26 March 2015
EMA/229285/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Apidra

International non-proprietary name: insulin glulisine

Procedure No. EMEA/H/C/000557/P46 039

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Invented name of the medicinal product:	Apidra
INN (or common name) of the active substance(s):	Insulin glulisine
MAH:	Sanofi-Aventis Deutschland GmbH
Currently approved Indication(s)	Treatment of adults, adolescents and children, 6 years or older with diabetes mellitus, where treatment with insulin is required.
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes, insulins and analogues for injection, fast-acting (A10AB06)
Pharmaceutical form(s) and strength(s):	Solution for injection Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg)

1. Introduction

On 18 December 2014, the MAH submitted a completed paediatric study for Apidra, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study APIDR_L_04884 'A study of effectiveness and safety of Apidra in combination with Lantus therapy in basal-bolus insulin regimen in inadequately controlled children and adolescents with Type 1 diabetes (T1DM) in the Russian Federation' is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The commercially available formulation was used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study APIDR_L_04884 'A study of effectiveness and safety of Apidra in combination with Lantus therapy in basal-bolus insulin regimen in inadequately controlled children and adolescents with Type 1 diabetes in the Russian Federation'.

2.3.2. Clinical study

Study APIDR_L_04884: 'A study of effectiveness and safety of Apidra in combination with Lantus therapy in basal-bolus insulin regimen in inadequately controlled children and adolescents with Type 1 diabetes in the Russian Federation'

Description

Methods

Objective(s)

Primary

- To observe the proportions of patients who achieved HbA1c level < 8% in children aged 6-12 years and < 7.5 % in adolescents aged 13-17 years, at 6 and 12 months of treatment. The target HbA1c was chosen to meet the American Diabetes Association (ADA) age-specific recommendations.

Secondary

- To observe changes from baseline in HbA1c levels at 6 and 12 months of insulin glulisine treatment

- To observe changes from baseline in daily dose of insulin glargine and insulin glulisine at 6 and 12 months of treatment
- To observe the monthly rate of hypoglycaemia events per patient reported from the baseline to the end of the study.

Study design

This was a national, multi-centre, non-comparative, open-label, prospective phase IV study, conducted between 17 May 2011 (date first patient enrolled) and 18 October 2012 (date last patient completed the study). The study was conducted in 8 centres in Russia.

The total duration of study participation for each patient was approximately 12 months, including the following 2 periods:

• A screening period of 1-2 weeks

• A treatment observation period of 12 months.

Study population /Sample size

Number of subjects

Originally 210 subjects were planned for enrolment in the study. However, samples of insulin glulisine were provided to patients during the study and during the study it became apparent that insulin glulisine was not included in the Federal reimbursement list as it was expected before the study start. In Russia all patients with T1 Diabetes have status of invalids and receive insulin free of charge mostly through the Federal Reimbursement list. Therefore, it was a common decision of the team (Medical, CSU) to limit the number of patients up to 100 to avoid further switching to another insulin after the study end and focus on enrolment only in regions where patients were capable to receive insulin glulisine after the study end. This study adjustment was approved by independent National Ethical Committee

Diagnosis and criteria for inclusion

Children and adolescents aged 6 to 17 years, with T1DM of duration of more than 1 year and inadequate glycaemic control (8% ≤ HbA1c ≤ 10%) were enrolled in the present study. Patients were treated, before the start of the study, with insulin glargine and any short acting insulin as a basal-bolus regimen; they were able to perform self-monitoring of blood glucose (SMBG) as requested by the study protocol; and they had a signed consent form.

Treatments

Investigational medicinal products:

Insulin glulisine: Apidra (100 U/ml) in a cartridge containing 3 ml for the reusable insulin pen OptiClick

Insulin glargine: Lantus (100 U/ml) in a cartridge containing 3 ml in the pre-filled insulin pen SoloStar

Route of administration:

Insulin glulisine: subcutaneous injection in accordance with labelling

Insulin glargin: subcutaneous injection in accordance with labelling

Dose regimen:

Patients were treated with insulin glargine and insulin glulisine in basal-bolus regimen.

Insulin glargine: continued titration according to recommendations of treatment children and adolescents. The administration of insulin glargine was done once daily through a subcutaneous injection. The dose of insulin glargine was individually adjusted.

