EUROPEAN MEDICINES AGENCY

Certificate: 01/19/127503
Request: 71011

Certificate of a Medicinal Product[1]
Certificado de Medicamento[1]
Certificat de Médicament[1]

This Certificate conforms to the format recommended by the World Health Organization. (Explanatory notes attached) / El presente certificado se adapta al formato recomendado por la Organización Mundial de la Salud. (Se adjuntan notas explicativas) / Ce Certificat est conforme à la présentation recommandée par l'Organisation Mondiale de la Santé. (Voir notes explicatives ci-jointes)

No. of Certificate / N° de certificado / N° du certificat: ***01/19/127503***

Exporting (Certifying) region / Región exportadora (que certifica) / Région d'exportation (certificateur) :
European Union / Unión Europea / Union Européenne :

Belgium, Bulgaria, Czech Republic, Denmark, Germany, Estonia, Greece, Spain, France, Croatia, Ireland, Italy, Cyprus, Latvia, Lithuania, Luxembourg, Hungary, Malta, Netherlands, Austria, Poland, Portugal, Romania, Slovenia, Slovak Republic, Finland, Sweden and United Kingdom.

Bélgica, Bulgaria, República Checa, Dinamarca, Alemania, Estonia, Grecia, España, Francia, Croatie, Irlanda, Italia, Chipre, Letonia, Lituania, Luxemburgo, Hungría, Malta, Paises Bajos, Austria, Polonia, Portugal, Rumanía Eslovenia, República Eslovaca, Finlandia, Suecia y Reino Unido.

Belgique, Bulgarie, République tchèque, Danemark, Allemagne, Estonie, Grèce, Espagne, France, Croacia, Irlande, Italie, Chypre, Lettonie, Lituanie, Luxembourg, Hongrie, Malte, Pays-Bas, Autriche, Pologne, Portugal, Roumanie, Slovénie, Slovaquie, Finlande, Suède et Royaume-Uni.

Importing (requesting) country / País importador (solicitante) / Pays importateur (sollicitant):

CHILE

1 Name and pharmaceutical form of the product / Nombre y forma farmaceútica del medicamento / Dénomination et forme pharmaceutique du médicament:

Apidra Solution for injection in a vial, in a cartridge, in a pre-filled pen (SoloStar)

1.1 Active substance(s)[2] and amount(s) per unit dose or unit volume[3]:
Principio(s) activo(s)[2] y cantidad(es) por unidad de dosis o unidad de volumen[3]:
Substance(s) active(s)[2] et quantité(s) par unité de dose ou unité de volume[3]:

Insulin glulisine; 100 Units/ml; 1, 2, 4 or 5 vials of 10 ml; 1, 3, 4, 5, 6, 8, 9 or 10 cartridges of 3 ml; 1, 3, 4, 5, 6, 8, 9 or 10 pre-filled pens (SoloStar) of 3 ml

For complete composition including excipients, see attached. [4]/ Para la composición completa incluidos los excipientes, véase información anexa. [4] / La composition complète du médicament, y compris les excipients, voir annexe. [4]

1.2 Is this product subject to a Community Marketing Authorisation? [5]
¿Está sujeto este medicamento a una autorización de comercialización comunitaria? [5]
Ce médicament fait-il l'objet d'une autorisation communautaire de mise sur le marché ? [5]

yes

EUROPEAN MEDICINES AGENCY

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30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5525
E-mail certificate@ema.europa.eu **Website** www.ema.europa.eu

1.3 Is this product actually on the market in the exporting region?
¿Se encuentra este medicamento en el mercado de la región exportadora?
Ce médicament est- il actuellement commercialisé dans la région exportatrice?

yes

2.1 Number in the Community Register of Medicinal Products [7] and date of issue:
Número de autorización de comercialización comunitaria [7] y fecha de emisión:
Numéro au registre communautaire de mise sur le marché [7] et date de délivrance:

EU/1/04/285/001-012 & 029-036, 27.9.2004

2.2 Community Marketing Authorisation Holder (name and address):
Titular de la autorización de comercialización comunitaria (nombre y dirección):
Titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) :

Sanofi-Aventis Deutschland GmbH, D-65926 Frankfurt am Main, Germany.

2.3 Status of the Community Marketing Authorisation Holder: [8]
Estatus del titular de la autorización de comercialización comunitaria: [8]
Statut du titulaire de l'autorisation communautaire de mise sur le marché : [8]

a

2.3.1 For categories (b) and (c) the name and address of the manufacturer producing the pharmaceutical form is: [9]
Para las categorías (b) y (c), el nombre y dirección del fabricante que produce la forma farmaceútica es: [9]
Pour les catégories (b) et (c), nom et l'adresse du fabricant de la forme pharmaceutique considérée : [9]

Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, D-65926 Frankfurt am Main, Germany (site also responsible for batch release in the EU, quality control, primary and secondary packaging).

