1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a vial.
Apidra 100 Units/ml, solution for injection in a prefilled pen SoloStar.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Apidra *100 Units/ml, solution for injection in a vial*
Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.

Apidra *100 Units/ml, solution for injection in a pre filled pen SoloStar*
Each pen contains 3 ml of solution for injection, equivalent to 300 Units.

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 100 Units/ml, solution for injection in a vial
Solution for injection in a vial.

Apidra 100 Units/ml, solution for injection in a pre filled pen SoloStar
Solution for injection in a pre filled pen SoloStar.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.

4.2 Posology and method of administration

Posology

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues (see section 5.1).

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dose of Apidra should be individually adjusted.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Pediatric population
There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Method of administration

Apidra 100 Units/ml solution for injection in a vial

Continuous subcutaneous insulin infusion
Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs. Patients using CSII should be comprehensively instructed on the use of the pump system.
The infusion set and reservoir used with Apidra must be changed at least every 48 hours using aseptic technique. These instructions may differ from general pump manual instructions. It is important that patients follow the Apidra specific instructions when using Apidra. Failure to follow Apidra specific instructions may lead to serious adverse events.
When used with a subcutaneous insulin infusion pump, Apidra must not be mixed with diluents or any other insulin.
Patients administering Apidra by CSII must have an alternative insulin delivery system available in case of pump system failure (see sections 4.4 and 4.8).

Apidra 100 Units/ml solution for injection in a vial
For further details on handling, see section 6.6

Apidra 100 Units/ml solution for injection in a pre-filled pen SoloStar
Apidra 100 Units/ml in pre-filled pen SoloStar is only suitable for subcutaneous injections. If administration by syringe or infusion pump is necessary, a vial should be used (see section 4.4).
For further details on handling, see section 6.6.

Subcutaneous use
Apidra should be given by subcutaneous injection shortly (0-15 min) before or soon after meals or by continuous subcutaneous pump Infusion .

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next in order to reduce the risk of lipodystrophy and cutaneous amyloidosis (see section 4.4 and 4.8).
The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

When administered as a subcutaneous injection, Apidra must not be mixed with other medicinal products except NPH human insulin.

For further details on handling, see section 6.6.

Before using SoloStar, the instructions for use included in the package leaflet must be read carefully (see section 6.6).

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Hypoglycaemia.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Transferring a patient to another type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, neutral protamine Hagedorn [NPH], lente, long-acting, etc.), origin (animal, human, human insulin analogue) and/or method of manufacture may result in the need for a change in dose. Concomitant oral antidiabetic treatment may need to be adjusted.

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, and dose adjustment of antidiabetic medications may be considered.

Hyperglycaemia
The use of inadequate doses or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dose may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

Medication errors

Medication errors have been reported in which other insulins, particularly long-acting insulins, have been accidentally administered instead of insulin glulisine. Insulin label must always be checked before each injection to avoid medication errors between insulin glulisine and other insulins.

Apidra 100 Units/ml solution for injection in a vial
Continuous subcutaneous insulin infusion
Malfunction of the insulin pump or infusion set or handling errors can rapidly lead to hyperglycaemia, ketosis and diabetic ketoacidosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis or diabetic ketoacidosis is necessary.

Cases of diabetic ketoacidosis have been reported when Apidra has been given in continuous subcutaneous insulin infusion in pump systems. Most of the cases were related to handling errors or pump system failure.
Interim subcutaneous injections with Apidra may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin delivery system available in case of pump system failure (see sections 4.2 and 4.8).

Excipients
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, i.e., it is essentially 'sodium-free'.
Apidra contains metacresol, which may cause allergic reactions.

