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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	ClinicalTrials.gov Identifier:	NCT00526513
		Study Code:	APIDR_L_01913
Generic drug name:	Insulin glulisine	Date:	10/Sep/2010

Title of the study:	Safety And Effectiveness Of Apidra® In Combination With Basal Insulin In Patients With Type 1 & 2 Diabetes Mellitus (SCALE) APIDR_L_01913		
Investigator(s):	Multicenter		
Study center(s):	Country: Egypt Opened sites: 30 Active sites: 27		
Publications (reference):	None		
Study period:	Date first subject enrolled: 18 July 2007 Date last subject completed: 14 May 2008		
Phase of development:	Post Marketing, Phase IV		
Objectives:	Primary: To determine the effect of insulin glulisine on glycemic control (HbA1c, FBG, 2-h ppBG) from baseline to the end of the study. Secondary: To evaluate the safety of insulin glulisine in a basal/bolus regimen by monitoring of the incidence of hypoglycaemia and other adverse events.		
Methodology:	This is a prospective, multi-center, open-label, non-comparative phase IV study of 24 weeks treatment duration. Each investigator was encouraged to enroll type 1 and type 2 patients in a ratio of 25/75%.		
Number of Subjects:	Planned: 240	Randomized: NA	Treated: 171
Evaluated:	Efficacy: Per protocol: 112 Intention-to-Treat: 145 (3 months) & 127 (6 months) Drop out: 14	Safety: 171	

Diagnosis and criteria for inclusion:	Inclusion criteria ▪ Patients with type 1 or type 2 diabetes mellitus previously treated for ≥ 6 months with prandial insulin (lispro or aspart) + basal insulin or premixed insulin (Type 1) or by either basal insulin + OAD or basal insulin+ RHI or other short acting insulin analogue (lispro or aspart) or premixed insulin (Type 2) with HbA1c >7.0%. ▪ Age 18-65 years ▪ Signed informed consent prior to beginning protocol specific procedures ▪ Adequate hepatic and renal functions Exclusion criteria ▪ Pregnant or lactating women or women of childbearing potential not using adequate contraception. ▪ Patients with hypersensitivity to insulin glulisine or to any of the excipients. ▪ History of diabetic ketoacidosis. ▪ Diabetic retinopathy with surgical treatment (laser photocoagulation or vitrectomy) in the 3 months prior to study entry or which may require surgical treatment within 3 months of study entry. ▪ Clinically relevant illnesses or uncontrolled medical conditions making implementation of the protocol difficult.
Investigational product: Dose:	Apidra® Optiset® Patients received insulin glulisine at meal times (0-15 minutes before each / any meal – breakfast, lunch & dinner), 1 to 3 injections a day based on the condition of the patient in addition to basal insulin SC injection at bedtime. Doses were titrated according to a predefined algorithm.
Administration:	Subcutaneous injection.
Duration of treatment: 6 months	Duration of observation: Not applicable
Criteria for evaluation:	
Efficacy:	Primary Analysis Variable ▪ HbA1c: mean change from baseline to endpoint. Secondary Analysis Variables ▪ Fasting blood glucose (FBG): mean change from baseline to endpoint. ▪ 2 hours post prandial blood glucose (2-h ppBG): mean change from baseline to endpoint.
Safety:	- All patients (intention-to-treat population) were analyzed for safety. - Incidence of hypoglycaemic events - Incidence of adverse events
Statistical methods:	The study group was analyzed for demographic variables, background variables, and other variables with appropriate statistics i.e. frequency tables (count and percent) and/or descriptive statistics (mean, standard deviation, standard error, minimum, lower quartile, median, upper quartile and maximum) Efficacy: Mean change of HbA1c, FBG and 2-h ppBG from baseline to endpoint. Analysis of all efficacy variables was performed for both evaluable populations (per protocol and intention-to-treat). Statistical analysis was performed using paired t- test (FBG; 2h-ppBG) or repeated measure ANOVA (HbA1c). Safety: Incidence of adverse events incl. serious adverse events, hypoglycaemic events. Analysis of safety variables was performed on intention-to-treat population. Statistical analysis was performed using frequency tables and chi-square tests.

