

Safety and Tolerability Assessment of Insulin Glulisine as Part of an Insulin Regimen in the Management of Filipino Diabetics

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Abstract

Background: Insulin glulisine is a new rapid-acting insulin analogue. Currently, few data are available on its safety and tolerability among patients in the Asia-Pacific region.

Objectives:

Primary Objective: To assess the safety and tolerability of insulin glulisine as part of an insulin treatment regimen in Filipinos with diabetes

Secondary Objectives:

1. To compare the change in glycosylated hemoglobin (HbA1c), fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) levels at baseline and after three and six months on an insulin treatment regimen with insulin glulisine
2. To measure patients' level of satisfaction in using the Insulin glulisine pen

Methods: This was a multicenter, observational, post-marketing surveillance study of adult patients (18 to <75 years old) with type 1 or type 2 diabetes mellitus who were prescribed with insulin glulisine as part of their diabetes treatment regimen, and signed a data release consent form. Patients who were pregnant and had known allergy to insulin glulisine and any of its excipients were excluded. Patients were followed up for treatment duration of six months inclusive of a baseline visit and two

follow up evaluations falling at third month and sixth months of treatment. The incidence of hypoglycemia and other adverse events was determined. Changes in baseline levels of HbA1c, FBG and PPBG were measured during follow-up visits at third and sixth months. Patient satisfaction with the Insulin glulisine pen was quantified using a five-point scale questionnaire.

Results: Among 1,805 patients included, 132 (7.31%) experienced hypoglycemia. The overall incidence of adverse events other than hypoglycemia was 0.78%. There was a significant reduction in baseline levels of HbA1c, FBG and PPBG during the follow-up visits at third and sixth months (all $p < 0.0001$). Patient satisfaction with using the pen was good to excellent.

Conclusion: This post-marketing surveillance study demonstrates the safety and tolerability of insulin glulisine when used as part of an insulin regimen in an actual clinical setting for the management of diabetes among Filipino patients. Insulin glulisine as part of a diabetes treatment regimen was effective in improving glycemic parameters. The glulisine pen was also well tolerated and accepted by patients.

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Keywords: insulin glulisine, diabetes mellitus, safety, hypoglycemia

Introduction

Achieving adequate glycemic control remains the primary goal of diabetes treatment. Traditionally, management has been through a staged approach, with stepwise intensification of pharmacological therapy matching disease progression. When oral antidiabetic drugs (OADs) fail to maintain HbA1c targets, use of

drug classes with greater and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, or consideration of insulin therapy may be required.¹

A consensus algorithm issued by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends the early use of basal insulin after third months of treatment with metformin in patients with HbA1c >8.5% or with episodes of hyperglycemia. According to this algorithm, intensification of the insulin regimen involves the addition of one to three pre-meal doses of short- or rapid-acting insulin to help control post-prandial glucose levels.¹

Relative to premixed insulin preparations, prandial plus basal insulin doses allow for better tailoring of

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treatment to individual patients' needs. Rapid-acting insulin analogues (RAIAs) were developed to provide greater flexibility in the administration of prandial insulin doses. Compared with regular human insulin, RAIAs have an earlier onset and shorter duration of action, allowing for finer titration of insulin and minimizing the risk of hypoglycemia.² When used with a basal insulin regimen, a single prandial RAIA dose before the main daily meal, with the stepwise addition of other boluses if needed, comprise the basal plus strategy. This allows for a smoother transition to a basal bolus regimen which involves the injection of basal insulin plus additional prandial insulin injections at each meal.³ RAIAs as prandial insulin in basal plus and basal bolus strategies currently provide the most physiological approach to insulin treatment.²

In the Philippines, close to half of patients on insulin were using newer insulin analogues in 2008.⁴ Insulin glulisine is a rapid-acting analogue insulin that was first introduced to the Philippine market in 2008. Yet, available data regarding its safety or acceptability among patients in the Philippine setting remains limited.

Objectives

The primary objective of this study was to assess the safety and tolerability of insulin glulisine as part of an insulin treatment regimen among Filipinos with diabetes. Secondary objectives were (1) to compare the change from baseline levels of HbA1c, FBG and PPBG after three and six months of treatment on an insulin treatment regimen with insulin glulisine; and (2) to measure patients' level of satisfaction with using the Insulin glulisine pen.

Methods

Study Design and Participants

This was a six-month multicenter, observational, post-marketing study. The doctors who participated in the study were endocrinologists, diabetologists, internists and general practitioners mostly based in Manila, Cebu and Davao. Patients between 18 to 74 years of age diagnosed with type 1 or type 2 diabetes mellitus and who were prescribed Insulin glulisine as part of their diabetes treatment regimen were eligible for study inclusion. Pregnant women or those with a known allergy to insulin glulisine or any of its excipients were excluded from the study. After a baseline evaluation, patients were started on insulin glulisine and scheduled for follow-up assessments after three and six months (Figure 1).

