European Medicines Agency

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ASSESSMENT REPORT FOR APIDRA

International Nonproprietary Name:
insulin glulisine

Procedure No. EMEA/H/C/557/II/0017

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

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1. Introduction

Insulin glulisine (Apidra, 3B Lys-29B Glu –human insulin) is a recombinant rapid-acting insulin analog produced by recombinant DNA technology in Escherichia coli (E. coli). It differs from human insulin by two amino-acid substitution on the B chain of the protein (replacement of asparagine in position B3 by lysine and lysine in position B29 by glutamic acid). Thus, insulin glulisine is a close structural relative to human insulin.

Apidra was authorised by the centralised procedure (EU/1/04/285) in 27 September 2004 for the treatment of adult patients with diabetes mellitus.

In this Type II variation the Marketing Authorisation Holder (MAH) applied to add a new indication to the Apidra SPC. The proposed therapeutic indication was for the use of Apidra in: "adolescents and children of 4 years or above with diabetes mellitus, where treatment with insulin is required". The MAH proposed to make changes to sections 4.1, 4.2 and 5.1 of the SPC to reflect the new indication.

In support of the indication results of two clinical trials have been submitted (Study HMR1964D/3001 and HMR1964A/1017).

2 Clinical aspects

2.1 Clinical efficacy

The clinical documentation consists of two clinical studies:

Study HMR1964D/3001 that investigated the efficacy and safety of insulin glulisine compared with insulin lispro in children and adolescents with type I diabetes mellitus: a 26-week, multicentre, open, parallel-group clinical trial.

Study HMR1964A/1017 that studied the pharmacokinetics and safety of 0.15 IU/kg HMR1964 (insulin glulisine) and regular human insulin injected subcutaneously as a single dose in paediatric subjects with type 1 diabetes in a single-centre, double-blind, randomised, two-way crossover study.

2.1.1 Study HMR1964D/3001

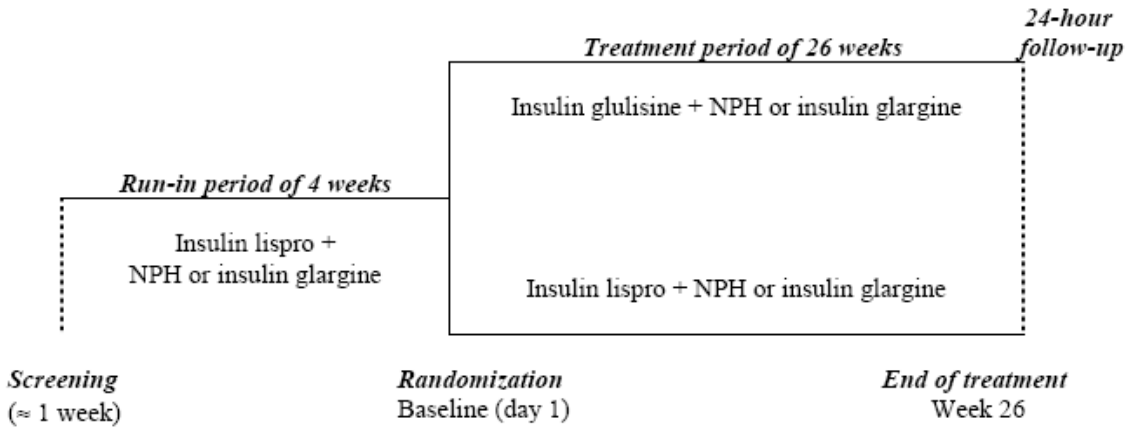
This study was a multicentre, multinational, open, parallel-group, controlled, 1:1 randomised study with a run-in phase of 4 weeks, and a treatment phase of 26 weeks with a total of 572 male and female patients with type 1 diabetes (aged 4 to 17 years), carried out between 12 April 2005 and 03 November 2006.

The MAH stated that "According to Article 8.3 (ib) of Directive 2001/83/EC, as amended, the applicant confirms that clinical trials carried out outside the European Union met ethical requirements of the Declaration of Helsinki and good clinical practice, applicable national laws and regulations and the ethical principles of Directive 2001/20/EC."

2.1.1.1 Study design

Study HMR1964D/3001 was a multicentre, multinational, open-label, controlled, centrally randomised (1:1), stratified, parallel-group study in children and adolescents with type 1 diabetes mellitus aged between 4 and 17 years. The study consisted, after a screening period of about 1 week, of a run-in phase of 4 weeks followed by a 26-week treatment phase, and by a 24-hour follow-up period.

Study design



Subjects were stratified within each centre according to whether they were taking NPH or insulin glargine as basal insulin at the time of randomisation. During the study, insulin glulisine or insulin lispro was given at least twice daily within 15 minutes prior to a meal in combination with NPH insulin administered twice daily or insulin glargine administered once daily in the evening. Total study duration was approximately 31 weeks. Male and female patients aged 4-17 years with established type 1 diabetes mellitus with an onset of at least one year prior to screening, an uninterrupted insulin therapy for at least one year on a stable insulin regimen consisting of either NPH or insulin glargine as the basal insulin, willing to have multiple daily injections of insulin, with a glycated haemoglobin (HbA1c) value in the range of ≥ 6.0 and ≤11.0%, able and willing to perform blood glucose (BG) monitoring, were eligible to participate in the study.

A total of 646 subjects were screened, 572 randomised with 276 subjects randomised into the glulisine group and 295 randomised into the lispro group. Of these, a total of 265 subjects completed the study with glulisine and 287 subjects completed with lispro. One subject randomised in the insulin lispro group was treated by error in the insulin glulisine group; he was therefore considered in the insulin glulisine group for all analyses and excluded from the PP population. Thus, 277 subjects were treated in the insulin glulisine group and 295 in the insulin lispro group.

The primary objective was to demonstrate non-inferiority of insulin glulisine compared to insulin lispro in the change in total glycated haemoglobin (GHb) from baseline to endpoint (week 26 or last observation on treatment) in children and adolescents with type 1 diabetes mellitus.

Secondary objectives were to compare insulin glulisine with insulin lispro in terms of secondary efficacy parameters (change in GHb at week 12 and week 26, self-monitored blood glucose [SMBG] parameters, symptomatic hypoglycaemia and insulin doses) and safety (adverse events [AEs], serious symptomatic hypoglycaemia, clinical chemistry and haematology, as well as insulin antibodies), in children and adolescents with type 1 diabetes mellitus.