Insulin glulisine: the initial dose of insulin glulisine was selected individually. Physicians were advised to use the calculation based on carbohydrate counting. The administration of insulin glargine was done before meal (0-15) minutes, or within 20 minutes after a meal start. Dose was titrated in accordance with the algorithm to achieve the following targets:

Plasma glucose levels before meals:

Children 6-12 years including 5-10 mmol / L;

Children 13-17 years old 5-7,3 mmol / L;

Plasma glucose levels at bedtime / night:

Children 6-12 years including 5,6-10 mmol/ L;

Children 13-17 years old 5-8,4 mmol / L;

Assessment of the treatment regimen compliance

The treating physician analysed the detailed information about the precise dose and the time to administrate insulin on days when the glycaemic profile was conducted. This information was inserted in the patient's self-control diary.

Dose titration was based on the results of the patient' own monitoring of glucose level. For this purpose patients used glucose meters to define the plasma glucose. The latter were provided by the sponsor at the beginning of the study.

No extra assessment of the treatment regimen compliance was conducted.

Outcomes/endpoints

Efficacy

Primary endpoint

- The proportions of patients who achieved HbA1c level < 8% in children aged 6-12 years old, and < 7.5 % in adolescents aged 13-17 years old, at 6 and 12 months of treatment.

Secondary endpoints

- Mean change from baseline in HbA1c levels at 6 and 12 months of treatment in the overall population and in each age subgroup (i.e. children and adolescents)
- Mean change from baseline in daily dose of insulin glulisine at 6 and 12 months of treatment in the overall population and in each age subgroup.

Safety

Safety was assessed through recording the monthly rate of hypoglycaemia events per patient from baseline to the end of the study; all adverse events (AEs) including serious adverse events (SAE) at each visit; and assessment of vital signs, physical examination (including body weight) and laboratory results.

Hypoglycaemic events were categorised based on the following definitions:

- *Symptomatic hypoglycaemia was* defined as event with typical symptoms of hypoglycaemia following blood glucose change ≤ 3.9 mmol/L
- *Nocturnal hypoglycaemia* was defined as event, which happened during the sleep time (after falling asleep or before wakeup)
- *Severe hypoglycaemia* was defined as an event with clinical symptoms that are considered to result from hypoglycaemia, requiring the assistance of another person for active administration of carbohydrate, glucagon or other countermeasure because the patient could not treat her/himself.

Statistical Methods

The study was aimed to observe the proportions of patients who achieved HbA1c target during the study period. It did not test any specific hypothesis.

All the studied populations were described using descriptive statistics.

Efficacy

The efficacy population was defined as population of patients who received at least one dose of insulin glulisine, signed an informed consent, and had no inclusion/exclusion criteria violations (modified ITT population).

Safety

Safety population was defined as population of patients who received at least one dose of insulin glulisine as reported in the case report form (CRF).

Hypoglycemic events were collected during the study treatment. Treating physicians collected information recorded in patient's "Self-control diary" and reported it in the CRF.

Results

Recruitment / Number analysed

Overall, 100 patients were enrolled in the study, of whom 90 patients were treated and analysed in the mITT population. The remaining 10 patients were excluded due to protocol non-compliance linked to the Investigational Product (insulin glargine): During the monitor's call it was noticed that the investigator in one study centre provided to these 10 enrolled patients insulin cartridges through a federal reimbursement program (like real practice) rather than the study samples of insulin.

In addition, one patient (age group from 6 to 12 years old) was lost to follow-up after refusal to take part on study visit 13.

A total of 89 patients completed the study.

Baseline data

The efficacy analysis population (mITT) included 44/90 (48.9%) female and 46/90 (51.1%) male patients.

The median age was 12.5 years: 45 patients were in range 6 -12 years old (50%) and the other 45 were in range 13 -17 years old (50%).

The mean ±SD diabetes mellitus duration was 5.51±3.08 years (median = 5 years).

Mean ±SD weight was 48.9±16.6 kg; mean ±SD body mass index (BMI) was 19.5±3.2 kg/m2.

Efficacy results

Primary efficacy analysis:

Patients 6-12 years old

In this subgroup, 22/45 (48.9%) of patients and 23/45 (51.1%) of patients achieved HbA1c < 8% at 6 and 12 months of treatment, respectively.

14/45 patients (31.1%) achieved HbA1c < 8% at 12 months of treatment without symptomatic hypoglycaemia episodes.

Patients 13-17 years old

In this subgroup, 10/45 (22.2%) of patients and 14/45 (31.1%) of patients achieved HbA1c < 7.5% at 6 and 12 months of treatment respectively.

