European Medicines Agency

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CHMP ASSESSMENT REPORT
FOR
Apidra

International Nonproprietary Name:**Insulin glulisine**

Procedure No. EMEA/H/C/557/X/0023

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

The applicant Sanofi-Aventis Deutschland GmbH submitted on 8 January 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Apidra under Annex II, point 2 (v) to Commission Regulation (EC) No 1085/2003.

Sanofi-Aventis Deutschland GmbH is the Marketing Authorisation Holder for Apidra which was authorised on 27 September 2004 through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. Apidra is currently approved for subcutaneous use, and the extension is sought for the addition of the intravenous use (applicable to the vial presentation).

Insulin glusilin (Apidra) displays a time-concentration and time-action profile with a more rapid onset, earlier peak effect in lowering blood glucose levels, and a shorter duration of action than the short-acting insulin preparation of regular insulin. However, when administered intravenously, insulin glusiline and regular insulin show equipotent glucose lowering activity, and thus, Apidra may provide an alternative approach for treating hyperglycaemia in a hospital setting.
The intravenous injection of Apidra should be performed after dilution of insulin glusiline 100 Units/ml in an infusion bag containing 0.9% sodium chloride.

2. Quality aspects

Introduction

Apidra is supplied as a 100 Units/ml clear, colourless solution in the following containers: vial, cartridge, pre-filled pen OptiSet, pre-filled pen SoloStar and cartridge for OptiClick.

The present application for a new administration route concerns only the vial presentation.

All aspects of the manufacture, formulation, release testing and immediate packaging are identical to that already approved for the original marketing authorisation. Consequently no new quality data have been submitted to support this except compatibility and stability data to support the choice of infusion fluid in which Apidra is to be diluted for this new route of administration and the in-use stability of diluted Apidra during i.v. infusion.

Reference is made to the Module 3 data submitted and already assessed for the initial application.

Active Substance

The active substance used in this formulation is identical with the one in the manufacture of the approved Apidra, thus no new information or assessment is required.

Medicinal Product

The applicant has confirmed that the medicinal product intended to be marketed is identical in all respects as that already approved. No changes have been made to the manufacturing process and the immediate container and consequently only the new information regarding pharmaceutical development and stability has been assessed as discussed below:

- **Pharmaceutical Development**

Microbiological Attributes

The applicant has not presented any additional studies of the microbiological attributes of Apidra for this new route of administration. Given that the formulation is designed for the current subcutaneous route for a multidose vial and has been shown to be adequate for this purpose, it is reasonable to rely on the preservatives present and the established procedures for hospital aseptic transfer from the vial to the infusion bag without any further data.

Compatibility with Diluent

Given that the intravenous product is intended to be used diluted in a pre-prepared intravenous infusion bag, the key aspect of this application is the demonstration that an appropriate choice of recommended infusion fluid has been made and that compatibility of Apidra with potential infusion fluids has been appropriately demonstrated.

The applicant has studied compatibility of diluted Apidra with three potential infusion fluids. Stability studies have confirmed that Apidra is not compatible with Glucose 5% solution or Ringer's solution due to the detection of visible and subvisible particles and these infusions fluids were excluded. The applicant considered dilution practices for infusions across all Member States and confirmed compatibility with 40 mM potassium chloride solution.

- **Stability of the Product**

The applicant has provided a stability report which contains a stability study covering dilution of the insulin product with a sterile solution for infusion, under aseptic conditions within a hospital setting. The aim was to create the conditions with respect to microbiological attributes as for any sterile infusion preparation process. Pre-defined in-use tests were performed based on accepted common practice for i.v. administration including the concentration of insulin diluent used, duration of infusion and administration device. The infusion bags and tubing used in these studies were justified as representative.

The applicant has provided data from three batches of Apidra solution for injection prepared from three different drug substance batches. The requested concentration of 1 U/ml was prepared in 250 ml or 1000 ml plastic containers with sterile 0.9% sodium chloride solution.