Overall, the mean age of subjects was 12.5 years. Approximately 7 % of subjects were <8 years (1.6% <6 years), 26% were between 8 and 12 years old, and 67% were above 12 years. Overall, the mean BMI was 20.6 kg/m².

Subject Demographics

Characteristic		Glulisine (N=277)	Lispro (N=295)
Gender	Female: n (%)	131 (47.3)	156 (52.9)
	Male: n (%)	146 (52.7)	139 (47.1)
Age (years)	Mean (SD)	12.5 (3.05)	12.6 (2.92)
	Median [min ; max]	13.0 [4 ; 17]	13.0 [4 ; 17]
	<8 years: n (%)	22 (7.9)	19 (6.4)
	≥8 years and <12 years: n (%)	78 (28.2)	71 (24.1)
	≥12 years: n (%)	177 (63.9)	205 (69.5)
Race	White: n (%)	246 (88.8)	275 (93.2)
	Black: n (%)	3 (1.1)	3 (1.0)
	Asian/Oriental: n (%)	8 (2.9)	7 (2.4)
	Multiracial: n (%)	17 (6.1)	10 (3.4)
	Other: n (%)	3 (1.1)	0 (0.0)
BMI (kg/m^2)	Mean (SD)	20.8 (3.4)	20.5 (3.3)
	Median [min ; max]	20.5 [14.1 ; 30.4]	20.1 [14.8 ; 30.8]
Tanner stage	Stage 1: n (%)	74 (26.7)	72 (24.4)
	Stage 2: n (%)	33 (11.9)	50 (16.9)
	Stage 3: n (%)	37 (13.4)	35 (11.9)
	Stage 4: n (%)	64 (23.1)	64 (21.7)
	Stage 5: n (%)	69 (24.9)	71 (24.1)

Treatments

Insulin glulisine (3mL cartridges and 10mL vials), individual titration based on the BG values. Subjects were administered a subcutaneous injection between 0 to 15 minutes prior to a meal, at least twice daily, in association with basal insulin therapy (NPH insulin or insulin glargine).

Insulin lispro (3mL cartridges and 10mL vials), individual titration based on the BG values. Subjects were administered a subcutaneous injection between 0 to 15 minutes prior to a meal, at least twice daily, in association with basal insulin therapy (NPH insulin or insulin glargine).

BG targets were adapted to the age of the subjects (<8 years or ≥8 years) and to the BG meters used (plasma-referenced or whole blood-referenced). Details are provided below.

The doses of insulin glulisine or insulin lispro were to be titrated based on the pre-meal BG values and those of insulin glargine or NPH insulin based on the fasting BG (FBG) and pre-meal BG values.

Titration goals (Blood glucose targets)

	Plasma-referenced blood glucose meters	Whole blood-referenced blood glucose meters
FBG or pre-meal BG value		
<8 years old	106 to 150 mg/dL (5.9 to 8.3 mmol/L)	100 to 140 mg/dL (5.6 to 7.8 mmol/L)
≥8 years old	95 to 150 mg/dL (5.3 to 8.3 mmol/L)	90 to 140 mg/dL (5.0 to 7.8 mmol/L)
2-hour post-prandial BG value		
<8 years old	128 to 194 mg/dL (7.1 to 10.8 mmol/L)	120 to 180 mg/dL (6.7 to 10.0 mmol/L)
≥8 years old	106 to 172 mg/dL (5.9 to 9.6 mmol/L)	100 to 160 mg/dL (5.6 to 8.9 mmol/L)

The two treatment groups had a similar distribution for diabetes duration (5.2 to 5.3 years), age at diagnosis (7.2 to 7.5 years), and duration of insulin treatment (5.2 to 5.3 years).

The CHMP concluded that the design, which is similar to that of the adult studies submitted previously, and analysis of the study are in accordance with the European Guidelines.

2.1.1.2 Results

Primary Efficacy Variable Analysis

The primary efficacy analysis was the change in GHb from baseline to endpoint using the mITT population, where endpoint was defined as the subject's last available measurement during the treatment phase. The PP population was analysed to check for the consistency of the results with the mITT population.

GHb (%): Change from baseline at endpoint (mITT and PP populations)

Timepoint	Glulisine		Lispro		Glulisine – Lispro	
	N	Mean (SD)*	N	Mean (SD)*	Difference in adjusted mean	95% CI
mITT population						
Baseline	271	8.20 (1.05)	291	8.17 (1.02)		
Endpoint	271	8.31 (1.37)	291	8.37 (1.32)		
Adjusted mean change from baseline at endpoint	271	0.10 (0.08)	291	0.16 (0.07)	- 0.06	(-0.24 ; 0.12)
PP population						
Baseline	259	8.21 (1.05)	273	8.13 (1.01)		
Endpoint	259	8.31 (1.36)	273	8.33 (1.26)		
Adjusted mean change from baseline at endpoint	259	0.09 (0.08)	273	0.14 (0.08)	- 0.05	(-0.23 ; 0.13)

*Standard deviation (SD) for mean and standard error (SE) for adjusted mean from ANCOVA model

The results appear to support the non-inferiority conclusion of insulin glulisine compared to insulin lispro. Nevertheless, CHMP initially had some concern over the effect on the analysis of the algorithm used for pooling small centres and whether the analysis was affected by empty strata within centres. The concern was in particular related to the fact that the results might be biased in favour of Apidra due to the chosen method of handling small centres.
In their responses to this concern the MAH provided a number of analyses of the primary variable that indicated that the upper limit of the 95% CIs for the difference in adjusted means for change from baseline at endpoint in HbA1c are well below the non-inferiority limit of 0,4%. These results were consistent with the primary efficacy analysis and with previous results of sensitivity analyses. The MAH therefore concluded that the strategy of pooling centres did not induce any bias in favour of Apidra. The CHMP agreed with the MAH conclusions.

Secondary Efficacy Variable Analysis
There were no changes from baseline in GHb at week 12 and a minimal increase in GHb in both groups at week 26 (+0.08% in the insulin glulisine group, +0.17% in the insulin lispro group). The change from baseline at each time-point in the two treatment groups was similar to the change observed for the primary analysis at endpoint. The 95% CIs of the between-treatment difference are consistent with the conclusion of non-inferiority as defined for the primary efficacy variable.