6/45 patients (13.3%) achieved HbA1c < 7.5% at 12 months of treatment without symptomatic hypoglycaemia episodes.

Assessor's Comments:

Patients recruited into Study APIDR_L_04884 had 'poor glycaemic control' as defined by '8% ≤ HbA1c ≤ 10%'. No details or discussion are provided by the MAH as to the potential reasons for their previous poor glycaemic control. Compliance in this study was assessed by review of entries in the patient's self-control diary.

On review of the percentage of patients that achieved age-specific pre-specified Hba1C levels, these are generally in-keeping with those seen in the previously conducted pivotal trial (HMR1964D-3001 – parallel-group controlled study) in paediatric subjects supporting the variation to extend the indication for Apidra to adolescents and children aged 6 years and above that was approved in 2008.

Secondary efficacy analysis*:*

Dynamics of the glycated (HbA1c) evaluation

Assessment of the dynamics of the level of HbA1c against the background of the conducted insulin therapy was carried out in each age group after 3 (visit 6), 6 (visit 10), 9 (visit 14) and 12 (visit 18) months since the beginning of therapy.

Dynamics of the HbA1c level with all the patients

		HbA1c (visit 1)	HbA1c (visit 6)	HbA1c (visit 10)	HbA1c (visit 14)	HbA1c (visit 18)
N	Valid	90	90	90	89	89
	Missed	0	0	0	1	1
Mean		8.7606	8.2967	8.3067	8.2978	8.0022
Median		8.6000	8.2000	8.2500	8.1000	7.9000
Std. deviation		0.58944	1.29289	1.16742	1.24234	1.08743
Minimum		8.00	3.70	4.40	5.70	4.50
Maximum		10.00	12.50	11.40	12.70	11.00
Percentiles	25	8.2000	7.6000	7.4750	7.4500	7.3000
	50	8.6000	8.2000	8.2500	8.1000	7.9000
	75	9.2000	9.1250	9.1250	9.0000	8.7500

At baseline mean ±SD HbA1c level was 8.8±0.6%. At 6 months of the therapy the mean ±SD HbA1c value was 8.3±1, 2%. At 12 months of the therapy, mean ±SD HbA1c value was 8.0±1.1%,(p<0.001 from baseline).

Dynamics of the HbA1c level in each group

Age groups			HbA1c (visit 1)	HbA1c (visit 6)	HbA1c (visit 10)	HbA1c (visit 14)	HbA1c (visit 18)
6 - 12 years old	N	Valid	45	45	45	44	44
		Missed	0	0	0	1	1
	Mean		8.75	8.27	8.30	8.39	8.05
	Median		8.60	8.10	8.00	8.00	7.90
	Std. deviation		0.60	1.27	1.14	1.27	1.06
	Minimum		0.36	1.61	1.30	1.62	1.12
	Maximum		8.00	5.30	6.30	6.60	6.20
	Percentiles		10.00	11.30	10.70	12.70	11.00
	N	25	8.20	7.50	7.35	7.50	7.30
		50	8.60	8.10	8.00	8.00	7.90
		75	9.20	9.15	9.40	9.45	8.78
13 - 17 years old	N	Valid	45	45	45	45	45
		Missed	0	0	0	0	0
	Mean		8.77	8.32	8.32	8.21	7.96
	Median		8.70	8.30	8.40	8.20	7.90
	Std. deviation		0.58	1.33	1.21	1.22	1.12
	Minimum		0.34	1.77	1.46	1.49	1.26
	Maximum		8.00	3.70	4.40	5.70	4.50
	Percentiles		10.00	12.50	11.40	12.70	10.40
	N	25	8.25	7.65	7.60	7.35	7.35
		50	8.70	8.30	8.40	8.20	7.90
		75	9.20	9.15	8.95	8.75	8.65

Patients 6-12 years old

At baseline mean ±SD HbA1c level in this subgroup was 8.6±0.6%. At 12 months of the therapy mean ±SD HbA1c value was 8.1±1.1%, (p=0.04).

Patients 13-17 years old

At baseline mean ±SD HbA1c level in this subgroup was 8.8±0.6%. At 12 months of the therapy, mean ±SD HbA1c value was 7.9±1.1% (p=0.02).

Assessor's Comments:

At 12 months, in both age groups, a clinically relevant reduction in mean Hba1c levels was seen. Reductions in HbA1c levels were apparent at the 3 month visit and continued through to 12 months.