The stability study was performed up to 48 hours at room temperature according to a pre-defined protocol. The Apidra containing solutions were tested for appearance, pH, content, impurities and particulate matter. Likewise, testing was performed on 1000 ml bags connected with administration sets with representative tubing and fitted with needles. Stability in this administration set up was studies for up to 8 hours with continuous infusion.

In conclusion additional stability data, including multiple lots, have been provided which justify the proposed in-use shelf life.

3. Clinical aspects

3.1 Introduction

The Apidra phase I programme included two PK/PD studies evaluating intravenous administration in healthy male volunteers (Table 1). No new studies were conducted to support this application.

Table 1 Summary of intravenous PK/PD studies

Objective(s) of Study [Reference]	Study Design	Test Product(s): Dosage Frequency Route	Number of Subjects	Population demographics	Duration of Treatment
PD and PK of APIDRA given at different body sites s.c. or by i.v. and bioavailability [5.3.1.1 *Study 1004*]	Euglycemic clamp. Randomized, open, 4-way, crossover, healthy subjects	APIDRA: 0.1 IU/kg body wt, s.c. or i.v.	16 men	Age: 19 - 28 years Weight: 69 - 103 kg (BMI: 20.6 - 26.0 kg/m^2) Ethnic group: white	Multiple dose, (4x single dose of each treatment)
Steady-state PK and PD during continuous i.v. infusion of APIDRA or regular human insulin [5.3.4.1 *Study 1016*]	Euglycemic clamp. Randomized, open, 2-way crossover, healthy subjects	APIDRA, or regular human insulin: 2-h i.v. continuous Infusion of 0.8 mIU/kg/min	16 men	Age: 18 - 32 years Weight: 71 - 100 kg (BMI: 19.9 - 26.0 kg/m^2) Ethnic group: white	2 h

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.2 Pharmacokinetics

Study 1004

Intravenous and subcutaneous doses of 0.1 U/kg Apidra each were administered in a randomised, open-label, four-way cross over study in 16 healthy male subjects using a euglycemic clamp technique. The highest systemic glulisine exposure was reached after intravenous bolus administration. The Cmax after intravenous bolus administration was approximately 40 times that after any of the subcutaneous injections (Table 2).

Table 2 Summary of PK results - Study 1004

Variable	Geometric mean (N = 16)			
	I.v.	Femoral s.c.	Deltoid s.c.	Abdominal s.c.
$AUC_{(0\text{-}1h)}$ [µIU.min/mL]	14411.0	2168.0	2892.6	3628.6
$AUC_{(0\text{-}1.5h)}$ [µIU.min/mL]	14703.1	3746.9	4710.7	5787.9
$AUC_{(0\text{-}2h)}$ [µIU.min/mL]	14813.2	5248.0	6407.5	7481.3
$AUC_{(0\text{-clamp end})}$ [µIU.min/mL]	14754.9	9624.9	10287.7	10550.7
$AUC_{(inf)}$ [µIU.min/mL]	14862.5	10107.4	10596.9	10910.1
C_{max} [µIU/mL]	3014.2	57	68.4	83.6
T_{max} [min]	N/A	65.8**	57.8**	44.3**
MRT [min]	11.7	114.3	102.7	88.6

** Median values. N/A Not Applicable

After intravenous administration, Apidra demonstrated a faster onset and shorter duration of action, as well as a greater peak response (GIRmax) with a smaller total glucose disposal (AUC (0-clamp end)) as compared with subcutaneous administration (Table 3).