2.4 Is the European Public Assessment Report (EPAR) appended? [10]
¿Se adjunta el informe europeo público de evaluación (EPAR)? [10]
Un rapport européen public d'evaluation (EPAR) est-il annexé ? [10]

no

2.5 Is the attached, officially approved product information included in the Community Marketing Authorisation?[11]
¿Se incluye la información sobre el medicamento adjunto en la autorización de comercialización comunitaria?[11]
L'information sur le médicament, officiellement approuvée, fait elle partie de l'autorisation communautaire de mise sur le marché ? [11]

yes

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2.6 Applicant for the Certificate, if different from the Community Marketing Authorisation Holder (name and address): [12]
Solicitante del Certificado, si es diferente del titular de la autorización de comercialización comunitaria (nombre y dirección): [12]
Demandeur du Certificat, s'il est autre que le titulaire de l'autorisation communautaire de mise sur le marché (nom et adresse) : [12]

3. Does the Certifying Authority arrange for periodic inspections of the manufacturing site in which the pharmaceutical form is produced?
¿La autoridad certificadora, dispone la inspección periódica de la planta de fabricación en que se produce la forma farmaceútica?
L'autorité certificatrice organise-t-elle des inspections périodiques de l'usine de production de la forme pharmaceutique?

yes

If no or not applicable, proceed to question 4 / Si no o no aplicable, pase a la pregunta 4 / Si la réponse est non ou sans objet, passer à la question 4.

3.1 Periodicity of routine inspections: ***Frequency of inspections is determined on risk-based approach.***
Periodicidad de las inspecciones de rutina: ***La frecuencia de las inspecciones esta basada en función del riesgo.***
Périodicité des inspections de routine: ***L'évaluation du risque détermine la fréquence des inspections.***

3.2 Has the manufacture of this type of pharmaceutical form been inspected?
¿Se ha inspeccionado la fabricación de este tipo de forma farmaceútica?
La fabrication de ce type de forme pharmaceutique a-t-elle fait l'objet d'une inspection?

yes

3.3 Do the facilities and operations conform to GMP as recommended by the World Health Organization? [15]
¿Se adaptan las instalaciones y procedimientos a las GMP recomendadas por la Organización Mundial de la Salud? [15]
Est-ce que l'établissement pharmaceutique est conforme aux BPF recommandées par l'Organisation Mondiale de la Santé ? [15]

yes

4. Does the information submitted by the applicant satisfy the Certifying Authority on all aspects of the manufacture of the product undertaken by another party? [16]
¿La información presentada por el solicitante satisface a la autoridad de certificación en relación a todos los aspectos de la fabricación del medicamento realizada por terceros? [16]
Les informations fournies par le demandeur satisfont-elles aux exigences des autorités certificatrices sur tous les aspects de la fabrication du médicament pris en charge par une tierce partie ? [16]

yes

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EUROPEAN MEDICINES AGENCY

Certificate: 01/19/127503
Request: 71011

Address of the Certifying Authority / Dirección de la autoridad certificadora / Adresse de l'autorité certificatrice :

European Medicines Agency
30 Churchill Place, Canary Wharf, London E14 5EU, United Kingdom

Telephone / Teléfono / Téléphone:	***+44 (0)20 3660 6000***
Facsimile / Fax / Télécopie:	***+44 (0)20 3660 5525***
E-mail / Correo electrónico / Courrier électronique:	***certificate@ema.europa.eu***

Name of authorised person / Nombre de la persona autorizada / Nom de la personne autorisée:

Monika Mayr

Signature / Firma / Signature:

Stamp and date / Sello y fecha / Tampon et date:

9.1.2019

EUROPEAN MEDICINES AGENCY

15/1/19

Signature Attested by Phillip Jones
Solicitor and Notary
Windsor House, Victoria Street,
Windsor, Berks, SL4 1EN, England,
Tel: 01753 851591

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APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1.	**Country:** Pays / Pais:	United Kingdom of Great Britain and Northern Ireland
	This public document Le présent acte public / El presente documento público	
2.	**Has been signed by** a été signé par ha sido firmado por	Phillip H Jones
3.	**Acting in the capacity of** agissant en qualité de quien actúa en calidad de	Notary Public
4.	**Bears the seal / stamp of** est revêtu du sceau / timbre de y está revestido del sello / timbre de	The Said Notary Public

Certified

Attesté / Certificado

5.	**at** á / en London	6.	**the** le / el día 16 January 2019
7.	**by** par / por	Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs	
8.	**Number** sous no / bajo el numero	APO-1260453	
9.	**Seal / stamp** Sceau / timbre Sello / timbre	FOREIGN AND COMMONWEALTH OFFICE LONDON	
10.	**Signature** Signature Firma	G. Sahdev	

This Apostille is not to be used in the UK and only confirms the authenticity of the signature, seal or stamp on the attached UK public document. It does not confirm the authenticity of the underlying document. Apostilles attached to documents that have been photocopied and certified in the UK confirm the signature of the UK official who conducted the certification only. It does not authenticate either the signature on the original document or the contents of the original document in any way.

