)

[b] p=0.0084 for Apidra compared with insulin lispro

[c] p=0.0465 for Apidra compared with insulin lispro

[d] p=0.0074 for Apidra compared with insulin lispro

[e] Analyses of symptomatic hypoglycaemia were performed on the safety population, defined as all subjects who had received at least one dose of study medication: Apidra (n=277), insulin lispro (n=295)

Type 2 Diabetes in Adults

A 26-week, randomised, open-label, active-control study (Study 3002, n=876) was conducted in insulin-treated patients with type 2 diabetes to assess the safety and efficacy of Apidra given within 15 minutes prior to a meal compared to regular human insulin administered 30 to 45 minutes prior to a meal. NPH human insulin was given twice a day as the basal insulin. All patients participated in a 4-week run-in period combining regular human insulin and NPH human insulin. The average body mass index (BMI) of patients was 34.55 kg/m2. At randomisation, 58% of the patients were on an oral antidiabetic agent and were instructed to continue use of their oral antidiabetic agent at the same dose. The majority of patients (79%) mixed their rapid-acting insulin with NPH human insulin immediately prior to injection.

A larger reduction from baseline A1C was seen in the Apidra group. The adjusted mean difference was statistically significant (p=0.0029). At end of treatment period, postprandial blood

glucose levels in the Apidra group were lower than in the regular human insulin group. The clinical value of these differences was not assessed in this study. The rates of hypoglycaemia, requiring intervention from a third party, were comparable for the two treatment regimens. No differences between Apidra and regular human insulin groups were seen in the number of daily injections or basal or rapid-acting insulin doses. (See Table 3).

Table 3: Type 2 Diabetes Mellitus - Adult

Treatment duration	**26 weeks**	
Treatment in combination with:	**NPH human insulin**	
	Apidra	**Regular Human Insulin**
Number of subjects treated	435	441
A1C (%)		
Endstudy mean	7.11	7.22
Adj. mean change from baseline	-0.46[a]	-0.30
APIDRA - Regular Human Insulin	-0.16	
95% CI for treatment difference	(-0.26; -0.05)	
Basal insulin dose (IU/day)		
Endstudy mean	65.34	63.05
Adj. mean change from baseline	5.73	6.03
Rapid-acting insulin dose (IU/day)		
Endstudy mean	35.99	36.16
Adj. mean change from baseline	3.69	5.00
Hypoglycaemia (events/month/patient)[b]	0.00	0.00
Mean number of rapid-acting insulin injections per day	2.27	2.24

[a] p=0.0029 for Apidra compared with Regular Human Insulin

[b] events requiring assistance from a third party during the last 3 months of the study

Pre- and Post-Meal Administration (Type 1 Diabetes)

A 12-week, randomised, open-label, active-control study (Study 3004, n=860) was conducted in patients with type 1 diabetes to assess the safety and efficacy of Apidra administered at different times with respect to a meal. Apidra was administered subcutaneously either within 15 minutes prior to a meal or immediately after a meal and regular human insulin was administered subcutaneously 30 to 45 minutes prior to a meal. The comparisons performed in this study were pre-meal Apidra compared to regular human insulin, post-meal Apidra compared to regular human insulin, and post-meal Apidra compared to pre-meal Apidra. Lantus® (insulin glargine) was administered once daily at bedtime as the basal insulin. Before start of the study there was a 4 week run-in period combining regular human insulin and Lantus followed by randomisation. Glycaemic control and the rates of hypoglycaemia requiring intervention from a third party were comparable for the treatment regimens. Significant reductions from baseline in A1C were observed in all three treatment regimens. No changes from baseline between the treatments were seen in the total daily number of insulin injections. An increase in daily rapid-acting insulin dose was seen with regular human insulin. At endpoint, the change in the rapid-acting insulin dose in the regular human insulin group was statistically significant compared to the changes seen in either the pre-meal Apidra group (p=0.0001) or post-meal Apidra group (p=0.0012). (See Table 4). The clinical value of this difference was not assessed in this study.