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

Apidra Solostar 100 Units/ml solution for injection in a pre-filled pen
Handling of the SoloStar pre-filled pen
Apidra SoloStar 100 units/ml in pre-filled pen is only suitable for subcutaneous injections.
If administration by syringe or infusion pump is necessary, a vial should be used.
Before using SoloStar, the Instructions for use included in the Package leaflet must be read carefully.
SoloStar has to be used as recommended in these Instructions for use (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic medicinal products, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulphonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic medicinal products (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, oestrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity 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 may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of insulin glulisine in pregnant women.
Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.
It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Breast-feeding
It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.
Breast-feeding mothers may require adjustments in insulin dose and diet.

Fertility
Animal reproduction studies with insulin glulisine have not revealed any adverse effects on fertility.

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 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 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

Summary of the safety profile
Hypoglycaemia, the most frequent adverse reactionof insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

Tabulated list of adverse reactions
The following related adverse reactions from clinical studies were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA Organ system classes	Very common	Common	Uncommon	Rare	Not known
Metabolism and nutrition disorders	Hypoglycaemia				Hyperglycaemia (potentially leading to Diabetic ketoacidosis [(1)])
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy	Cutaneous amyloidosis
General disorders and administration site conditions			Systemic hypersensitivity reactions		

[1)] *Apidra 100 Units/ml solution for injection in a vial:* Most of the cases were related to handling errors or pump system failure when Apidra was used with CSII.

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.

Apidra 100 Units/ml solution for injection in a vial
Cases of hyperglycaemia have been reported with Apidra when used with CSII (see section 4.4) that has led to Diabetic Ketoacidosis (DKA); most of the cases were related to handling errors or pump system failure. The patient should always follow the Apidra specific instructions and always have access to alternative insulin delivery system in case of pump system failure.

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.
Lipodystrophy and cutaneous amyloidosis may occur at the injection site and delay local insulin absorption. Continuous rotation of the injection site within the given injection area may help to reduce or prevent these reactions (see section 4.4).
General disorders and administration site conditions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnoea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il/.

4.9 Overdose

Symptoms
Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.
There are no specific data available concerning overdoses with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Management
Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.
Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5mg to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a healthcare professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

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, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insulin glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. After intravenous administration, a faster onset and shorter duration of action, as well as a greater peak response were observed as compared with subcutaneous administration. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route.
One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 Units/kg, and less than proportional increase in glucose lowering effect with 0.3 Units/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 Units/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycaemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycaemic control as regular human insulin given 2 minutes before the meal (see figure 1).

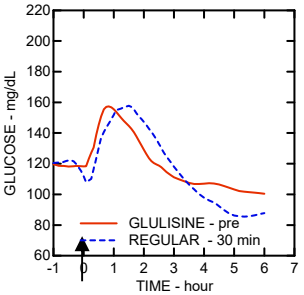

FIGURE 1 A

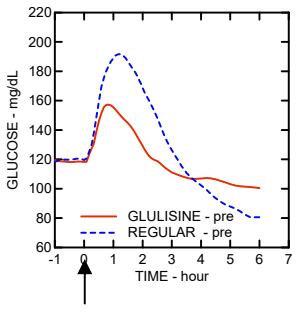

FIGURE 1B

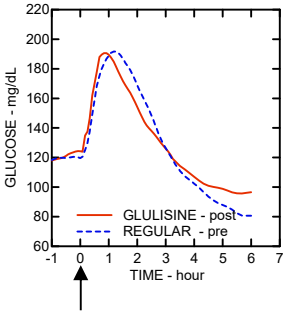

FIGURE 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the $AUC_{(0-2h)}$ representing the early glucose lowering activity were respectively of 114 minutes and 427 mg/kg for insulin glulisine, 121 minutes and 354 mg/kg for lispro, 150 minutes and 197 mg/kg for regular human insulin (see figure 2).