GHb (%): change from baseline at weeks 12 and 26 – mITT population

Timepoint	Glulisine		Lispro		Glulisine – Lispro	
	N	Mean (SD)*	N	Mean (SD)*	Difference in adjusted mean	95% CI
Week 12						
GHb value	259	8.19 (1.26)	276	8.17 (1.24)		
Adjusted mean change from baseline at week 12	259	-0.01 (0.07)	276	-0.03 (0.06)	0.01	(-0.14 ; 0.17)
Week 26						
GHb value	254	8.32 (1.36)	269	8.39 (1.34)		
Adjusted mean change from baseline at week 26	254	0.08 (0.08)	269	0.17 (0.08)	-0.09	(-0.28 ; 0.09)

* Standard deviation (SD) for mean and standard error (SE) for adjusted mean from ANCOVA model.

Proportion of subjects reaching different pre-specified GHb thresholds
The proportion of subjects reaching two different pre-specified GHb thresholds: GHb <8.5%, and decrease in GHb from baseline ≥0.7% are displayed below.

Number of subjects reaching GHb categories (mITT population)

Timepoint	Glulisine		Lispro	
	N	(%)	N	(%)
Subjects with GHb <8.5%				
Baseline	161	(59.4)	181	(62.2)
Week 12	167	(64.5)	174	(63.0)
Week 26	156	(61.4)	152	(56.5)
Endpoint	168	(62.0)	167	(57.4)
Subjects with a decrease of GHb of ≥0.7%				
Week 12	49	(18.9)	54	(19.6)
Week 26	46	(18.1)	49	(18.2)
Endpoint	48	(17.7)	53	(18.2)

There was a greater percentage of adolescents (13 to 17 years) in the insulin glulisine group reaching a GHb level <7.5% (31.1% versus 21.1%). Globally, the number of subjects reaching their respective GHb goals according to their age category was significantly higher in the insulin glulisine group (38.4% versus 32.0%, p=0.0386).

Number (%) of subjects reaching GHb age-categories (mITT population)

Age/GHb category	Glulisine		Lispro	
Timepoint	n/N	(%)	N	(%)
Subjects <6 years with 7.5%<GHb<8.5%				
Baseline	1/3	(33.3)	2/5	(40.0)
Endpoint	1/3	(33.3)	2/5	(40.0)
Subjects aged 6 to 12 with GHb <8.0%				
Baseline	53/120	(44.2)	55/120	(45.8)
Endpoint	57/120	(47.5)	56/120	(46.7)
Subjects aged 13 to 17 with GHb <7.5%				
Baseline	36/148	(24.3)	40/166	(24.1)
Endpoint	46/148	(31.1)	35/166	(21.1)
All ages combined and GHb in the targeted interval				
Baseline	90/271	(33.2)	97/291	(33.3)
Endpoint	104/271	(38.4)	93/291	(32.0)

Insulin Doses

The mean daily insulin doses are shown below.

Mean daily insulin dose (in U) during the treatment phase (mITT population)

Timepoint	Glulisine		Lispro	
Daily insulin doses (U)	N	Mean (SD) *	N	Mean (SD) *
Baseline				
Total daily insulin dose	275	51.30 (23.75)	294	50.86 (22.07)
Daily rapid-acting insulin dose	274	24.26 (14.64)	294	24.34 (14.72)
Daily basal insulin dose	275	27.20 (13.96)	294	26.55 (14.14)
Endpoint				
Total daily insulin dose	275	53.85 (24.09)	294	55.80 (23.70)
Daily rapid-acting insulin dose	274	25.48 (14.93)	294	26.97 (16.29)
Daily basal insulin dose	275	28.44 (14.40)	294	28.86 (14.82)
Change from baseline at endpoint				
Total daily insulin dose	275	2.53 (0.68)	294	4.91 (0.65)
Daily rapid-acting insulin dose	274	1.36 (0.52)	294	2.71 (0.49)
Daily basal insulin dose	275	1.09 (0.32)	294	2.22 (0.31)

*Standard deviation (SD) for mean and standard error (SE) for adjusted mean from ANCOVA model

Post-prandial glycaemic control, as assessed by self-monitored blood glucose (SMBG) values and BG excursions, was similar in the two treatment groups at endpoint, with no statistically significant difference between the treatment groups. At endpoint, subjects treated with insulin lispro required significantly greater increases from baseline in basal, rapid-acting and total insulin daily doses in order to achieve similar glycaemic control than subjects treated with insulin glulisine.

There were no noteworthy differences between the two treatment groups in the incidence of all symptomatic hypoglycaemia, severe symptomatic hypoglycaemia, and severe nocturnal symptomatic hypoglycaemia. The incidence of nocturnal symptomatic hypoglycaemia was higher in the insulin glulisine group than the insulin lispro group in the time period "entire treatment phase"; this between-group difference was mainly observed in the first month of treatment and decreased in the latter part of the treatment phase.

Number (percentage) of subjects with all symptomatic hypoglycaemia (Safety population)

Treatment phase	Glulisine			Lispro		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
Screening/Run-in phase	198/277	(71.5)	1269	213/295	(72.2)	1144
Month 1	195/277	(70.4)	1212	184/295	(62.4)	973
Month 4 - Treatment end	199/268	(74.3)	2686	199/291	(68.4)	2747
Entire treatment phase	230/277	(83.0)	5543	238/295	(80.7)	5346

Note: n = number of subjects reporting at least one episode of symptomatic hypoglycemia; N = number of randomized and treated subjects evaluable.

Number of subjects with severe symptomatic hypoglycaemia (Safety population)

Treatment phase	Glulisine			Lispro		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
Screening/run-in phase	22/277	(7.9)	29	27/295	(9.2)	46
Month 1	17/277	(6.1)	38	22/295	(7.5)	36
Month 4 - Treatment end	27/268	(10.1)	47	34/291	(11.7)	63
Entire treatment phase	45/277	(16.2)	125	57/295	(19.3)	132

Note: n = number of subjects reporting at least one episode of severe symptomatic hypoglycemia; N = number of randomized and treated subjects evaluable.