If this document is to be used in a country not party to the Hague Convention of the 5th of October 1961, it should be presented to the consular section of the mission representing that country

To verify this apostille go to www.verifyapostille.service.gov.uk

Explanatory notes

[1] This Certificate, which is in the format recommended by WHO, establishes the status of the medicinal product and of the applicant for the Certificate in the exporting region at the time of issue. It is for a single product at a given point in time since manufacturing arrangements and approved information for different pharmaceutical forms and different strengths can vary.

[2] Whenever possible, International Non-proprietary Names (INNs) or national non-proprietary names are used.

[3] The formula (complete composition) of the pharmaceutical form is appended.

[4] Provision of the details of quantitative composition is attached on request of the Community Marketing Authorisation Holder.

[5] When applicable, details are appended of any conditions or restrictions applied to the supply and use of the product that is entered into the Community Marketing Authorisation.

[6] Not applicable.

[7] Indicated, when applicable, if the Community Marketing Authorisation has been granted under exceptional circumstances, conditional approval or if the product has not yet been approved.

[8] The person responsible for placing the product on the market:

(a) manufactures the pharmaceutical form;
(b) packages and/or labels a pharmaceutical form manufactured by an independent company; or
(c) is involved in none of the above.

[9] This information can only be provided with the consent of the Community Marketing Authorisation Holder or, in the case of non-registered products, the applicant. Non-completion of this section (2.3.1) indicates that the party concerned has not agreed to inclusion of this information. It should be noted that information concerning the site of production is part of the Community Marketing Authorisation. If the production site is changed, the Community Marketing Authorisation has to be updated or it is no longer valid.

[10] This refers to the document that summarises the technical basis on which the product has been authorised.

[11] This refers to the product information which forms a part of the Community Marketing Authorisation, such as the Summary of Product Characteristics (SPC).

[12] In this circumstance, permission for issuing the Certificate is required from the Community Marketing Authorisation Holder. This permission has to be provided to the European Medicines Agency by the applicant.

[13] If applicable the reason why the medicinal product does not have a Community Marketing Authorisation, e.g.:

(a) the product has been developed exclusively for the treatment of conditions – particularly tropical diseases - not endemic in the exporting region;
(b) the product has been reformulated with a view to improving its stability under tropical conditions;
(c) the product has been reformulated to exclude excipients not approved for use in medicinal products in the country of import;
(d) the product has been reformulated to meet a different maximum dosage limit for an active substance;
(e) any other reason, as specified.

[14] "Not applicable" means the manufacture is taking place in a region other than that issuing the Certificate and inspection is conducted under the aegis of the country of manufacture.

[15] The requirements for good practices in the manufacture and quality control of medicinal products referred to in the Certificate are those included in the thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series No 823, 1992, Annex 1). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (WHO Technical Report Series, No 822, 1992, Annex 1).

[16] This section is to be completed when the Community Marketing Authorisation Holder or applicant conforms to status (b) or (c) as described in note 8 above. It is of particular importance when foreign contractors are involved in the manufacture of the product. In these circumstances the applicant should supply the Certifying Authority with information to identify the contracting parties responsible for each stage of manufacture of the pharmaceutical form, and the extent and nature of any controls exercised over each of these parties.

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

APIDRA 100 Units/ml, solution for injection in a vial

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché :

EU/1/04/285/001 to EU/1/04/285/004: Apidra–100 Units/ml–Solution for injection–Subcutaneous use–vial (glass)–10 ml–1, 2, 4, 5 vials

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento
Composition qualitative et quantitative du médicament:

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units : Cantidades y unidades : Quantités et unités :
	Each vial contains 10 ml equivalent to 1 000 Units.
	<u>Per 1 ml</u>
Insulin glulisine ***(equimolar to Units of insulin)***	**3.49 mg** ***(100 Units)***
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades : Quantités et unités :
1. Metacresol ***2. Trometamol*** ***3. Sodium chloride*** ***4. Polysorbate 20*** ***5. Sodium hydroxide*** ***6. Hydrochloric acid, concentrated*** ***7. Water for injections*** ***8. Nitrogen (filtration aid)***	***3.15 mg*** ***6.00 mg*** ***5.00 mg*** ***0.01 mg*** ***q.s. ad pH 7.3*** ***q.s. ad pH 7.3*** ***ad 1.00 ml*** ***Not contained in the finished product***

