Apidra® 100 IU/ml

Insulin glulisine

Apidra 100 Units/ml solution for injection in a vial
Apidra 100 Units/ml solution for injection in a cartridge
Apidra 100 Units/ml solution for injection in a pre-filled pen Solostar

This package insert is continually updated:
Please read carefully before using a new pack!

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution for injection contains 3.49 mg of the active substance insulin glulisine, corresponding to 100 IU human insulin.
Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.
Each cartridge and SoloStar contains 3 ml, equivalent to 300 Units.
Excipients: Metacresol, Sodium chloride, Trometamol, Polysorbate 20, Hydrochloric acid concentrated, Sodium hydroxide, Water for injections.
Insulin glulisine is an insulin analogue produced by recombinant DNA technology using *Escherichia coli*.

PHARMACEUTICAL FORM

Solution for injection
Clear, colourless, aqueous solution.

THERAPEUTIC INDICATION

Treatment of adults, adolescents and children, 8 years or older with diabetes mellitus, where treatment with insulin is required.

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 *Pharmacodynamic properties)*.
Apidra should be given by injection within 15 minutes before or immediately after a meal.
Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycemic agents.
The dosage of Apidra should be individualized and determined based on the physician's advice in accordance with the needs of patients.

Special population

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 *Pharmacokinetic properties*).

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.

Children and adolescents

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
Intravenous use
Apidra can also be administered intravenously. This should be carried out by health care professionals.
Apidra must not be mixed with glucose or Ringer's solution or with any other insulin.

Continuous Subcutaneous Infusion Pump
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 an 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 section *Special Warning and Precautions* and *Undesirable effect*).

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

Apidra 100 Units/ml solution for injection in a cartridge
Apidra 100 Units/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used (see section *Special warnings and precautions for use)*. For further details on handling, see section *Preparation and handling*.

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
Apidra SoloStar 100 Units/ml in pre-filled pen is only suitable for subcutaneous injections. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used (see section *Preparation and handling*).

Subcutaneous use
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. 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 injections sites (see *Pharmacokinetic properties)*.
Care should be taken to ensure that 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
Apidra must not be mixed with any preparation other than NPH (Neutral Protamine Hagedom) human insulin. If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing. Mixtures should not be administered intravenously. No data are available on mixing insulin glulisine with insulin preparations other than NPH human insulin.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.
Hypoglycemia

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Any change of insulin should be made cautiously and only under medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycemia and diabetic ketoacidosis; conditions which are potentially lethal.
Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Pens to be used with Apidra 100 units/ml solution for injection in a cartridges
Apidra 100 units/ml in cartridges is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.
The Apidra cartridges should only be used with the following pens: OptiPen, ClickStar, Autopen, and Allstar, and should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens.

Hypoglycemia
The time of occurrence of hypoglycemia 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 hypoglycemia 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 dosage 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 hypoglycemia.

When compared with soluble human insulin, if hypoglycemia occurs after an injection with rapid acting analogues, it may occur earlier. Uncorrected hypoglycemic or hyperglycemic reactions can cause loss of consciousness, come, or death.
Insulin requirements may be altered during illness or emotional disturbances.

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 effect and increase susceptibility to hypoglycemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

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

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

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.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

A limited amount of data on pregnant women (less than 300 pregnancy outcomes reported) exposed to marketed insulin glulisine indicates no safety issues in use of insulin glulisine during pregnancy or on the foetus and newborn child.

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. Patients with diabetes must inform their doctor if they are pregnant or are contemplating pregnancy.

Lactation

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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The patient's ability to concentrate and react may be impaired as a result of hypoglycemia or hyperglycemia 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 hypoglycemia or have frequent episodes of hypoglycemia. The advisability of driving should be considered in the circumstances.

UNDESIRABLE EFFECTS

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

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 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).

Description of selected adverse reactions

Metabolism and nutrition disorders

Very common: Hypoglycemia

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.

Hypoglycemia 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 *Special warning and precaution*) 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
Common: injection site reactions and local hypersensitivity reactions.
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.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

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

OVERDOSE
Hypoglycemia 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 overdose with insulin glulisine. However, hypoglycemia may develop over sequential stages:

Mild hypoglycemia episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patients constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycemia episodes, where the patients has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patients does not respond to glucagons 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 glucagons, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycemia and prevent other similar episodes.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapy group: insulin and analogues, fast-acting, ATC code: A10AB06.
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 insulin and insulin analogues, including glulisine, is regulation of glucose metabolism. Insulin 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 I aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/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 profile of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minutes standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic 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 glycemic control as regular human insulin given 2 minutes before the meal (see Figure 1).

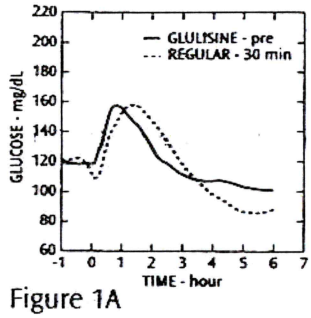

Figure 1A

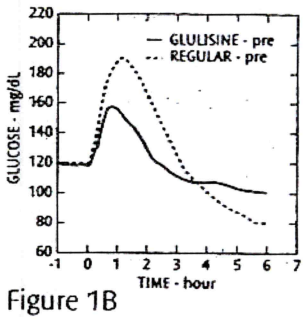

Figure 1B

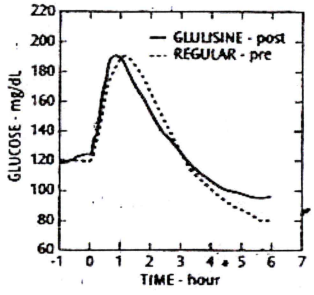

Figure 1C

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 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 minutes 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 (0-2 h) representing the early glucose lowering activity were respectively of 114 minutes and 427 $mg.kg^{-1}$ for insulin glulisine, 121 minutes and 354 $mg.kg^{-1}$ for lispro, 150 minutes and 197 $mg.kg^{-1}$ for regular human insulin (see Figure 2).