Table 3 Summary of PD results - Study 1004

Variable	Sample mean (N = 16)			
	I.v.	Femoral s.c.	Deltoid s.c.	Abdominal s.c.
$AUC_{(0\text{-}1h)}$ [mg/kg]	606.9	127.5	161.9	183.1
$AUC_{(0\text{-}1.5h)}$ [mg/kg]	840.1	302.4	324.7	396.7
$AUC_{(0\text{-}2h)}$ [mg/kg]	987.2	476.9	496.4	612.0
$AUC_{(0\text{-clamp end})}$ [mg/kg]	1227.7	1520.2	1463.9	1498.4
Maximum GIR* [$mg.min^{-1}.kg^{-1}$]	14.3	7.9	7.3	8.0
Time of maximum GIR* [min]	23.5**	156.5**	134.5**	127.0**
Onset of action [min]	6.48**	28.6**	21.8**	22.8**
Duration of action [min]	159.6**	267.7**	270.4**	250.5**
Early $ts_{50\%}$* [min]	10.4**	38.5**	29.7**	31.1**
Late $ts_{50\%}$* [min]	77.0**	245.4**	249.1**	231.7**

* Maximum GIR, time of maximum GIR as well as time to early and late half-maximum GIRs were determined from "smoothed" GIR profiles.
** Median values.

Study 1016

The glucodynamic efficacy (potency) of Apidra versus regular human insulin using a euglycemic clamp technique was assessed in a single centre, randomised, open-label, two-way cross over study in 16 healthy male subjects. Subjects received an intravenous infusion of Apidra or regular human insulin with saline diluent at a rate of 0.8m U/kg/min for two hours. The glucodynamic efficacy (potency) of Apidra and regular human insulin was assessed by comparing the glucodynamic efficacy under steady state condition.

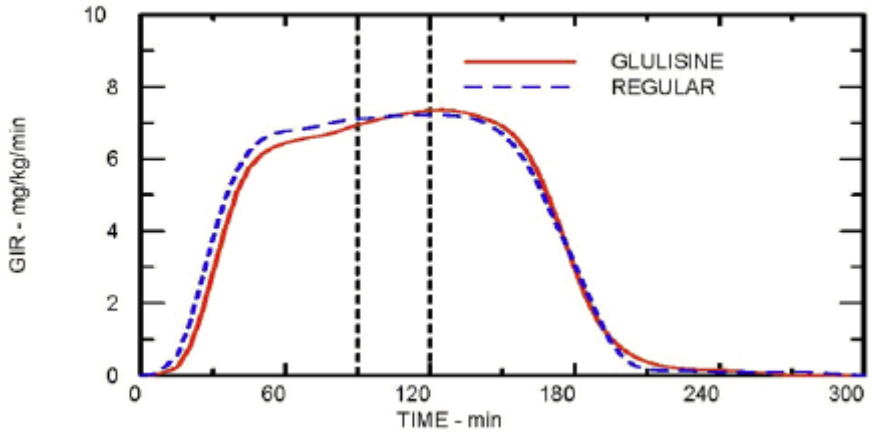
Infusion of the same dose of Apidra or regular human insulin produced equivalent glucose disposal at steady state as displayed by equivalent glucose infusion rates (GIRSS) and equivalent glucose utilisation (AUCSS). Also, the total glucose disposal [AUC(0-clamp end)] was equivalent after either insulin (Table 4). Apidra and regular human insulin showed equivalent potency on a molar basis (at the same dose) as attested by superimposable glucose infusion rate time profiles, leading to equivalent glucose disposal under steady state conditions (Figure 1).

Table 4 Summary of PD results - Study 1016

Variable	Sample mean (n = 16)		Point estimate (90% confidence interval)#
	Regular human insulin	Glulisine	Glulisine/ Regular human insulin
AUCss [mg/kg]	214.2	209.0	97.6% (88.4 ; 107.6%)
GIRss* [$mg.min^{-1}.kg^{-1}$]	7.2	7.0	98.4% (89.3 ; 108.5%)
$AUC_{(0\text{-clamp end})}$ [mg/kg]	1049.7	994.8	94.8% (84.5 ; 106.2%)

* Glucose infusion rate at steady state (GIRss) was determined from "smoothed" GIR profiles.
# Point estimates and 90% confidence intervals for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data.