Table 4: Type 1 Diabetes Mellitus - Adult

Treatment duration	**12 weeks**	**12 weeks**	**12 weeks**
Treatment in combination with:	**Lantus®**	**Lantus®**	**Lantus®**
	Apidra pre-meal	**Apidra post-meal**	**Regular Human Insulin**
Number of subjects treated	286	296	278
A1C (%)			
Endstudy mean	7.46	7.58	7.52
Adj. mean change from baseline[a]	-0.26	-0.11	-0.13
Basal insulin dose (IU/day)			
Endstudy mean	29.49	28.77	28.46
Adj. mean change from baseline	0.99	0.24	0.65
Rapid-acting insulin dose			
Endstudy mean (IU/day)	28.44	28.06	29.23
Adj. mean change from baseline	-0.88	-0.47	1.75[b,c]
Hypoglycaemia (events/month/patient)[d]	0.05	0.05	0.13
Mean number of rapid-acting insulin injections per day	3.15	3.13	3.03

[a] Adj. mean change from baseline treatment difference (98.33% CI for treatment difference): Apidra pre-meal vs Regular Human Insulin - 0.13 (-0.26; 0.01); Apidra post-meal vs Regular Human Insulin 0.02 (-0.11; 0.16); Apidra post-meal vs pre-meal 0.15 (0.02; 0.29).

[b] p=0.0001 for Regular Human Insulin compared to Apidra pre-meal

[c] p=0.0012 for Regular Human Insulin compared to Apidra post-meal

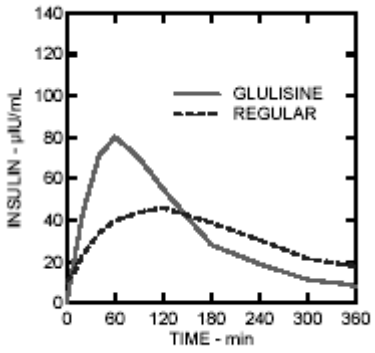
[d] events requiring assistance from third party for the entire treatment phase

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Pharmacokinetic profiles in healthy volunteers and patients with diabetes (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high compared to regular human insulin.

In a study in patients with type 1 diabetes (n=20) after subcutaneous administration of 0.15 IU/kg, the Tmax was 55 minutes and Cmax was 82 μIU/mL for insulin glulisine compared to a Tmax of 82 minutes and a Cmax of 46 μIU/mL for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min).



Pharmacokinetic profile of insulin glulisine (GLULISINE) and regular human insulin (REGULAR) in patients with type 1 diabetes after a dose of 0.15 IU/kg.

When insulin glulisine was injected subcutaneously into different areas of the body, the time-concentration profiles were similar with a slightly faster absorption when administered in the abdomen compared to the deltoid or thigh. The absolute bioavailability of insulin glulisine after subcutaneous administration is about 70%, regardless of injection area (abdomen 73%, deltoid 71%, thigh 68%).

Distribution

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration are similar, with volumes of distribution of 13 L and 21 L and half lives of 13 and 17 minutes, respectively.

Elimination

After subcutaneous administration in diabetic and non-diabetic subjects, insulin glulisine is eliminated more rapidly than regular human insulin, with an elimination half life ranging from 37 to 75 minutes, compared to 86 minutes for regular human insulin.

Special Populations

Paediatric Patients

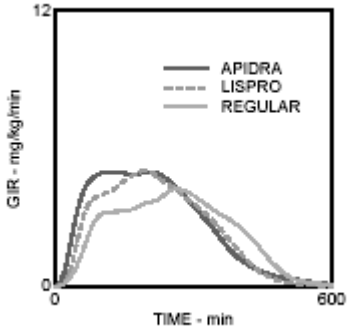
The pharmacokinetic and pharmacodynamic properties of insulin glulisine and regular human insulin were assessed in a study conducted in paediatric patients with type 1 diabetes (children [7 - 11 years, n=10] and adolescents [12 - 16 years, n=10]). The relative differences in pharmacokinetics and pharmacodynamics between insulin glulisine and regular human insulin in paediatric patients with type 1 diabetes were similar to those in healthy adult subjects and adults with type 1 diabetes.

Race and Gender

Information on the effect of race and gender on the pharmacokinetics of insulin glulisine is not available. However, in phase 3 clinical trials in adults (n=1617), subgroup analyses based on gender did not show differences in safety and efficacy between insulin glulisine and other rapid-acting insulin formulations.

Obesity

The pharmacokinetic and pharmacodynamic properties of insulin glulisine, regular human insulin and insulin lispro were compared in a study conducted in obese (30-40 kg/m2), otherwise healthy non-diabetic subjects (n=18). The more rapid onset of action and shorter duration of activity of insulin glulisine and insulin lispro compared to regular human insulin were maintained in this population. The rapid onset of action was better maintained with insulin glulisine than with insulin lispro.