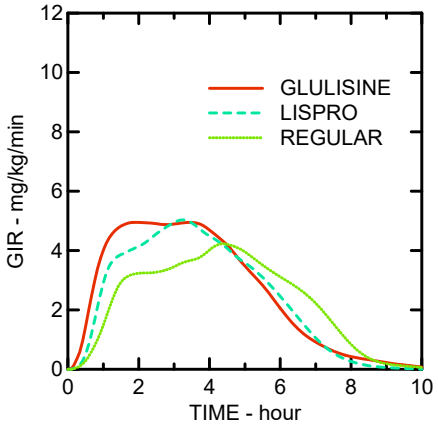

Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices (BMI), while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 Units/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 Units/kg insulin lispro, respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)]has shown that insulin glulisine effectively controls diurnal postprandial blood glucose excursions.

Clinical efficacy and safety

Type 1 diabetes mellitus- Adults

In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro, both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate pos-tmeal administration of insulin glulisine provides efficacy that was comparable to immediate pre-meal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the pre-meal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Paediatric

A 26-week phase III clinical study compared insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in children (4-5 years: n=9; 6-7 years: n=32 and 8-11 years: n=149) and adolescents (12-17 years: n=382) with type 1 diabetes mellitus using insulin glargine or NPH as basal insulin. Insulin glulisine was comparable to insulin lispro for glycaemic control as reflected by changes in glycated haemoglobin (GHb expressed as HbA_{1c} equivalent) from baseline to endpoint and by self-monitored blood glucose values.
There is insufficient clinical information on the use of Apidra in children younger than the age of 6 years.

Type 2 diabetes mellitus- Adults

A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycaemic agents at randomization and were instructed to continue to use them at the same dose.

Race and gender
In controlled clinical studiesin adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favours more rapid absorption.
In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4 Units/kg.

Absorption and bioavailability

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

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 Units/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µUnits/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µUnits/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

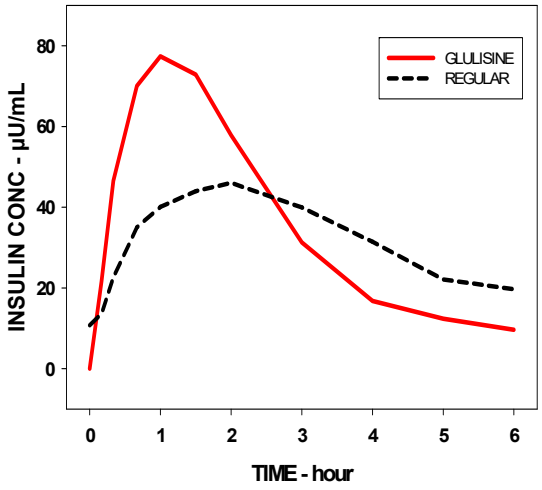

Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 Units/kg insulin glulisine, the C_{max} was 91 µUnits/ml with the interquartile range from 78 to 104 µUnits/ml. When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV).

Obesity
Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices. The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.
After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).
Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly

Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801 $mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Apidra 100 Units/ml, solution for injection in a vial
Subcutaneous use
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.
When used with an insulin infusion pump, Apidra must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first use or removal from the refrigerator:

Apidra 100 Units/ml, solution for injection in a vial
Shelf life after first use or removal from the refrigerator of the vial:
The product may be stored for a maximum of 4 weeks at a temperature not exceeding 25°C away from direct heat or direct light. Keep the vial in the outer carton in order to protect from light.
It is recommended that the date of the first use from the vial be noted on the label.

Apidra *100 Units/ml, solution for injection in a pre filled pen SoloStar*
Shelf life after first use or removal from the refrigerator of the pen
The product may be stored for a maximum of 4 weeks at a temperature not exceeding 25°C away from direct heat or direct light.
Pens in use must not be stored in the refrigerator. The pen cap must be put back on the pen after each injection in order to protect from light.

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6.4 Special precautions for storage

Apidra 100 Units/ml solution for injection in a vial

Unopened vials
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Opened vials
For storage conditions after first opening of the medicinal product, see section 6.3.

Apidra 100 Units/ml solution for injection in a pre-filled pen SoloStar

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

In-use pens
For storage conditions after first opening of the medicinal product, see section 6.3.

.