Analysis of the insulin dosage dynamics in the course of the treatment

Insulin Glargine

At baseline mean ±SD insulin glargine dose was 17.0±8.2 IU (median= 15.5 IU) or 0.3 IU/kg. After 6 months of the therapy mean ±SD insulin glargine dose was 17.9±8.1 IU (median = 17 IU). At 12 months mean ±SD insulin glargine dose was 18.4±8.2 IU (median =18IU) or 0.4 IU/kg (p=0,80). Most of all patients used insulin glargine at bedtime.

Insulin Glulisine

At baseline mean ±SD insulin glulisine dose was 23.8 ± 10.3 IU (median= 22 IU) or 0. 5 IU/kg. After 6 months of the therapy mean ±SD insulin glulisine dose was 24.5 ± 11.4 IU, (median = 22 IU). At 12 months mean ±SD insulin glulisine dose was 25.9±11.6 IU (median =24.0 IU) or 0.6 IU/kg. Mean SD dose change from baseline was not statistically significant (p=0, 65)

Insulin dosage calculated by body weight

The average daily insulin glargine dosage calculated by body weight on visit 2 (baseline) was 0.349 IU/kg. By visit 18 (end of study) it increased to 0.388 IU/kg.

The average daily insulin glulisine dosage calculated by body weight on visit 2 (baseline) was 0.5 IU/kg. By visit 18 (end of study) it further increased to 0.599 IU/kg.

Insulin dosage calculated by body weight (IU/kg)

	Visit №				
	2	**6**	**10**	**14**	**18**
Insulin glargine dosage/BW	0.349	0.392	0.376	0.397	0.388
Insulin glulisine dosage before breakfast/BW	0.168	0.179	0.171	0.180	0.185
Insulin glulisine dosage before lunch/BW	0.168	0.180	0.177	0.184	0.190
Insulin glulisine dosage before dinner/BW	0.164	0.180	0.178	0.182	0.184

The average total daily insulin dosage by body weight was 0.85 IU/kg at baseline. By Visit 18 (end of study) it increased to 0.94 IU/kg.

Assessor's Comments:

The increases in rapid acting and basal insulin requirements are in-line with those seen during the 6 month period of study HMR1964D-3001.

Analysis of glycaemic profile

Analysis of the weekly glycaemic profile

The glycemic profile was analyzed with all the patients in the course of the conducted treatment. The self-monitoring of the glucose level was performed by all the patients of both age groups. The

glucose level before breakfast, before the main meal and 2 hours later after the main meal was assessed on each day of the therapy.

Dynamics of the weekly glycaemic profile in the age group 6-12 years old group:

	Visit №							
	3	4	5	6	7	8	9	10
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Fasting Plasma Glucose	8.79	8.58	8.89	8.03	9.42	8.81	9.13	9.48
Plasma glucose before the main meal	9.54	8.98	8.99	10.12	9.23	9.48	10.16	9.89
Glycemia 2 hours after the main meal	8.57	8.97	8.22	8.37	8.28	8.67	8.24	8.56

	Visit №							
	11	12	13	14	15	16	17	18
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Fasting Plasma Glucose	9.08	9.00	9.06	8.56	9.90	8.99	8.71	9.31
Plasma glucose before the main meal	9.42	9.49	8.93	9.30	9.53	9.24	8.95	9.02
Plasma glucose 2 hours after the main meal	8.55	8.89	8.68	7.77	8.18	8.30	7.94	8.96

Dynamics of the weekly glycaemia profile in the 13-17 years old group:

	Visit №							
	3	4	5	6	7	8	9	10
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Fasting Plasma Glucose	8.00	8.16	8.30	6.77	7.54	7.89	7.93	7.61
Plasma glucose before the main meal	8.25	9.50	8.46	8.44	8.70	8.12	8.92	8.14
Plasma glucose 2 hours after the main meal	8.60	8.96	9.01	7.95	8.31	8.12	8.44	8.42

	Visit №							
	11	12	13	14	15	16	17	18
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Fasting Plasma Glucose	7.07	7.36	7.05	7.33	7.19	7.38	7.47	7.21
Plasma glucose before the main meal	7.96	8.17	7.69	7.88	8.39	8.02	7.89	8.77
Plasma glucose 2 hours after the main meal	7.85	8.09	8.01	7.98	8.39	8.17	8.12	8.24

Analysis of the plasma glucose profile by 3 points

The glucose profile analysis was conducted at the same time. This analysis was carried out taking into account the following 3 points (before breakfast, before the main meal and 2 hours after the main meal). The variables were recorded during 3 different days of the week prior to each visit.