Figure 1 Steady state pharmacodynamics of 0.8 mIU/kg/min glulisine and regular human insulin - Study 1016



The comparative bioanalytical quantification of insulin glulisine and human insulin posed an analytical challenge as different RIAs had to be applied. Cross-reactivity and matrix effects in serum samples from clinical studies are potential limiting factors for any comparison of analytes determined with different RIAs, and so, quantitative comparisons of insulin glulisine and human insulin concentrations have to be viewed with caution.
The AUCSS values of insulin glulisine were measured higher by about 30% than that of regular human insulin. The insulin concentration at steady state (CSS) and the total systemic exposure (AUC(0-clamp end)) of insulin glulisine were also measured higher, both by about 21% compared to regular human insulin (Table 5).

Table 5 Summary of PK results - Study 1016

Variable	Geometric mean (arithmetic mean) (n = 16)		Point estimate (90% confidence interval)#
	Regular human insulin	Glulisine	Glulisine/ Regular human insulin
AUCss [µIU.min/mL]	1855.74 (1876.47)	2393.20 (2402.67)	129.0% (120.7 ; 137.8%)
C_{ss} [µIU/mL]	58.11 (59.25)	70.23 (71.01)	120.9% (115.8 ; 126.1%)
$AUC_{(0\text{-clamp end})}$ [µIU.min/mL]	7651.95 (7717.65)	9262.79 (9295.13)	121.1% (116.2 ; 126.2%)

Point estimates and 90% confidence intervals for the ratio of treatment means, based on ln-transformed data.

The inter-individual variability of insulin concentrations at steady state (90, 105 and 120 min) was about twice as high for regular human insulin than for insulin glulisine with coefficients of variation of 13%, 9%, and 19% for insulin glulisine and 40%, 19% and 17% for regular human insulin.

The mean total insulin clearance (CLtot) was similar for insulin glulisine and regular human insulin with 915 mL/min and 1113 mL/min, indicating similar elimination rates for insulin glulisine and regular human insulin. As a result from the higher measured exposure the total insulin glulisine clearance (CLtot) is somewhat lower. The volume of distribution (VSS) for both insulin glulisine (13 L) and regular human insulin (22 L) approximate the volume of the extra cellular fluid.

Conclusion

These data have already been assessed with the initial application. In the current SPC, PD and PK data for the intravenous route are already described. "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." "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."

Overall, these data support the effective use of Apidra via the intravenous route.

3.3 Clinical efficacy

No efficacy data have been submitted. This is acceptable since the pharmacodynamic study showed no difference in the activity of insulin glulisine compared to human insulin when given intravenously.

Of note, the intravenous route was not tested in diabetes patients. However, pharmacodynamic studies showed similar PD profile in healthy volunteers and in diabetes patients when using the subcutaneous route. Pharmacodynamic and clinical data using the subcutaneous route support the equipotency of insulin glulisine and regular human insulin. Therefore, it is considered acceptable to bridge with the subcutaneous data and to extrapolate the equipotency of insulin glulisine and regular human insulin to diabetes patients.

3.4 Clinical safety

Clinical trials

In study 1004, 9 adverse events were reported in 6 subjects. None were considered to be related to the study drug. No serious adverse events were reported. The most frequently reported adverse event was headache (8 events were reported by 5 subjects), a side-effect frequently observed in clamp studies and most probably procedure-related (not drug related).

Observed decreases in haemoglobin concentrations (and correspondingly hematocrit and erythrocyte counts) were due to the significant blood loss during the study. No clinically relevant changes in clinical variables were observed.

Local tolerance was regarded to be good. No reactions were observed apart from a slight burning sensation that lasted only during injection and was reported in a total of 2 cases.

In study 1016, one case of headache of moderate intensity 6 days after administration of insulin glulisine was reported and assessed not related to the study medication by the investigator.