Number (percentage) of subjects with nocturnal symptomatic hypoglycaemia (Safety population)

Treatment phase	Glulisine			Lispro		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
Screening/Run-in phase	51/277	(18.4)	90	51/295	(17.3)	82
Month 1	55/277	(19.9)	105	33/295	(11.2)	63
Month 4 - Treatment end	77/268	(28.7)	181	64/291	(22.0)	188
Entire treatment phase	110/277	(39.7)	398	90/295	(30.5)	336

Note: n = number of subjects reporting at least one episode of nocturnal symptomatic hypoglycemia; N = number of randomized and treated subjects evaluable.

Number (percentage) of subjects with severe nocturnal symptomatic hypoglycaemia (Safety population)

Treatment phase	Glulisine			Lispro		
	n/N	(%)	Number of episodes	n/N	(%)	Number of episodes
Safety population						
Screening/Run-in phase	3/277	(1.1)	3	7/295	(2.4)	7
Month 1	4/277	(1.4)	4	3/295	(1.0)	3
Month 4 - Treatment end	6/268	(2.2)	8	7/291	(2.4)	10
Entire treatment phase	10/277	(3.6)	13	13/295	(4.4)	17

Note: n = number of subjects reporting at least one episode of severe nocturnal symptomatic hypoglycemia; N = number of randomized and treated subjects evaluable.

When GHb and hypoglycaemia were analysed in subgroups of subjects based on age, sex, race, duration of diabetes, basal insulin, and baseline GHb, the results observed in each subgroup were consistent with those seen in the population as a whole.

Summary of subgroup factor analyses of GHb (mITT population)

Subgroup factor	Mean treatment differences in change from baseline		p-value for treatment by factor interaction
Category	Adjusted Mean (SE)	95% CI	
Age			
< 8 years	0.23 (0.32)	(-0.42 ; 0.88)	ND*
≥ 8 - < 12 years	-0.06 (0.19)	(-0.45 ; 0.32)	
≥ 12 years	-0.13 (0.11)	(-0.35 ; 0.09)	
Duration of diabetes			
< 5 years	-0.12 (0.13)	(-0.39 ; 0.14)	0.6329
≥ 5 years	-0.03 (0.13)	(-0.29 ; 0.21)	
Baseline GHb			
< 8.5%	-0.09 (0.10)	(-0.29 ; 0.09)	0.9423
≥ 8.5%	-0.08 (0.18)	(-0.44 ; 0.26)	
Basal insulin			
Glargine	-0.07 (0.11)	(-0.28 ; 0.14)	0.7391
NPH	-0.13 (0.18)	(-0.50 ; 0.22)	

Note: adjusted mean (SE) and p-value for interaction from ANCOVA model

ND: not done ; interaction not tested for age due to the small number of subjects in one age category (<8 years).

2.1.2 Study HMR1964A/1017

This study was a single-centre, double-blind, randomised, two-way crossover study to investigate the pharmacokinetics and safety of 0.15 IU/kg HMR1964 (insulin glulisine) and regular human insulin injected subcutaneously as a single dose in paediatric subjects with type I diabetes.

2.1.2.1 Study design

Study HMR1964A/1017 was a single-centre, single-dose, double-blind, randomised, two-way crossover study design in subjects with type 1 diabetic. All subjects were to be girls or boys aged 5-11 years and 12-17 years with established type 1 diabetes mellitus with an onset of at least one year prior to screening and stable insulin regimen for at least two years prior to study conduct, body weight not less than 20kg, glycated haemoglobin (HbA1c) ≤11.0%, daily insulin dose ≥0.5 U/kg, normal findings in medical history and physical examination and normal laboratory values. The subjects were randomised to treatment sequences in a stratified manner with age class as the stratification factor.

Subjects treated with common individualised paediatric antidiabetic regimen employing insulins were to be included. The study consisted of four trial periods as follows: Trial period 0 (screening), Trial periods 1 and 2 (treatment) and Trial period 3(follow-up examination). At trial periods 1 and 2 each subject received 0.15 IU/kg insulin glulisine or 0.15 IU/kg regular human insulin, injected subcutaneously in the periumbilical abdomen, according to the randomisation schedule.

A total of 20 subjects were enrolled and treated in the study. Ten subjects were children aged between 5 and 11 years and 10 subjects were adolescents aged between 12 and 17 years. All 20 subjects were evaluable for safety and pharmacodynamics. Nineteen subjects were fully evaluable for pharmacokinetics.

The primary objective was to investigate the pharmacokinetics of insulin glulisine and regular human insulin (HOE31HPR100) in paediatric type 1 diabetic subjects. The secondary objectives were to investigate prandial glucose profiles of insulin glulisine and regular human insulin (HOE31HPR100) administered before a standardised meal in paediatric type 1 diabetic subjects and to investigate the safety following a single subcutaneous dose of insulin glulisine in paediatric type 1 diabetic subjects.

Overall, the mean age of subjects was 12.4 years and the mean BMI was 20.9 kg/m².

Subject Demographics

Demographic data	Arithmetic mean (range)					
	All subjects (n=20)					
	all (n = 20)	male (n = 9)	female (n = 11)			
Age (years)	12.4 (7 – 16)	12.6 (8 – 16)	12.3 (7 – 16)			
Weight (kg)	52.1 (26.0 – 82.5)	54.1 (26.0 – 82.5)	50.5 (27.5 – 65.0)			
BMI (kg/m²)	20.9 (16.4 – 26.3)	20.9 (16.4 – 26.3)	20.9 (17.6 – 24.5)			
	Children (n=10)			Adolescents (n=10)		
	all (n = 10)	male (n = 5)	female (n = 5)	all (n = 10)	male (n = 4)	female (n = 6)
Age (years)	10.1 (7 – 11)	10.2 (8 – 11)	10.0 (7 – 11)	14.7 (12 – 16)	15.5 (14 – 16)	14.2 (12 – 16)
Weight (kg)	40.0 (26.0 – 50.0)	39.1 (26.0 – 50.0)	40.8 (27.5 – 49.0)	64.2 (51.0 – 82.5)	72.7 (53.0 – 82.5)	58.6 (51.0 – 65.0)
BMI (kg/m²)	19.4 (16.4 – 22.7)	19.2 (16.4 – 21.1)	19.7 (17.6 – 22.7)	22.4 (17.7 – 26.3)	23.1 (17.7. – 26.3)	22.0 (20.2 – 24.5)