The dynamics of the average daily plasma glucose level was also analysed with all the included patients.

Dynamics of the average daily glycaemia mean variable on a visit:

		Visit №							
		3	4	5	6	7	8	9	10
		Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
	6 - 12 years old	9.03	9.57	9.07	9.20	9.04	9.17	9.46	9.04
	13 - 17 years old	8.79	8.42	8.71	8.09	8.24	8.24	8.36	8.47

		Visit №							
		11	12	13	14	15	16	17	18
		Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
	6 - 12 years old	9.38	9.02	8.87	8.70	8.92	8.24	8.68	8.79
	13 - 17 years old	8.02	8.00	7.83	7.98	7.74	7.89	7.95	7.75

Safety results

Adverse events

Summary of the adverse event profile

Adverse events were reported with 53 (58.9%) patients, with a total of 182 adverse events.

Three patients experienced 10 AE each; 22 (24.4%) of patients experienced 3 to 9 AEs; 12 (13.3%) patients experienced 2 AEs: and 16 patients (17.7%) experienced only 1 AE during the overall treatment period.

The most frequently reported AEs in terms of System Organ Class (SOC) were systemic general state disturbances (85/182 events, 46.7%), followed by nervous system disorders (23/182 events, 12.6%), then infections and invasions (18/182 events, 9.9%).

The most frequently reported AEs in terms of Preferred Terms (PT) were flu-like symptoms (83/182 cases, 45.6%), headache (16/182 cases, 8.8%), and acute rhinitis (10/182 cases, 5.5%). Acute pharyngitis and vomiting were each reported in 5/182 cases (2.7%).

The majority of the cases were of mild and mild-to-moderate severity.

Serious adverse events were reported with 5 patients (5.56%), with a total of 7 serious AEs.

Hospitalization was necessary in 7/182 (3.84%) of reported adverse events.

Serious adverse events and deaths

Overall 7 serious adverse events were reported with 5 patients. There were no fatal cases reported

Serious adverse events

	Number	Percentage
Hypoglycemia	4	57.1
Diabetic ketoacidosis	1	14.3
Polyneuropathy	1	14.3
Epileptic seizure	1	14.3
Total	**7**	**100.0**

- Patient 1- serious hypoglycaemia. The cause of hypoglycaemia was not mentioned by the investigator.
- Patient 2- diabetic ketoacidosis. The investigator didn't associate the SAE with the investigational product. Same patient– 2 episodes of serious hypoglycaemia. In both cases

the investigator associated the SAE with the investigational product (insulin glargine). Patient continued to receive insulin glargine.

- Patient 3 - chronic inflammatory demyelinating polyradiculopathy. The investigator didn't associate the SAE with the investigational product.
- Patient 4 - epileptic seizure. Assessed by the investigator as related to insulin glargine and evaluated as life-threatening. The study drug was discontinued.
- Patient 5- serious hypoglycaemia. The investigator didn't associate the SAE with the investigational product.

Assessor's Comments:

The number of patients that reported a serious adverse event was low. Only one patient discontinued the study drug – in this case the patient had an epileptic seizure that was assessed as related to insulin glargine.

No deaths were reported in the study.

No new safety signals were identified.

Analysis of hypoglycaemia events

Overall 1866 events of hypoglycaemia were reported in 77/90 (85.6%) patients. The distribution of the hypoglycaemia events was analysed and three categories were reported: symptomatic, asymptomatic, and severe hypoglycaemia. Testing hypoglycaemia incidence difference by group was not planned in the safety analysis.

The highest frequency of hypoglycaemia events was reported for symptomatic hypoglycaemia with 1844 (98.8%) events *versus* 22 (1.2%) events of asymptomatic hypoglycaemia.

In total, 1672 (90.7%) events of symptomatic hypoglycaemia were reported during daytime and 172 (9.3%) at night time. All 22 events of asymptomatic hypoglycaemia occurred during daytime.

A total of 53 (2.84%) events of severe hypoglycaemia were reported.

Thirteen (14.4%) patients did not report any episode of hypoglycaemia during the study period.

Overall 20.7 events per patient per year were reported during the study. Overall, 4 serious hypoglycaemia events were reported. In all these cases patients had to be hospitalized; in 3 out of 4 cases the reason for serious hypoglycaemia according to the physician was intensive physical activity, and in one case the reason was not provided.

In total hospitalisation was required in 5 (0.3%) of the hypoglycaemia episodes.