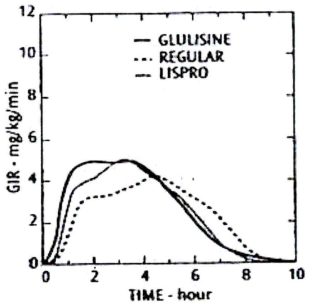

Figure 2:
Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

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/m^2) has demonstrated that rapid action is generally maintained across a wide range of body mass indices, 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 U/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 U/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 post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus-Adults

In a 26-weeks 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 glycemic 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 postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal 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 premeal glulisine group compared with the regular insulin group.

Type 1 diabetes mellitus-Pediatric
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 glycemic control as reflected by changes in glycated hemoglobin (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-weeks phase III clinical study followed by a 26-weeks 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-months endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58% of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

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

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 favors 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 U/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 patient with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µU/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µU/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).

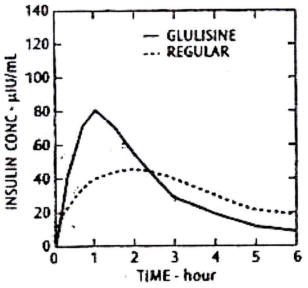

Figure 3:
Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 U/kg.
In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the C_{max} was 91 µU/ml with the interquartile range from 78 to 104 µU/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 sited was in between (see *Posology and method of administration*) the absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intrasubject variability (11% CV). Intravenous bolus administration of insulin glulisine resulted in a higher systemic exposure when compared to subcutaneous injection, with a C_{max} approximately 40-fold higher.

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/m^2) 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 *Posology and method of administration*).

Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see *Pharmacodynamic properties*). The glucose

excursion ($AUC_{0\text{-}6\,h}$) was 641 mg.h.dl^{-1} for insulin glulisine and 801 mg.h.dl^{-1} for regular human insulin.

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

PHARMACEUTICAL PARTICULARS

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

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.
Intravenous use
Apidra was found to be incompatible with Glucose 5% solution and Ringer's solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.

~~*Apidra 100 Units/ml solution for injection in a cartridge*~~
~~*Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen*~~
~~In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except NPH human insulin.~~

Shelf life
2 years.

Apidra 100 Units/ml solution for injection in a vial
Shelf life after first use of the vial
The product may be stored for a maximum of 4 weeks below 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.
Shelf life for intravenous use
Insulin glulisine for intravenous use at a concentration of 1 Unit/ml is stable between 15°C and 25°C for 48 hours (see section *Preparatian and handling).*

Apidra 100 Units/ml solution for injection in a cartridge
Shelf life after first use of the cartridge
The product may be stored for a maximum of 4 weeks below 25°C away from direct heat or direct light.
The pen containing a cartridge 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.

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
Shelf life after first use of the pen

The product may be stored for a maximum of 4 weeks below 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.

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.
Do not put Apidra next to the freezer compartment or a freezer pack.
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 *Shelf-life*

Apidra 100 Units/ml solution for injection in a cartridge
Unopened cartridges
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
Keep the cartridge in the outer carton in order to protect from light.
In-use cartridges
For storage conditions after first opening of the medicinal product, see section *Shelf-life*.

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
Not in-use pens
Store in a refrigerator (2°C-8°C).
Do not freeze.
Do not put Apidra next to the freezer compartment or a freezer pack.
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 *Shelf-life*.

PREPARATION AND 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.
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.

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 section Method of Admnistration

Intravenous use
Apidra should be used at a concentration of 1 Unit/ml insulin glulisine in infusion systems with sodium chloride 9 mg/ml (0.9%) solution for infusion with or without 40 mmol/l potassium

chloride using coextruded polyolefin/polyamide plastic infusion bags with a dedicated infusion line. Insulin glulisine for intravenous use at a concentration of 1 Unit/ml is stable at room temperature for 48 hours.

After dilution for intravenous use, the solution should be inspected visually for particulate matter prior to administration. It must only be used if the solution is clear and colourless, not when cloudy or with visible particles.

Apidra was found to be incompatible with Glucose 5% solution and Ringer's solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.

Apidra 100 Units/ml solution for injection in a cartridge
Apidra 100 units/ml in a cartridge is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.
The Apidra cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar.

The pen should be used as recommended in the information provided by the device manufacturer. The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection. Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

~~If the pen malfunctions (see instructions for using the pen), the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected~~.
If the insulin pen is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new insulin pen has to be used.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only. Insulin label must always be checked before each injection to avoid medication errors between insulin glulisine and other insulins (see section Special warning and precaution).

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
Apidra SoloStar 100 units/ml in a pre-filled pen is only suitable for subcutaneous injections. If administration by syringe, intravenous injection 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 reused 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 Special warning and precaution).

~~Mixing with insulins (for all packs)~~
~~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.~~

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

Keep out of the reach and sight of children.

Presentation
Solution for injection
Apidra in Vial
Box contains: 1 vial each containing 10 ml (1000 IU)
Reg. No. : DKI0559201843A1
Apidra in Cartridge
Box contains: 5 Cartridges each containing 3 ml (300 IU)
Reg. No. : DKI0559201843A2
Apidra SoloStar
Box contains: 5 SoloStar Injection Pens with Cartridges
Reg. No. : DKI0559201843A5

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Manufactured by:
Sanofi Aventis Deutschland GmbH, Frankfurt (Main), Germany

Registered by:
PT. Aventis Pharma, Jakarta, Indonesia

Date of text revision:
As on approval date