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

APIDRA 100 Units/ml, solution for injection in a cartridge

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché :

EU/1/04/285/005 to EU/1/04/285/012: Apidra–100 Units/ml–Solution for injection–Subcutaneous use–cartridge (glass)-1, 3, 4, 5, 6, 8, 9, 10 cartridges

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento
Composition qualitative et quantitative du médicament:

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units : Cantidades y unidades : Quantités et unités :
	Each cartridge contains 3 ml equivalent to 300 Units.
	<u>Per 1 ml</u>
Insulin glulisine ***(equimolar to Units of insulin)***	**3.49 mg** ***(100 Units)***
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades : Quantités et unités :
1. Metacresol ***2. Trometamol*** ***3. Sodium chloride*** ***4. Polysorbate 20*** ***5. Sodium hydroxide*** ***6. Hydrochloric acid, concentrated*** ***7. Water for injection*** ***8. Nitrogen (filtration aid)***	***3.15 mg*** ***6.00 mg*** ***5.00 mg*** ***0.01 mg*** ***q.s. ad pH 7.3*** ***q.s. ad pH 7.3*** ***ad 1.00 ml*** ***Not contained in the finished product***

STATEMENT OF QUANTITATIVE COMPOSITION
DECLARACIÓN DE COMPOSICIÓN CUANTITATIVA
ÉNONCÉ DE LA COMPOSITION QUANTITATIVE

1. Name and pharmaceutical form of the Medicinal Product:
Nombre y forma farmacéutica del medicamento:
Dénomination et forme pharmaceutique du médicament:

APIDRA 100 Units/ml, solution for injection in a pre-filled pen (Solostar)

2. Number(s) in the Community Register of Medicinal Products:
Número(s) de autorización de comercialización comunitaria:
Numéro(s) au registre communautaire de mise sur le marché :

EU/1/04/285/029 to EU/1/04/285/036: Apidra–100 Units/ml–Solution for injection–Subcutaneous use–pre-filled pen (glass) (Solostar)-1, 3, 4, 5, 6, 8, 9, 10 pre-filled pens

3. Qualitative and quantitative composition of the Medicinal Product:
Composición cualitativa y cuantitativa del medicamento
Composition qualitative et quantitative du médicament:

Active ingredient(s): Principio(s) activo(s): Substance(s) active(s):	Quantities and units : Cantidades y unidades : Quantités et unités :
	Each pre-filled pen contains 3 ml equivalent to 300 Units.
	<u>Per 1 ml</u>
Insulin glulisine ***(equimolar to Units of insulin)***	**3.49 mg** ***(100 Units)***
Other ingredient(s): Otros ingrediente(s): Excipient(s):	Quantities and units: Cantidades y unidades : Quantités et unités :
1. Metacresol *2. Trometamol* *3. Sodium chloride* *4. Polysorbate 20* *5. Sodium hydroxide* *6. Hydrochloric acid, concentrated* *7. Water for injections* *8. Nitrogen (filtration aid)*	*3.15 mg* *6.00 mg* *5.00 mg* *0.01 mg* *q.s. ad pH 7.3* *q.s. ad pH 7.3* *ad 1.00 ml* *Not contained in the finished product*

SUMMARY OF PRODUCT CHARACTERISTICS

as relevant example

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

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 cartridge
Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.

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

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

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.

Paediatric 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

Intravenous use

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

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 section 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 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 4.4). For further details on handling, see section 6.6.

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 4.4).

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. 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

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.

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.

Apidra 100 Units/ml solution for injection in a cartridge
Pens to be used with 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.
The Apidra cartridges should only be used with the following pens:
- JuniorSTAR which delivers Apidra in 0.5 unit dose increments
- OptiPen, ClikSTAR, Tactipen, Autopen 24, AllStar and AllStar PRO which all deliver Apidra in 1 unit dose increments.

These cartridges should not be used with any other reusable pen as the dosing accuracy has only been established with the listed pens (see section 4.2 and 6.6).
Not all of these pens may be marketed in your country.

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 alternative insulin delivery system available in case of pump system failure (see section 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, intravenous injection 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 sulfonamide 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 reaction of 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	Unknown
Metabolism and nutrition disorders	Hypoglycaemia				Hyperglycaemia (potentially leading to Diabetic ketoacidosis[(1)])
Skin and subcutaneous tissue disorders		Injection site reactions Local hypersensitivity reactions		Lipodystrophy	
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 may occur at the injection site as a consequence of failure to rotate injection sites within an area.

- 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. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 (0.5 mg 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).