2.1.2.2 Results

Pharmacokinetic data

The *serum insulin* profile was characterised by the following pharmacokinetic parameters:

- Area under the insulin concentration-time curve between
  - 0 h and 1 h after injection ($AUC_{(0-1h)}$, µIU.min/mL)
  - 0 h and 2 h after injection ($AUC_{(0-2h)}$, µIU.min/mL)
  - 0 h and 4 h after injection ($AUC_{(0-4h)}$, µIU.min/mL)
  - 0 h and 6 h after injection ($AUC_{(0-6h)}$, µIU.min/mL)
- Maximum concentration (C_{max}, µIU/mL)
- Time to maximum concentration (T_{max}, min)
- Mean residence time (MRT, min)

Comparison of pharmacokinetic results for all subjects

Variable	Geometric mean (*arithmetic mean*)		Point estimate (95% confidence interval)[#]
	Glulisine (n = 20)	RHI (n = 19)	Glulisine / RHI (n=19)
$AUC_{(0-1h)}$ [µIU.min/mL]	2287 (*2491*)	1246 (1440)	176 % (126.9 ; 243.8 %)
$AUC_{(0-2h)}$ [µIU.min/mL]	5232 (5637)	2994 (3335)	169 % (126.9 ; 224.3 %)
$AUC_{(0-4h)}$ [µIU.min/mL]	7624 (8190)	5703 (6231)	130 % (99.3 ; 170.3 %)
$AUC_{(0-6h)}$ [µIU.min/mL]	8361 (8922)	7052 (7673)	116 % (89.5 ; 149.8 %)
C_{max} [µIU/mL]	58 (62)	33 (37)	171 % (126.9 ; 229.4 %)
T_{max} [min]	54**	66**	-8 min (-24 ; 7 min)[##]
MRT [min]	88 (90)	137 (139)	64 % (59.0 ; 70.4 %)

[#] Point estimates and 95% confidence intervals for the ratio of treatment means, based on (ln) transformed data
[##] Point estimates and 95% confidence intervals for the respective median differences from non-parametric data analysis
** Median

In both age classes, children (5 to 11 years, inclusive) and adolescents (12 to 17 years, inclusive), insulin glulisine was more rapidly absorbed than RHI. The concentration time profile of insulin glulisine showed initial fractional areas under the curves (AUCs) being higher after insulin glulisine. The maximum concentration (C_{max}) of insulin glulisine was 71% higher and was reached earlier, with a median T_{max} of 54 minutes, compared to 66 minutes after regular insulin (RHI). The mean residence time (MRT) for insulin glulisine was distinctly shorter, at 88 minutes compared to 137 minutes for RHI.

Pharmacodynamic Data

The analysis variables were taken from profiles up to 6 hours:

- Area under the baseline subtracted glucose concentration time curve between
  - 0 h and 1 h ($AUC_{(0\text{-}1h)}$, mg.h/dL)
  - 0 h and 2 h ($AUC_{(0\text{-}2h)}$, mg.h/dL)
  - 0 h and 4 h ($AUC_{(0\text{-}4h)}$, mg.h/dL)
  - 0 h and 6 h ($AUC_{(0\text{-}6h)}$, mg.h/dL)
- Time to maximum baseline subtracted blood glucose concentration (t_{max}, min)
- Maximum blood glucose concentration (GLU_{max}, mg/dL)
- Maximum blood glucose excursion from baseline (ΔGLU_{max}, mg/dL)
- Minimum blood glucose concentration (GLU_{min}, mg/dL)
- Time to minimum blood glucose concentration (t_{min}, min)

Additional analyses of glucose exposure and excursion were confined to data obtained within 4 hours after injection.

- Time to maximum baseline subtracted glucose concentration within 4 hours (tmax-4h, min)
- Maximum blood glucose concentration within 4 hours ($GLU_{max\text{-}4h}$, mg/dL)
- Maximum blood glucose excursion from baseline within 4 hours ($\Delta GLU_{max\text{-}4h}$, mg/dL)
- Minimum blood glucose concentration after $GLU_{max\text{-}4h}$ within 6 hours ($GLU_{min\text{-}4h}$, mg/dL)
- Time to minimum blood glucose concentration after $GLU_{max\text{-}4h}$ within 6 hours ($t_{min\text{-}4h}$, min)

Comparison of pharmacodynamic results for all subjects: baseline corrected data

Variable	Sample mean		Point estimate (95% CI)[#]
	Glulisine (n = 20)	RHI (n = 20)	Glulisine / RHI (n = 20)
$AUC_{(0\text{-}1h)}$ [mg.h/dL]	57	79	73% (58.8 ; 89.6%)
$AUC_{(0\text{-}2h)}$ [mg.h/dL]	179	263	68% (55.9 ; 81.5%)
$AUC_{(0\text{-}4h)}$ [mg.h/dL]	419	627	67% (55.3 ; 79.6%)
$AUC_{(0\text{-}6h)}$ [mg.h/dL]	641	801	80% (66.6 ; 95.4%)
$GLU_{max\text{-}4h}$ [mg/dL]	298	352	85% (76.8 ; 93.3%)
$\Delta GLU_{max\text{-}4h}$ [mg/dL]	166	224	74% (63.4 ; 85.8%)
$t_{max\text{-}4h}$ [min]	120**	120**	0.0 (-24.0 ; 29.0)[##]
$GLU_{min\text{-}4h}$ [mg/dL]	211	193	109% (93.3 ; 128.2%)
$t_{min\text{-}4h}$ [min]	243**	330**	-53 (-90.0 ; -15.0)##

\# Point estimates and 95% CIs for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data.
Point estimates and 95% CIs for the respective median differences, from non-parametric data analysis.
** Median