Assessor's Comments:

The percentage and incidence of hypoglycaemic events is in-keeping with that seen previously.

The number of severe hypoglycaemic events was low and within that seen previously.

Laboratory variables

Laboratory variables assessment was conducted after 6 and 12 months since the beginning of therapy. Values were available for all 90 patients at baseline and 6 months, data was available for 89 patients at 12 months.

AST, ALT and creatinine

There were no clinically significant changes in the mean variables of transaminase during the overall treatment period. The mean ± SD AST level did not change between baseline (16.8 ± 9.5 IU/l) and end of study (16.8 ± 8.7 IU/l). The mean ± SD ALT levels did not change between baseline (13.1 ± 6.7 IU/l) and end of study (13.6 ± 7.7 IU/l).

The mean ± SD serum creatinine levels during the treatment period slightly increased from 59.5±16.8 mmol/l at baseline to 61.2±18.8 mmol/l at end of study, but this small change was not clinically significant.

Blood pressure, body weight and waist-hip circumference

Blood pressure, body weight and waist-hip circumference were measured at baseline, 6 and 12 months.

Blood pressure

The mean ± SD systolic blood pressure at baseline was 105.97 ± 10.62 mmHg, and diastolic blood pressure was 63.26±6.35 mmHg. Blood pressure median was 110/60 mmHg.

At study end (visit 18), the mean ± SD systolic blood pressure was 107.82 ± 9.67 mmHg, diastolic blood pressure was 63.66 ± 7.16 mmHg. Blood pressure median was 110/60 mmHg.

Body weight

The mean ± SD weight of the patients in the overall population was 48.88 ± 16.59 kg on Visit 1. On the final visit (visit 18) the mean ± SD weight increased to 52.43±15.97 kg. No significant weight increase in the course of the therapy was detected by the ANOVA statistical test.

		Weight (visit 1)	Weight (visit 2)	Weight (visit 6)	Weight (visit 10)	Weight (visit 14)	Weight (visit 18)
N	Valid	90	90	90	90	89	89
	Missed	0	0	0	0	1	1
Mean		48.88	48.94	49.72	50.73	51.59	52.43
Median		49.05	49.65	51.85	53.20	53.70	53.00
Std. deviation		16.59	16.60	16.37	16.16	16.01	15.97
Minimum		21.00	21.00	21.00	22.00	21.00	22.30
Maximum		90.00	90.00	91.20	90.20	91.20	90.00
Percentile	25	36.00	36.18	37.00	38.22	39.05	41.00
	50	49.05	49.65	51.85	53.20	53.70	53.00
	75	60.63	60.63	61.25	60.75	61.15	62.00

Waist-hip circumference

Waist circumference**,** measured on all patients, was 68.0 ± 10.8 cm (median, 67.0 cm) at baseline and increased to 69.9 ± 11.0 cm (median, 69.0 cm) at the end of study. Waist-hip circumferences ratio (WHR) was 0.80 ± 0.064 at baseline, and did not change (0.81±0.09) at end of study.

2.3.3. Discussion on clinical aspect

This was an open-label, stand-alone study with no comparator arm in inadequately controlled children and adolescents with Type 1 Diabetes. Originally it was planned to enrol 210 subjects in the study. However, during the study it became apparent that insulin glulisine was not included in the Federal reimbursement list. Therefore, a decision was made to limit the number of patients up to 100 to avoid subjects having to switch to another insulin after the study end and focus on enrolment only in regions where patients were capable to receive insulin glulisine after the study end.

There are a number of limitations to this study, including the open-label non-comparator design, the number of patients enrolled and the lack of details on the reasons for subjects having poor glycaemic control prior to inclusion in the study – for example whether this was due to previous poor compliance.

However, notwithstanding above, the improvements seen in Hba1c levels seen in children aged 6-12 years and 13-17 years are generally in-keeping with those seen in the previous pivotal clinical trial in children and adolescents.

There were no deaths during the study. The number of serious adverse events and serious hypoglycaemic events was low. The percentage and event rate for hypoglycaemia is within that seen previously. No new safety signals were identified in this trial.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

The MAH has submitted the results of a completed paediatric study for Apidra (APIDR_L_04884), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. This is a stand-alone study.

Based on the data submitted, there are no changes to the risk benefit balance of Apidra in the licensed indication and no changes to the product information are required.

Recommendation

☒ Fulfilled:

No regulatory action required.

Additional clarifications requested

Not applicable.