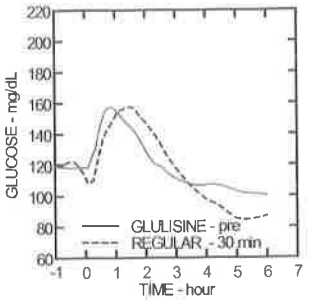


Figure 1A

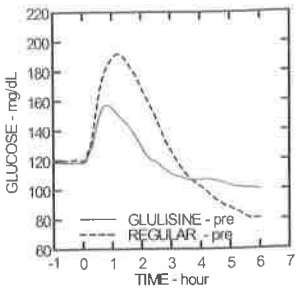


Figure 1B

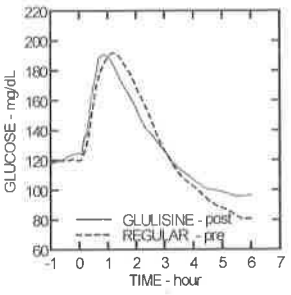


Figure 1C

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 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).

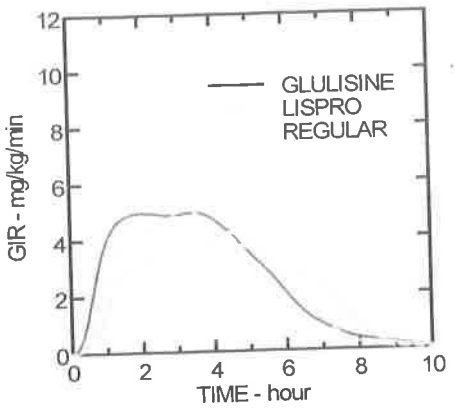


Figure 2: Glucose infusion rates (GIR) after subcutaneous injection of 0.3 Units/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

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/m²) 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 post-meal 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 studies in 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).

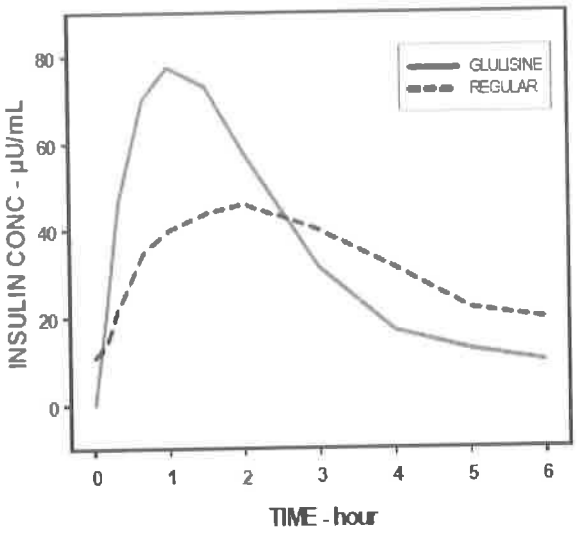


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 Units/kg.

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). 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/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.

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.

6.3 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 6.6).

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.

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.
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 6.3.

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 6.3.

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 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 cartridge
3 ml solution in a cartridge (type I colourless glass) with a plunger (elastomeric bromobutyl rubber) and a flanged cap (aluminium) with a stopper (elastomeric bromobutyl rubber). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available.
Not all pack sizes may be marketed.

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
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 section 4.2 and 4.4 for advice.

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.

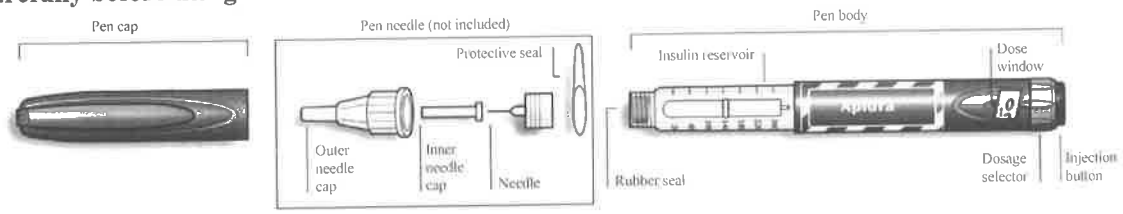
Apidra 100 Units/ml solution for injection in a cartridge
Apidra 100 units/ml in a cartridge is only suitable for subcutaneous injections from a reusable pen. If administration by syringe, intravenous injection or infusion pump is necessary, a vial should be used.
The Apidra cartridges are to be used only in conjunction with the pens: OptiPen, ClikSTAR, Autopen 24, Tactipen, AllStar, AllStar PRO or JuniorSTAR (see section 4.2 and 4.4). Not all of these pens may be marketed in your country.
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 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 4.4).

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 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 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.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany.