Observed decreases in haemoglobin concentrations (and correspondingly hematocrit and erythrocyte counts) were due to the blood sampling during the study. No evidence of study medication related changes in the repolarisation patterns was seen in any of the subject's ECG during the study. No clinically relevant changes in clinical variables were observed.

Post-marketing experience

A cumulative search of the sanofi-aventis Pharmacovigilance database through 12 December 2008 was conducted in order to identify all spontaneous reports of Adverse Drug Reactions (ADRs) associated with IV administration of insulin glulisine.

This database search identified a total of two cases, both non-serious, one medically confirmed and one reported by a consumer. The consumer report (200711380GDDC), although reported as IV route

of administration, the insulin glulisine dose was injected using an insulin delivery device (Autopen) which is used for subcutaneous (SC) administration. The reported event was *"injection site irritation"*, which seems consistent with SC administration.

The medically confirmed report (200712646FR) involved a female patient, age unknown, who received IV insulin glulisine in error with no adverse reaction observed. The hospital pharmacist used to supply the hospital with a rapid acting insulin that can be used IV. When the rapid acting insulin was changed to insulin glulisine, the pharmacist did not realise insulin glulisine was authorised only for subcutaneous route.

3.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The applicant submitted version 2.2 of the Detailed Description of the Pharmacovigilance System, dated 09 October 2008. Minor clarifications were requested on its content, therefore version 2.4 dated 31 July 2009 was submitted as part of the responses to the request for supplementary information.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant submitted version 1.2 of the Risk Management Plan (RMP), dated 20 January 2009. In this version, the risk of diabetic ketoacidosis was considered exclusively as a result of medication error. While it is acknowledged by the CHMP that medication errors may be a cause of hyperglycaemia leading to diabetic ketoacidosis, it is also possible for the condition to occur as a result of increased insulin requirements due to the development of anti-insulin antibodies. Therefore,the MAH was requested to amend the RMP to reflect the risk of diabetic ketoacidosis in such context. Version 1.3 dated 8 July 2009 was submitted and considered as satisfactory.

Table 6 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Hypoglycaemia	Routine pharmacovigilance Description of ADRs reported in children aged between 6 and 12 years in the section "Specific populations" of the planned 6-month PSURs Post-marketing observational prospective cohort study of diabetic children in Europe	SmPC sections 4.4, 4.8 and 4.9: provide description of the risk, and give full considerations of conditions that may cause hypoglycaemia and require dosage reduction
Injection site reaction	Routine pharmacovigilance Description of ADRs reported in children aged between 6 and 12 years in the section "Specific populations" of the planned 6-month PSURs Post-marketing observational prospective cohort study of diabetic children in Europe	SmPC section 4.8 (skin and subcutaneous tissue disorders): informs about this risk
Systemic hypersensitivity reactions	Routine pharmacovigilance Description of ADRs reported in children aged between 6 and 12 years in the section "Specific populations" of the planned 6-month PSURs Post-marketing observational prospective cohort study of diabetic children in Europe	SmPC section 4.3: known hypersensitivity to insulin glulisine or to any of the excipients is a contraindication to its use SmPC section 4.8 (general disorders): informs about this risk
Medication error *(including the potenital risk of diabetic ketoacidosis)*	Routine pharmacovigilance *Special attention in PSURs (for the potential risk of diabetic ketoacidosis)* Analyse in the section "Drug abuse or misuse" of the planned 6-month PSURs Post-marketing observational prospective cohort study of diabetic children in Europe	Medical devices issues are being handled in the SmPC of the relevant presentations *SmPC section 6.6: states that:* ▪ *For continuous subcutaneous infusion pump: Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs. Patients using CSII should be comprehensively instructed on the use of the pump system. The infusion set and reservoir should be changed every 48 hours using aseptic technique. Patients administering Apidra by CSII must have alternative insulin available in case of pump system failure.* ▪ *For intravenous use: Apidra should be used at a concentration of 1 unit/mL insulin glulisine in infusion systems with the infusion fluid sterile 0.9% sodium chloride solution using coextruded polyolefin/polyamide plastic infusion bags with a dedicated infusion line. After dilution for intraveous use, the solution should be inspected before use visually for particulate matter prior to administration, whenever solution and container permit. Never use the solution if it has become cloudy or contains particles; use it only if it is clear and colorless. Apidra was found to be incompatible with Dextrose solution and Ringers solution and, therefore, must not be used with these solution fluids. The use of other solutions has not been studied.* *SmPC section 4.4: warns about the use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, that may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal*