Pharmacodynamic results: Children versus Adolescents

Variable	Corrected glucose concentrations: Sample mean (n = 20)					
	Glulisine			RHI		
	All subjects	Children	Adolescents	All subjects	Children	Adolescents
$AUC_{(0\text{-}1h)}$ [mg.h/dL]	57	50	65	79	75	82
$AUC_{(0\text{-}2h)}$ [mg.h/dL]	179	149	208	263	258	267
$AUC_{(0\text{-}4h)}$ [mg.h/dL]	419	320	518	627	590	664
$AUC_{(0\text{-}6h)}$ [mg.h/dL]	641	492	790	801	729	872
$GLU_{max\text{-}4h}$ [mg/dL]	298	273	324	352	349	355
$\Delta GLU_{max\text{-}4h}$ [mg/dL]	166	142	189	224	216	232
$t_{max\text{-}4h}$ [min]	120**	90**	135**	120**	120**	125**
$GLU_{min\text{-}4h}$ [mg/dL]	211	180	242	193	179	207
$t_{min\text{-}4h}$ [min]	243**	240**	261**	330**	315**	330**

** Median values.

Comparison of pharmacodynamic results for insulin glulisine: baseline corrected data

Variable	Sample mean		Point estimate (95% CI)#
	Children (n = 10)	Adolescents (n = 10)	Adolescents/Children (n=20)
$AUC_{(0\text{-}1h)}$ [mg.h/dL]	50	65	131% (68.9 ; 286.6%)
$AUC_{(0\text{-}2h)}$ [mg.h/dL]	149	208	140% (81.9 ; 269.1%)
$AUC_{(0\text{-}4h)}$ [mg.h/dL]	320	518	162% (86.5 ; 394.9%)
$AUC_{(0\text{-}6h)}$ [mg.h/dL]	492	790	161% (88.0 ; 368.6%)
$GLU_{max\text{-}4h}$ [mg/dL]	273	324	119% (92.1 ; 155.0%)
$\Delta GLU_{max\text{-}4h}$ [mg/dL]	142	189	133% (83.5 ; 226.1%)
$t_{max\text{-}4h}$ [min]	90**	135**	30 (-56.0 ; 80.0)##
$GLU_{min\text{-}4h}$ [mg/dL]	180	242	135% (95.1 ; 199.0%)
$t_{min\text{-}4h}$ [min]	240**	261**	28 (-59.0 ; 120.0)##

\# Point estimates and 95% CIs for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data.
Point estimates and 95% CIs for the respective median differences, from non-parametric data analysis.
** Median

Comparison of pharmacodynamic results for regular human insulin: baseline corrected data, children versus adolescents

Variable	Sample mean		Point estimate (95% CI)#
	Children (n = 10)	Adolescents (n = 10)	Adolescents/Children (n=20)
$AUC_{(0\text{-}1h)}$ [mg.h/dL]	75	82	108% (69.7 ; 170.5%)
$AUC_{(0\text{-}2h)}$ [mg.h/dL]	258	267	103% (74.4 ; 144.4%)
$AUC_{(0\text{-}4h)}$ [mg.h/dL]	590	664	113% (80.8 ; 159.3%)
$AUC_{(0\text{-}6h)}$ [mg.h/dL]	729	872	120% (82.3 ; 178.5%)
$GLU_{max\text{-}4h}$ [mg/dL]	349	355	102% (84.0 ; 123.5%)
$\Delta GLU_{max\text{-}4h}$ [mg/dL]	216	232	107% (81.1 ; 143.0%)
$t_{max\text{-}4h}$ [min]	120**	125**	30 (0.0 ; 35.0)##
$GLU_{min\text{-}4h}$ [mg/dL]	179	207	115% (83.3 ; 162.2%)
$t_{min\text{-}4h}$ [min]	315**	330**	5 (-28.0 ; 60..0)##

\# Point estimates and 95% CIs for the ratio of treatment means, according to Fieller's Theorem, based on untransformed data.
Point estimates and 95% CIs for the respective median differences, from non-parametric data analysis.
** Median

Blood glucose exposure and excursions were lower (AUCs, GLUmax-4h and ΔGLUmax-4h) after insulin glulisine than after RHI, when given immediately before meal, in the paediatric population as a whole as well as in both age classes, children and adolescents.

2.1.2.3 Conclusions on pharmacokinetic and pharmacodynamic

Insulin glulisine displays pharmacokinetic and pharmacodynamic properties in paediatric type 1 diabetic patients, which in this population also, classify insulin glulisine as a rapid-acting insulin analogue and which do not differ from adult data. The CHMP considered that there is adequate evidence to show that the results from this study are in agreement with those of the adult population.

2.2. Clinical safety

2.2.1. Study HMR1964D/3001

Extent of Exposure
A total of 572 subjects were treated with study medication: 277 with insulin glulisine and 295 with insulin lispro. The mean treatment duration was 176.6 (±27.0) days in the insulin glulisine group and 178.9 (±18.7) days in the insulin lispro group.

Adverse Events
In general, both insulin glulisine and insulin lispro were well tolerated and overall, the kind, intensity and frequency of treatment-emergent adverse events (TEAEs) were similar in the two treatment groups. A total of 148 (53.4%) glulisine subjects and 173 (58.6%) lispro subjects had at least one reported TEAE. Possibly related TEAEs were reported in 25 (9.0%) glulisine and 28 (9.5%) lispro subjects. A total of 30 (10.8%) glulisine and 37 (12.5%) lispro subjects reported at least one serious TEAE.

There were no noteworthy differences between treatment groups in the number of subjects reporting hypoglycaemia as a serious adverse event (SAE), including events of coma/unconsciousness or seizures associated with hypoglycaemia. The percentage of subjects with hypoglycaemia reported as SAEs was 7.2% in the insulin glulisine group, and 8.1% in the insulin lispro group.
A summary of treatment emergent adverse events (TEAEs) is presented below.

Overview of TEAEs (Safety population)

Parameter	Number (%) of subjects	
	Glulisine (N=277)	Lispro (N=295)
Subjects with any TEAE(s)	148 (53.4)	173 (58.6)
Subjects with possibly related TEAE(s)	25 (9.0)	28 (9.5)
Subjects with serious TEAE(s)	30 (10.8)	37 (12.5)
Hypoglycemia reported as serious TEAE	20 (7.2)	24 (8.1)
Serious TEAE other than hypoglycemia	11 (4.0)	15 (5.1)
Possibly related serious TEAEs	20 (7.2)	24 (8.1)
Possibly related serious TEAEs other than hypoglycemia	0 (0.0)	1 (0.3)
Leading to withdrawal	0 (0.0)	0 (0.0)
Leading to death	0 (0.0)	0 (0.0)
Subjects with TEAE leading to withdrawal	1 (0.4)	0 (0.0)
Possibly related TEAE leading to withdrawal	1 (0.4)	0 (0.0)

Note: As per protocol, non-serious hypoglycemic episodes are not reported as AEs.
Note: all hypoglycemia reported as serious adverse events were by the Sponsor's definition, assessed as possibly related to the study medication (insulin glulisine, or insulin lispro).