8. MARKETING AUTHORISATION NUMBER(S)

Apidra 100 Units/ml solution for injection in a vial
EU/1/04/285/001-004

Apidra 100 Units/ml solution for injection in a cartridge
EU/1/04/285/005-012

Apidra SoloStar 100 Units/ml solution for injection in a pre-filled pen
EU/1/04/285/029-036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004
Date of latest renewal: 20 August 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

LABELLING

as relevant example

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 ml vial)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a vial
Insulin glulisine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).
Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections (see leaflet for further information).

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a vial.
1 vial of 10ml.
2 vials of 10ml.
4 vials of 10ml.
5 vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous or intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Use only clear and colourless solutions.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials
Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first use: The product may be stored for a maximum of 4 weeks below 25°C. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001 1 vial of 10ml
EU/1/04/285/002 2 vials of 10ml.
EU/1/04/285/003 4 vials of 10ml
EU/1/04/285/004 5 vials of 10ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (10 ml vial)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100 Units/ml solution for injection

Insulin glulisine

Subcutaneous or intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PACKAGE LEAFLET

as relevant example

Package leaflet: Information for the user

Apidra 100 Units/ml solution for injection in a vial
Insulin glulisine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Apidra is and what it is used for

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus; it may be given to adults, adolescents and children, 6 years of age and older. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

It is made by biotechnology. It has a rapid onset within 10-20 minutes and a short duration, about 4 hours.

2. What you need to know before you use Apidra

Do not use Apidra

- If you are allergic to insulin glulisine or any of the other ingredients of this medicine (listed in section 6).
- If your blood sugar is too low (hypoglycaemia), follow the guidance for hypoglycaemia (see box at the end of this leaflet).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Apidra.
Follow closely the instructions for dose, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups
If you have liver or kidney problems, speak to your doctor as you may need a lower dose.

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

Travel

Before travelling consult your doctor. You may need to talk about

- the availability of your insulin in the country you are visiting,
- supplies of insulin, injection syringes etc,
- correct storage of your insulin while travelling,
- timing of meals and insulin administration while travelling,
- the possible effects of changing to different time zones,
- possible new health risks in the countries to be visited,
- what you should do in emergency situations when you feel unwell or become ill.

Illnesses and injuries

In the following situations, the management of your diabetes may require extra care:

- If you are ill or have a major injury then your blood sugar level may increase (hyperglycaemia).
- If you are not eating enough your blood sugar level may become too low (hypoglycaemia).

In most cases you will need a doctor. **Make sure that you contact a doctor early.**

If you have type 1 diabetes (insulin dependent diabetes mellitus), do not stop your insulin and continue to get enough carbohydrates. Always tell people who are caring for you or treating you that you require insulin.

Some patients with long-standing type 2 diabetes mellitus and heart disease or previous stroke who were treated with pioglitazone and insulin experienced the development of heart failure. Inform your doctor as soon as possible if you experience signs of heart failure such as unusual shortness of breath or rapid increase in weight or localised swelling (oedema).

Other medicines and Apidra

Some medicines cause changes in the blood sugar level (decrease, increase or both depending on the situation). In each case, it may be necessary to adjust your insulin dose to avoid blood sugar levels that are either too low or too high. Be careful when you start or stop taking another medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar level to fall (hypoglycaemia) include:

- all other medicines to treat diabetes,
- angiotensin converting enzyme (ACE) inhibitors (used to treat certain heart conditions or high blood pressure),
- disopyramide (used to treat certain heart conditions),
- fluoxetine (used to treat depression),
- fibrates (used to lower high levels of blood lipids),
- monoamine oxidase (MAO) inhibitors (used to treat depression),
- pentoxifylline, propoxyphene, salicylates (such as aspirin, used to relieve pain and lower fever),
- sulfonamide antibiotics.

Medicines that may cause your blood sugar level to rise (hyperglycaemia) include:

- corticosteroids (such as "cortisone" used to treat inflammation),
- danazol (medicine acting on ovulation),
- diazoxide (used to treat high blood pressure),
- diuretics (used to treat high blood pressure or excessive fluid retention),
- glucagon (pancreas hormone used to treat severe hypoglycaemia),
- isoniazid (used to treat tuberculosis),
- oestrogens and progestogens (such as in the contraceptive pill used for birth control),
- phenothiazine derivatives (used to treat psychiatric disorders),
- somatropin (growth hormone),

- sympathomimetic medicines (such as epinephrine [adrenaline], salbutamol, terbutaline used to treat asthma),
- thyroid hormones (used to treat thyroid gland disorders),
- protease inhibitors (used to treat HIV),
- atypical antipsychotic medicines (such as olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take:
- beta-blockers (used to treat high blood pressure),
- clonidine (used to treat high blood pressure),
- lithium salts (used to treat psychiatric disorders).