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Antigenicity	Routine pharmacovigilance	Theoretical risk only, not described in the SmPC
Off-label use in children below 6	Routine pharmacovigilance Analyse in the section "Off-label use" of the planned 6-month PSURs Monitoring of insulin glulisine prescriptions through a prescription survey	SmPC sections 4.1, 4.2 and 5.1: give the age range for APIDRA use, and state that there is insufficient clinical information on the use of APIDRA in children younger than the age of 6 years
Use in pregnancy	Routine Pharmacovigilance	SmPC section 4.6: informs about the lack of adequate data in pregnancy, and that caution should be exercised when prescribing to pregnant women, careful monitoring of glucose control being essential

Periodic Safety Update Reports

As a consequence of the approval of the new route of administration, the PSUR cycle for Apidra should be re-started as follows:

- Six-monthly PSURs until two full years of experience with the intravenous route in the EU has been gained
- Yearly PSURs for the following two years
- Thereafter submission at 3-yearly intervals

3.6 Changes to the Product Information

Changes were introduced to sections 4.2, 4.4, 5.1, 5.2, 6.2, 6.3 and 6.6 of the SPC for the vial presentation, to reflect the new administration route. The labelling and package leaflet were updated accordingly.

As for the remaining presentations (cartridge and pre-filled pens), information on the intravenous use was inserted in section 5.2 to complete the pharmacokinetic profile of Apidra.

Changes were also made to the PI to bring it in line with the current EMEA/QRD template and SPC guideline, which were reviewed by QRD and accepted by the CHMP.

4. Overall conclusions, risk/benefit assessment and recommendation

Quality

As all aspects of manufacture, formulation, release testing and immediate packaging of Apidra are identical to that already approved for the original marketing authorisation application, only compatibility and stability data was submitted to support the choice of infusion fluid. The product was shown to be incompatible with Glucose 5% solution but compatible with 40 mM potassium chloride solution. Stability data supports the proposed in-use shelf life.

Efficacy

Pharmacokinetic and pharmacodynamic data were already submitted with the initial application and do support the use of the intravenous use route. Indeed, this route may be necessary in the hospital setting for the control of blood glucose levels in acute conditions e.g. during ketoacidosis, acute illnesses or during intra and post operative periods.

Safety

From the safety database all the adverse reactions reported both in clinical trials and post-marketing setting are appropriately reflected in the Summary of Product Characteristics. While limited data is available for the intravenous route of administration, no specific safety concern is foreseen.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.4 adequately addressed the risks.

As a consequence of the approval of the new route of administration, the PSUR cycle for Apidra should be re-started.

User consultation was recently performed for Apidra, for a type II variation (EMEA/H/C/201/II/19) which was approved on 20 June 2008. As no significant changes are introduced to the package leaflet as a consequence of this extension application, no user testing was conducted, which was considered acceptable by the CHMP.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that no additional risk minimisation activities are required beyond those included in version 1.3 of the RMP.

Recommendation

Based on the CHMP review of data on quality and safety, the CHMP considered by consensus that the risk-benefit balance of the intravenous administration of Apidra in the treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required, was favourable (for the vial presentation) and therefore recommended the modification of the marketing authorisation.