Glucose infusion rates (GIR) after subcutaneous injection of 0.3 IU/kg of insulin glulisine (APIDRA), insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Renal Impairment

Studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. In a study performed in 24 non-diabetic subjects covering a wide range of renal function (CrCl >80 mL/min; 30-50 mL/min; <30 mL/min), the pharmacokinetic properties of insulin glulisine were generally maintained. (See section 4.4).

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of insulin glulisine has not been studied. However, some studies with human insulin have shown increased circulating levels of insulin in patients with liver failure. (See section 4.4).

Pregnancy

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of insulin glulisine has not been studied (See section 4.6).

5.3 PRECLINICAL SAFETY DATA

Non-clinical data did not reveal toxicity findings different from regular human insulin or of clinical relevance for humans, other than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycaemia).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Metacresol, trometamol, sodium chloride, polysorbate 20, hydrochloric acid and sodium hydroxide for adjustment to pH 7.3, and water for injections.

6.2 INCOMPATIBILITIES

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 SHELF LIFE

2 years.

Unopened vials, cartridges and pre-filled pens

Unopened vials, cartridges and pre-filled pens (such as Apidra SoloStar) should be stored in a refrigerator where the temperature is between +2°C and +8°C. Do not freeze. Discard if frozen. Keep in the outer carton in order to protect from light. Do not store next to the freezer compartment or freezer packs.

Before first use, Apidra must be kept at room temperature for 1 to 2 hours.

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

Open (in use) or unrefrigerated vials, cartridges and pre-filled pens

Apidra vials, cartridges or pre-filled pens, whether or not refrigerated, must be discarded after 28 days from first use.

Unrefrigerated vials, cartridges or pre-filled pens, whether in use or not, must be discarded after 28 days. This applies irrespective of whether the vial, cartridge or pre-filled pen is used immediately or is first carried as a spare for a while.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Vials

Once in use, vials of Apidra should be stored away from direct light between +2°C and +8°C. Do not freeze. Discard if frozen. If refrigeration is not possible, the vial of Apidra in use may be kept unrefrigerated for up to 28 days, as long as the temperature is not greater than 25°C and it is kept away from direct heat and light. Whether or not it is refrigerated, the vial that is in use must be used within a 28 day period. Any unused contents must be discarded 28 days after opening.

Cartridges and pre-filled pens

Once in use, Apidra pre-filled pens (such as Apidra SoloStar) or a reusable injection pen containing a cartridge of Apidra must not be stored in the refrigerator. Apidra that is in use in injection pens may be kept unrefrigerated for up to 28 days, as long as the temperature is not greater than 25°C and it is kept away from direct heat and light. It must be used within a 28 day period or must be discarded 28 days after commencement of use.

For storage conditions after first use of the medicine, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Apidra [insulin glulisine injection] 100 units per mL (U 100) is available in packs of 10 mL vials, 3mL cartridges for use with reusable injection devices and 3mL cartridges in SoloStar disposable injection devices.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Vials

Before withdrawing Apidra from the vial for the first time, remove the plastic protective cap. Do not shake the vial vigorously as this may cause frothing. Froth may interfere with the correct measurement of dose.

Apidra can be mixed with NPH human insulin for subcutaneous injections. If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be made immediately after mixing. Mixtures should not be administered intravenously.

Cartridges and pre-filled pens

Apidra cartridges are not designed to allow any other insulin to be mixed in the cartridge.

Manufacturer instructions for using Apidra in reusable or pre-filled disposable injection devices must be followed carefully for loading the cartridge into a reusable pen, and for attaching the needle, performing the safety test and administering the insulin injection. If the injection device is damaged, it should be discarded and a new injection device should be used.

If the reusable injection device malfunctions (see instructions for using the pen supplied with the pen), or no pen is available, Apidra may be withdrawn from the cartridge into a U100 syringe and injected subcutaneously. The syringe must not contain any other medicinal product or residue.

An empty vial, cartridge or pre-filled pen must never be reused and must be properly discarded. Any unused medicine or waste material should be disposed of in accordance with local requirements.

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

01 February 2007 for Apidra.

21 June 2007 for Apidra SoloStar.

10 DATE OF REVISION OF THE TEXT

20 June 2022

SUMMARY TABLE OF CHANGES

Section	Updated text
8	Change of sponsor