TEAE preferred terms occurring in ≥3% of subjects in either treatment group (Safety population)

Preferred term	Number (%) of subjects	
	Glulisine (N=277)	Lispro (N=295)
Total number of subjects with TEAEs	**148 (53.4)**	**173 (58.6)**
Nasopharyngitis	25 (9.0)	28 (9.5)
Upper respiratory tract infection	23 (8.3)	32 (10.8)
Headache	19 (6.9)	33 (11.2)
Hypoglycaemic seizure	17 (6.1)	14 (4.7)
Influenza	13 (4.7)	5 (1.7)
Vomiting	12 (4.3)	11 (3.7)
Gastroenteritis	11 (4.0)	8 (2.7)
Cough	11 (4.0)	3 (1.0)
Ear infection	9 (3.2)	4 (1.4)
Abdominal pain upper	8 (2.9)	12 (4.1)
Pharyngitis	8 (2.9)	10 (3.4)
Pharyngolaryngeal pain	7 (2.5)	14 (4.7)
Abdominal pain	7 (2.5)	9 (3.1)
Diarrhoea	3 (1.1)	10 (3.4)

Note: Preferred terms are listed in descending order of frequency in the insulin glulisine group.
Numbers in columns are not additive because a subject may have had more than one AE.

Similar percentages of subjects in the two treatment groups had possibly related TEAEs. The most common possibly related preferred terms were related to the underlying disease (hypoglycaemic seizure, hypoglycaemia NOS, and hypoglycaemic coma) or to treatment of the disease (injection site hypertrophy). Similar percentages of subjects in the two treatment groups experienced these possibly-related preferred terms. All other possibly related preferred terms occurred in ≤2 subjects in either treatment group.

TEAE preferred terms considered possibly related to study medication occurring in ≥1% of subjects in either treatment group (Safety population)

Preferred term	Number (%) of subjects	
	Glulisine (N=277)	Lispro (N=295)
Total number of subjects with possibly related TEAEs	**25 (9.0)**	**28 (9.5)**
Hypoglycaemic seizure	17 (6.1)	14 (4.7)
Hypoglycaemia NOS	6 (2.2)	7 (2.4)
Injection site hypertrophy	3 (1.1)	1 (0.3)
Hypoglycaemic coma	1 (0.4)	3 (1.0)

Note: Preferred terms are listed in descending order of frequency in the insulin glulisine group.
Numbers in columns are not additive because a subject may have had more than one AE.

Deaths, serious adverse events and other significant adverse events

There were no deaths. The number of SAEs reported for two treatment groups was similar with 30 subjects (10.8%) in the insulin glulisine group and 37 subjects (12.5%) in the insulin lispro group. There were no noteworthy differences between the two groups with respect to the types of SAEs. None of the SAEs led to discontinuation of the subjects from the study. There were no noteworthy differences between the treatment groups in the numbers/percentages of subjects experiencing hypoglycaemia reported as SAEs, including events of coma/unconsciousness or seizures associated with hypoglycaemia. The overall frequency of serious hypoglycaemic events was 7.2% (20 subjects) in the insulin glulisine group, and 8.1% (24 subjects) in the insulin lispro group.

Hypoglycaemia reported as serious adverse event (Safety population)

Preferred term	Number (%) of subjects	
	Glulisine (N=277)	Lispro (N=295)
Total number of subjects with hypoglycemia reported as a serious TEAE	**20 (7.2)**	**24 (8.1)**
Hypoglycaemic seizure	17 (6.1)	14 (4.7)
Hypoglycaemia NOS	6 (2.2)	7 (2.4)
Hypoglycaemic coma/unconsciousness	1 (0.4)	3 (1.0)

Note: Preferred terms are listed in descending order of frequency in the insulin glulisine group.
Numbers in columns are not additive because a subject may have had more than one AE.

Serious adverse events other than hypoglycaemia are presented below.

Serious adverse events other than hypoglycaemia (Safety population)

Preferred term	Number (%) of subjects	
	Glulisine (N=277)	Lispro (N=295)
Total number of subjects with serious TEAEs other than hypoglycemia	**11 (4.0)**	**15 (5.1)**
Diabetic ketoacidosis	6 (2.2)	4 (1.4)
Vomiting	2 (0.7)	0 (0.0)
Abdominal pain	1 (0.4)	0 (0.0)
Upper respiratory tract infection	1 (0.4)	0 (0.0)
Head injury	1 (0.4)	0 (0.0)
Interstitial lung disease	1 (0.4)	0 (0.0)
Acute abdomen	0 (0.0)	1 (0.3)
Appendicitis	0 (0.0)	2 (0.7)
Gastroenteritis	0 (0.0)	1 (0.3)
Gastroenteritis viral	0 (0.0)	2 (0.7)
Tonsillitis	0 (0.0)	1 (0.3)
Accidental overdose	0 (0.0)	1 (0.3)
Polytraumatism	0 (0.0)	1 (0.3)
Skull fracture	0 (0.0)	1 (0.3)
Hyperglycaemia	0 (0.0)	1 (0.3)
Ketonuria	0 (0.0)	2 (0.7)

Note: Preferred terms are listed in descending order of frequency in the insulin glulisine group.
Numbers in columns are not additive because a subject may have had more than one AE.

Withdrawals

One subject in the insulin glulisine group was withdrawn from this study due to a non-serious adverse event of injection site swelling, which was possibly related to study medication.

Other AES

A slightly higher percentage of subjects in the insulin glulisine group experienced potential systemic hypersensitivity reactions (8 subjects, i.e. 2.9% insulin glulisine, versus 3 subjects, i.e. 1.0% insulin lispro). All potential systemic hypersensitivity events were mild or moderate in intensity. None were considered possibly related to study medication, and no subjects discontinued treatment due to a hypersensitivity reaction. In all but two cases, the outcome was coded as recovered without sequelae; in the remaining two cases, the outcome was unknown (TEAEs of asthma and seasonal allergy). Potential systemic hypersensitivity reactions are summarised below.