Summary:

Baseline characteristics of patients:

Parameter	Type 1 N=67	Type 2 N=104	Overall N=171
Mean age ± SD (years)	28.0 ± 12.1	53.6 ± 8.9	43.7 ± 16.2
Gender (N/%)			
Males	22 (33%)	45 (43%)	67 (39%)
Females	45 (67%)	59 (57%)	104 (61%)
BMI (kg/m²)	26	31	29
Mean diabetes duration ± SD (years)	11.7 ± 9.3	11.1 ± 7.1	11.3 ± 8.0
Pretreatments (N/%)			
Basal insulin			
- NPH	14 (21%)	33 (32%)	47 (28%)
- Lantus (glargine)	28 (42%)	35 (34%)	63 (38%)
- Levemir (detemir)	0 (0%)	6 (6%)	6 (4%)
Bolus insulin			
- regular human insulin	23 (34%)	25 (24%)	48 (29%)
- short-acting analog	3 (4.5%)	4 (3.9%)	7 (4%)
Premixed insulin	25 (37%)	33 (32%)	58 (35%)
OADs	7 (10%)	69 (66%)	76 (46%)

Efficacy results:

One patient was excluded from the efficacy analysis due to protocol violation (HbA1c <7.0%). This patient was included in all safety analyses.

Results for the Intention-to-Treat population:

Overall population				
Measure	Baseline	3 months	6 months	Intention-To-Treat
HbA1c (%)				
Number of patients	158	145	127	ANOVA p<0.0001
Mean	9.98	8.66	8.10	
SD	2.14	1.95	2.02	
difference from baseline		-1.32	-1.88	
Fasting blood glucose (mg/dL)				
Number of patients	164		102	t-test p<0.0001
Mean	221.7		158.5	
SD	95.9		82.2	
difference from baseline			-63.2	
2-h pp blood glucose (mg/dL)				
Number of patients	156		100	t-test, p<0.0001
Mean	276.2		185.4	
SD	109.5		78.8	
difference from baseline			-90.8	

Results for the per protocol population:

Overall Population				
Measure	Baseline	3 months	6 months	Per Protocol
HbA1c (%)				
Number of patients	112	112	112	Repeated Measures ANOVA, p<0.0001
Mean	9.96	8.72	8.01	
SD	2.05	1.94	1.96	
difference from baseline		-1.24	-1.95	
Fasting blood glucose (mg/dL)				
Number of patients	99		99	Paired t-test, p<0.0001
Mean	219.0		159.0	
SD	96.5		82.9	
difference from baseline			-60.0	
2-h pp blood glucose (mg/dL)				
Number of patients	91		91	Paired t-test, p<0.0001
Mean	278.8		188.1	
SD	109.4		78.9	
difference from baseline			-90.7	

Results for type 1 diabetes patients (intention-to-treat population):

Type 1 patients				
Measure	Baseline	3 months	6 months	Intention-to-Treat
HbA1c (%)				
Number of patients	59	54	51	ANOVA, p<0.001
Mean	10.28	9.18	8.77	
SD	2.14	2.07	2.27	
difference from baseline		-1.10	-1.51	
Fasting blood glucose (mg/dL)				
Number of patients	63		39	t-test, p<0.01
Mean	232.9		171.9	
SD	117.0		105.6	
difference from baseline			-61.0	
2-h pp blood glucose (mg/dL)				
Number of patients	59		37	t-test, p<0.001
Mean	247.5		176.0	
SD	111.0		79.5	
difference from baseline			- 71.5	

Results for type 1 diabetes patients (per protocol population):