Pentamidine (used to treat some infections caused by parasites) may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (such as clonidine, guanethidine and reserpine) may weaken or suppress entirely the first warning symptoms which help you to recognise a hypoglycaemia.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Apidra with alcohol

Your blood sugar levels may either rise or fall if you drink alcohol.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dose may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no or limited data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if:
- you have hypoglycaemia (low blood sugar levels),
- you have hyperglycaemia (high blood sugar levels).

Keep this possible problem in mind in all situations where you might put yourself and others at risk (such as driving a car or using machines).
You should contact your doctor for advice on driving if:
- you have frequent episodes of hypoglycaemia,
- the first warning symptoms which help you to recognise hypoglycaemia are reduced or absent.

Important information about some of the ingredients of Apidra

This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially 'sodium-free'.

Apidra contains metacresol

Apidra contains metacresol, which may cause allergic reactions.

3. How to use Apidra

Dose

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Based on your life-style and the results of your blood sugar (glucose) tests and your previous insulin usage, your doctor will determine how much Apidra you will need.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate, long-acting insulin, a basal insulin or with tablets used to treat high blood sugar levels.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors so that you are able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of this leaflet for further information.

Method of administration

Apidra is injected under the skin (subcutaneously). It may also be given intravenously by healthcare professionals under close supervision by a doctor.

Your doctor will show you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. The effect will be slightly quicker if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

Frequency of administration

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Instructions for proper use

How to handle the vials

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system.

Look at the vial before you use it. Only use it if the solution is clear, colourless and has no visible particles in it.
Do not shake or mix it before use.

Always use a new vial if you notice that your blood sugar control is unexpectedly getting worse. This is because the insulin may have lost some of its effectiveness. If you think you may have a problem with Apidra, have it checked by your doctor or pharmacist.

If you have to mix two types of insulin

Apidra must not be mixed with any preparation other than NPH 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.

How to handle an infusion pump system

Before using Apidra in the pump system you should have been given detailed instructions on how to use the pump system. In addition, you should have been provided with information about what to do if you become ill or if your blood sugar levels get too high or too low, or if the pump system fails.
Use the pump system recommended by your doctor. Read and follow the instructions that come with your insulin infusion pump. Follow your doctor's instructions about the basal infusion rate and the mealtime insulin boluses to be taken. Measure your blood sugar level regularly to make sure you get the benefit of the insulin infusion and to make sure that the pump is working properly.

Change the infusion set and reservoir at least every 48 hours using aseptic technique. These instructions may differ from the instructions that come with your insulin infusion pump. When you use Apidra in the pump system, it is important that you always follow these specific instructions. Failure to follow these specific instructions may lead to serious adverse events.

Apidra must never be mixed with diluents or any other insulin when used in a pump.

What to do if the pump system fails or when the pump is used incorrectly

Pump or infusion set problems or using the pump incorrectly can result in you not getting enough insulin. This can quickly cause you to have high blood sugar and diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar).
If your blood sugar level starts to rise, contact your doctor, pharmacist or nurse as soon as possible. They will tell you what needs to be done.
You may need to use Apidra with syringes or pens. You should always have an alternative insulin delivery system available for injection under the skin in case the pump system fails.

If you use more Apidra than you should

- If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see box at the end of this leaflet.

If you forget to use Apidra

- If you **have missed a dose of Apidra** or if you **have not injected enough insulin,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. For information on the treatment of hyperglycaemia, see box at the end of this leaflet.
- Do not take a double dose to make up for a forgotten dose.

If you stop using Apidra

This could lead to severe hyperglycaemia (very high blood sugar) and ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar). Do not stop Apidra without speaking to a doctor, who will tell you what needs to be done.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

Insulin Mix-ups

You must always check the insulin label before each injection to avoid mix-ups between Apidra and other insulins.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Hypoglycaemia (low blood sugar) can be very serious. Hypoglycaemia is a very commonly reported side effect (may affect more than 1 in 10 people). **Hypoglycaemia (low blood sugar) means that there is not enough sugar in the blood.** If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. If you have symptoms of low blood sugar, take actions to increase your blood sugar level **immediately.** See the box at the end of this leaflet for important further information about hypoglycaemia and its treatment.