Subjects with potential systemic hypersensitivity reactions (Safety population)

Preferred term	Number (%) of subjects			
	All TEAEs		Possibly related TEAEs	
	Glulisine (N=277)	Lispro (N=295)	Glulisine (N=277)	Lispro (N=295)
Total number of subjects with potential systemic hypersensitivity reaction	**8 (2.9)**	**3 (1.0)**	**0 (0.0)**	**0 (0.0)**
Asthma	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Conjunctivitis allergic	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchospasm	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Drug hypersensitivity	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis allergic	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)
Seasonal allergy	1 (0.4)	2 (0.7)	0 (0.0)	0 (0.0)

Note: Preferred terms are listed in descending order of frequency in the insulin glulisine group.
Numbers in columns are not additive because a subject may have had more than one AE.

Significant overdose
Three subjects reported accidental overdoses during the treatment phase of the study.

Clinical Laboratory Evaluations
Comparison of mean and median values for clinical laboratory values, as well as mean and median change in values, showed no relevant differences between the treatment groups.

Cross-reactive insulin antibodies
In the insulin glulisine group, there was an increase in the median cross-reactive antibody values which was maximal at week 12 (+0.540% B/T) and then decreased between week 12 and endpoint (+0.260% B/T). In the insulin lispro group, there was a decrease in the median value at endpoint (–0.190% B/T). Overall, no correlation was found between cross-reactive antibody levels and changes seen in GHb levels, insulin doses, or in symptomatic and severe symptomatic hypoglycemia.

2.2.2 Study HMR1964A/1017

Adverse Events
A total of 19 AEs were reported by nine patients (seven adolescents and two children) over the entire study period. The most common adverse events were upper respiratory infection (five events) and rhinitis (four events). All events were mild in intensity and patients recovered without sequelae. Only one AE was assessed as possibly related: this was a case of mild urticaria on the face, which occurred after RHI administration.

Only hypoglycaemia confirmed by a BG value below 50 mg/dL (=2.8 mmol/L), whether symptomatic or not, was recorded and analysed. Twelve patients had symptomatic hypoglycaemia (18 events) during the study, which in nine patients occurred before administration of study medication. Countermeasures were confined to oral carbohydrates with the exception of one patient, who received an electrolyte-glucose infusion to prevent imminent nocturnal hypoglycaemia about nine hours before administration of insulin glulisine. There were no cases of severe hypoglycaemia.

Deaths, serious adverse events and other significant adverse events
There were no deaths, no SAEs, no AEs leading to withdrawal, no hypoglycaemia reported as a serious TEAE, no eye abnormalities and no episodes of diabetic ketoacidosis reported in this study. No clinically relevant abnormalities in laboratory variables were observed.

2.2.3 Conclusions on safety

The CHMP considered that there was sufficient evidence to characterise the safety profile of Apidra in the paediatric population aged 8 to 17 years of age and that this safety profile was acceptable. However, only 22 and 19 patients under the age of 8 years old had been randomised to insulin glulisine and lispro, respectively. The CHMP therefore considered that the analysis of the subgroup of younger patients did not provide reliable evidence for the consistency of the results in patients at the lower end of the range studied.

In their response to this concern the MAH proposed to lower this age limit to 6 years instead of 8 years, arguing that in the age category ≥6 and < 8 years the number of subjects studied was 32 (18 in the glulisine group and 14 in the lispro group). Although relatively low, this number corresponds to 6.5% of the population exposed in the glulisine group and is consistent with the current epidemiologic data available for this age category. The MAH argued that it seems possible to extrapolate the data observed for the population over 8 years exposed in the study to the particular age category ≥6 and < 8 years. The MAH also put forward that according to general experience in insulin therapy, there is no medical rationale supporting a difference in efficacy when considering the paediatric population below or above the age of 8 years.

The CHMP acknowledged the MAH arguments and agreed to an indication in the age group 6 to 17 years of age. However, since experience in the younger children is regarded as limited while the incidence of serious hypoglycaemia was somewhat higher in the younger subgroups of the trial, the MAH was requested to undertake certain activities as defined in the RMP (section 2.4) and in the list of follow-up measures in order to gain further knowledge in the younger patients.

2.3 SPC and PL

Further to the new indication, the SPC sections 4.1, 4.2 and 5.1 have been updated. Sections 1 and 2 of the PL have been updated accordingly. Annex II has been updated to include the revised PSUR cycle.

2.4 Pharmacovigilance and Risk Management Plan

The MAH did not consider there was a need for a Risk Management Plan (RMP) for this application, as it was to extend the target population in an approved indication, and there were no new or unexpected safety signals identified in the newly submitted data. However, within this type II variation procedure the CHMP considered a RMP to be necessary in view of the still limited data in the younger population. The MAH was therefore requested to submit a RMP. A summary of the RMP is presented in the table below.

The CHMP, having assessed the data submitted in the application, was of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Summary of the RMP

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	SPC 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	SPC sections 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	SPC section 4.3: known hypersensitivity to insulin glulisine or to any of the excipients is a contraindication to its use SPC SPC section 4.8 (general disorders): informs about this risk
Medication error	Routine pharmacovigilance 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 SPC of the relevant presentations
Antigenicity	Routine pharmacovigilance	Theoretical risk only, not described in the SPC
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	SPC sections 4.2 and 5.1: states 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	SPC section 4.6: informs about the lack of adequate data in pregnancy

3. OVERALL CONCLUSION AND BENEFIT RISK ASSESSMENT

The MAH submitted one pharmacokinetic study and one safety and efficacy clinical trial in support of the proposed extension of indication to the treatment of adolescents and children of 4 years old or above with diabetes mellitus where treatment with insulin is required.
The data provided for children below 6 years of age were regarded by the CHMP as too limited but it was considered acceptable to extrapolate the results observed in the study population over 8 years to the subgroup of children aged between 6 and 8 years.

The CHMP was therefore of the opinion that the benefit-risk is positive for the treatment of diabetes mellitus in the adolescents and children from the age of 6 years. However, in order to gain further knowledge in the younger patients the MAH is to undertake certain activities as defined in the RMP (section 2.4) and in the list of follow-up measures. In particular the MAH is to submit 6 monthly PSURs until the renewal of the marketing authorisation.