6.5 Nature and contents of container

Apidra 100 Units/ml solution for injection in a vial

10 ml solution in a vial (type I colourless glass) with a stopper (flanged aluminium overseal, elastomeric chlorobutyl rubber) and a polypropylene tear-off cap. Packs of 1, 2, 4 and 5 vials are available. Not all pack sizes may be marketed.

Apidra 100 Units/ml solution for injection in a pre-filled pen SoloStar
3 ml solution in a cartridge (colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). The cartridge is sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Apidra 100 Units/ml, solution for injection in a vial
Subcutaneous use
Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system (see section 4.2).
Inspect the vial before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Since Apidra is a solution, it does not require resuspension before use.
Insulin label must always be checked before each injection to avoid medication errors between insulin glulisine and other insulins (see section 4.4).

Mixing with insulins
When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

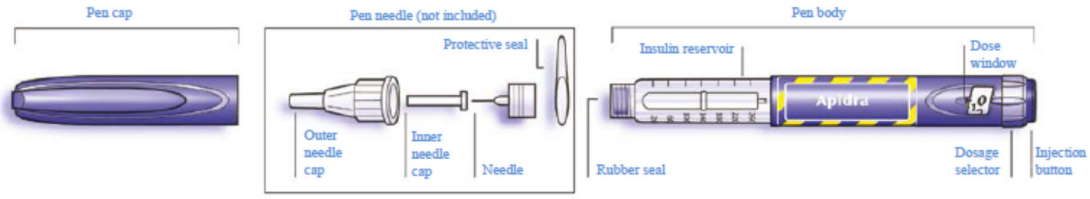
Continuous subcutaneous infusion pump
Refer to sections 4.2 and 4.4 for advice.

Apidra 100 Units/ml solution for injection in a pre-filled pen SoloStar

Apidra SoloStar 100 units/ml in a pre-filled pen is only suitable for subcutaneous injections. If administration by syringe or infusion pump is necessary, a vial should be used. Before first use the pen must be stored at room temperature for 1 to 2 hours.

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.
Empty pens must never be used and must be properly discarded.
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.
Insulin label must always be checked before each injection to avoid medication errors between insulin glulisine and other insulins (see section 4.4).

Handling of the pen
The patient should be advised to read the instructions for use included in the package leaflet carefully before using the pre-filled pen SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

- Before each use, a new needle must always be carefully attached and a safety test must be performed. A dose should not be selected and/or the injection button should not be pressed without a needle attached. Only use needles that are compatible for use with SoloStar.
- Special caution must be taken to avoid accidental needle injury and transmission of infection.
- SoloStar must never be used if it is damaged or if the patient is not sure if it is working properly.
- The patient must always have a spare SoloStar available in case the SoloStar is lost or damaged.

Storage instructions

Please check section 6.4 of this SPC for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of the SoloStar can be cleaned by wiping it with a damp cloth.

The pen must not be soaked, washed or lubricated as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. The patient should avoid situations where SoloStar may be damaged. If the patient is concerned that the SoloStar may be damaged, he must use a new one.

Step 1 Check the insulin

The label on the pen should be checked to make sure it contains the correct insulin. The Apidra SoloStar is blue. It has a dark blue injection button with a raised ring on the top. After removing the pen cap, the appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.

Step 2 Attach the needle

Only needles that are compatible for use with SoloStar should be used.
A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3 Perform a safety test

Prior to each injection a safety test has to be performed to ensure that pen and needle work properly and to remove air bubbles.

A dose of 2 units has to be selected.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4 Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show “0” following the safety test. The dose can then be selected.

Step 5 Inject the dose

The patient should be informed on the injection technique by his health care professional.

The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6 Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles must not be reused.

Special caution must be taken when removing and disposing the needle. Recommended safety measures for removal and disposal of needles must be followed (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.

Manufacturer: Sanofi-Aventis Deutschland GmbH, Germany.

License holder: sanofi-aventis Israel ltd, P.O.B 8090, Netanya 4250499

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