If you experience the following symptoms, contact your doctor immediately:
Systemic allergic reactions are side effects reported uncommonly (may affect up to 1 in 100 people)
Generalised allergy to insulin: Associated symptoms may include large-scale skin reactions (rash and itching all over the body), severe swelling of skin or mucous membranes (angiooedema), shortness of breath, a fall in blood pressure with rapid heart beat and sweating. These could be symptoms of severe cases of **generalised allergy to insulin, including anaphylactic reaction, which may be life-threatening.**

Hyperglycaemia (high blood sugar) means that there is too much sugar in the blood. The frequency of hyperglycaemia cannot be estimated. If your blood sugar level is too high, this tells you that you may need more insulin than you have injected.
Hyperglycaemia can cause diabetic ketoacidosis (build-up of acid in the blood because the body is breaking down fat instead of sugar).
These are serious side effects.
These conditions can happen when there are problems with the infusion pump or when the pump system is used incorrectly.
This means you may not always get enough insulin to treat your diabetes.
If this happens you must seek urgent medical help.
Always have available an alternative insulin delivery system for injection under the skin (see section 3 under "How to handle an infusion pump system" and "What to do if the pump system fails or when the pump is used incorrectly").
For more information on signs and symptoms of hyperglycaemia refer to the box at the end of this leaflet.

Other side effects
Common reported side effects (may affect up to 1 in 10 people)
- Skin and allergic reactions at the injection site

Reactions at the injection site may occur (such as reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Rare reported side effect (may affect up to 1 in 1,000 people)
- Skin changes at the injection site (lipodystrophy)

If you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may either shrink or thicken. Insulin that you inject in such a site may not work very well. Changing the injection site with each injection may help to prevent such skin changes.

Side effects where the frequency cannot be estimated from the available data

- **Eye reactions**

A marked change (improvement or worsening) in your blood sugar control can disturb your vision temporarily. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause temporary loss of vision.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Apidra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and on the label of the vial after "EXP". The expiry date refers to the last day of that month.

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
Once in use, the vial may be stored for a maximum of 4 weeks in the outer carton below 25°C away from direct heat or direct light. Do not use the vial after this time period.
It is recommended that the date of the first use be noted on the label.

Do not use this medicine if it does not appear clear and colourless.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Apidra contains

- The active substance is insulin glulisine. Each ml of the solution contains 100 Units of insulin glulisine (equivalent to 3.49 mg). Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.
- The other ingredients are: metacresol (see section 2 under "Apidra contains metacresol"), sodium chloride (see section 2 under "Important information about some of the ingredients of Apidra"), trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in a vial is a clear, colourless, aqueous solution with no particles visible.

Each vial contains 10 ml solution (1000 Units). Packs of 1, 2, 4 and 5 vials are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main
Germany

Manufacturer:
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

Other source of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

HYPERGLYCAEMIA AND HYPOGLYCAEMIA

Always carry some sugar (at least 20 grams) with you.
Carry some information with you to show you are a person with diabetes.

HYPERGLYCAEMIA (high blood sugar levels)

If your blood sugar is too high (hyperglycaemia), you may not have injected enough insulin.

Why does hyperglycaemia occur?
Examples include:
- you have not injected your insulin or not injected enough, or if it has become less effective, for example through incorrect storage,
- you are doing less exercise than usual, you are under stress (emotional distress, excitement), or you have an injury, operation, infection or fever,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Apidra").

Warning symptoms of hyperglycaemia
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, and glucose and ketone bodies in urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

What should you do if you experience hyperglycaemia?
Test your blood sugar level and your urine for ketones as soon as any of the above symptoms occur. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

HYPOGLYCAEMIA (low blood sugar levels)

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause a heart attack or brain damage and may be life-threatening. You normally should be able to recognise when your blood sugar is falling too much so that you can take the right actions.

Why does hypoglycaemia occur?
Examples include:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you are doing more exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from an illness or from fever,
- you are taking or have stopped taking certain other medicines (see section 2, "Other medicines and Apidra").

Hypoglycaemia is also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (for example from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Warning symptoms of hypoglycaemia

- In your body

Examples of symptoms that tell you that your blood sugar level is falling too much or too fast: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

- In your brain

Examples of symptoms that indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be weaker or may be missing altogether if:

- you are elderly,
- you have had diabetes for a long time,
- you suffer from a certain type of nervous disease (diabetic autonomic neuropathy),
- you have recently suffered hypoglycaemia (for example the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Other medicines and Apidra).

In such a case, you may develop severe hypoglycaemia (and even faint) before you are aware of the problem. Be familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that may otherwise be overlooked. If you are not confident about recognising your warning symptoms, avoid situations (such as driving a car) in which you or others would be put at risk by hypoglycaemia.

What should you do if you experience hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, such as glucose, sugar cubes or a sugar-sweetened beverage. Caution: Artificial sweeteners and foods with artificial sweeteners (such as diet drinks) are of no help in treating hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (such as bread or pasta). Your doctor or nurse should have discussed this with you previously.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Tell your relatives, friends and close colleagues the following:
If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

Apidra can be administered intravenously, which should be carried out by healthcare professionals.

Instruction for intravenous administration

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. Never use the solution if it has become cloudy or contains particles; use it only if it is clear and colourless.

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.