Type 1 patients				
Measure	Baseline	3 months	6 months	Per Protocol
HbA1c (%)				
Number of patients	40	40	40	Repeated Measures ANOVA, p<0.0001
Mean	10.45	9.39	8.71	
SD	2.03	2.02	2.24	
difference from baseline		-1.06	-1.74	
Fasting blood glucose (mg/dL)				
Number of patients	36		36	Paired t-test, p<0.01
Mean	220.7		174.6	
SD	114.1		108.8	
difference from baseline			-46.1	
2-h pp blood glucose (mg/dL)				
Number of patients	31		31	Paired t-test, p<0.001
Mean	244.2		183.5	
SD	106.1		80.0	
difference from baseline			-60.7	

Results for type 2 diabetes patients (intention-to-treat population):

Type 2 patients				
Measure	Baseline	3 months	6 months	Intention-to-Treat
HbA1c (%)				
Number of patients	99	91	76	ANOVA, p<0.0001
Mean	9.81	8.35	7.65	
SD	2.13	1.81	1.71	
difference from baseline		-1.46	-2.16	
Fasting blood glucose (mg/dL)				
Number of patients	101		63	t-test, p<0.0001
Mean	214.7		150.2	
SD	79.9		63.1	
difference from baseline			-64.5	
2-h pp blodd glucose (mg/dL)				
Number of patients	97		63	t-test, p<0.0001
Mean	293.6		190.8	
SD	105.3		78.5	
difference from baseline			-102.8	

Results for type 2 diabetes patients (per protocol population):

Type 2 patients				
Measure	Baseline	3 months	6 months	Per Protocol
HbA1c (%)				
Number of patients	72	72	72	Repeated Measures ANOVA, p<0.0001
Mean	9.69	8.35	7.62	
SD	2.03	1.81	1.68	
difference from baseline		-1.34	-2.07	
Fasting blood glucose (mg/dL)				
Number of patients	63		63	Paired t-test, p<0.0001
Mean	218.0		150.2	
SD	85.8		63.1	
difference from baseline			-67.8	
2-h pp blood glucose (mg/dL)				
Number of patients	60		60	Paired t-test, p<0.0001
Mean	296.7		190.5	
SD	107.6		79.0	
difference from baseline			-106.2	

Safety results:

Overall Adverse Events	Number	% from total study population
Adverse events	6	3.5%
Serious adverse events	3	1.8%
All hypoglycaemia	68	39.8%
Severe hypoglycaemia	2	1.2%

Type 1 patients: Adverse Events	Number	% from total study population
Adverse Events	3	5.1%
Serious adverse events	2	3.4%
All hypoglycaemia	51	86.4%
Severe hypoglycaemia	2	3.4%

Type 2 patients: Adverse Events	Number	% from total study population
Adverse events	3	3.0%
Serious adverse events	1	1.0%
All hypoglycaemia	17	17.2%
Severe hypoglycaemia	0	0.0%

IP Dosages & Titration:

Apidra (insulin glulisine):
91 out of 168 (54.2%) subjects had Apidra dose adjustment at visit 2. The mean initial dose of Apidra was 39.4 IU/day. In 80.2% of study subjects who had any dose adjustment the initial dose was increased on average by 29.6%, 42.3%, 58.3%, and 70.1% at visits 2, 3, 4 and 5, respectively. In contrast, in 19.8% of study subjects who had any dose adjustment the initial dose was decreased on average by -29.7%, -25.5%, -22.5%, and -18.3% at visits 2, 3, 4 and 5, respectively.

Basal insulin:
Basal insulin used during the study was 68% glargine, 25% NPH insulin, and 7% insulin detemir; 80 out of 168 (47.6%) subjects had basal insulin dose adjustment at visit 2. The mean initial basal insulin dose was 33.96 IU/day. In 67.5% of subjects who had any dose adjustment the initial dose was increased on average by 28.9%, 45.6%, 50.2%, and 60.0% at visits 2, 3, 4 and 5, respectively. In contrast, in 32.5% of study subjects who had any dose adjustment the initial dose was decreased on average by -31.9%, -28.2%, -25.1%, and -25.3% at visits 2, 3, 4 and 5, respectively.

Date of report: 04 May 2010