Procedures and data collection

Physicians who were using insulin glulisine in their

patient management were invited to participate in this study. All eligible patients signed a data release consent form before participating in the study. Baseline data, including HbA1c, FBG and PPBG levels were collected at the beginning of the study and patients were re-evaluated during follow-up visits scheduled at third and sixth months.

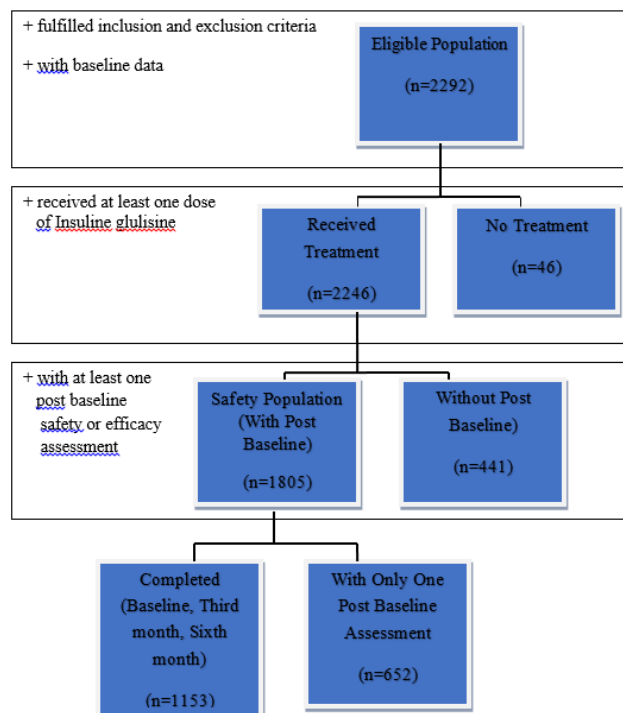


Figure 1: Study design of SPRINT

The assessment of the safety of insulin glulisine was based on the incidence of hypoglycemia as defined by the ADA Workgroup on Hypoglycemia:⁵

Severe hypoglycemia. An event requiring assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

Documented symptomatic hypoglycemia. An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL

Asymptomatic hypoglycemia. An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dL

Probable symptomatic hypoglycemia. An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose

determination, but was presumably caused by a plasma glucose concentration ≤ 70 mg/dL.

Relative hypoglycemia. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL.

Spontaneously reported adverse events other than hypoglycemia were also recorded based on their severity, seriousness, relationship to Insulin glulisine and outcome.

Patient satisfaction with the glulisine pen was evaluated using a standard validated Patient Satisfaction Questionnaire. Patients evaluated particular features of the pen (ie, ease of selecting the dose, ease of correcting a misdialled dose, ease of reading the insulin dose, ease of feeling and hearing the dialing clicks, force or effort needed to inject the insulin, smoothness or gentleness of injection, and ease of determining whether the desired dose was completely delivered) using a five-point rating scale (1 – excellent; 2 – good; 3 – acceptable; 4 – poor; and, 5 – very poor).

Data collection forms (DCFs) were used to record patient data and any adverse events (serious or non-serious). Investigators were instructed to report serious adverse events to the Sanofi Pharmacovigilance Office within 24 hours.

Data management was performed at the Clinical Studies Unit of Sanofi Philippines. Completed DCFs were collected from sites and encoded using Microsoft Access. Data rectification forms were generated using manual and system checks and sent to physicians for clarification. Query resolutions were used to update the clinical database.

The patient's medical history, pre-existing conditions and adverse events were summarized using the Medical Dictionary for Regulatory Activities (MedDRA) standard. MedDRA version 15.1 was used to code the terms into each respective system organ class and preferred term. Concomitant medications were coded by generic name (ATC5) and by anatomical subgroup (ATC1) using the World Health Organization Drug Dictionary Enhanced standard (WHO DDE, September 2012).

Statistical analysis

The Philippine FDA's sample size requirement was 3,000 or 10% of patients who received the study drug under monitored release. The Investigators who recruited patients in this study were representatives of the physicians in the Philippines who manage diabetes patients with insulin therapy.

Two analysis populations were defined. The safety population included all patients who received any

amount of Insulin glulisine with at least one post-baseline safety assessment. Analyses of effectiveness of outcomes were based on the effectiveness population, which included the patients enrolled in the study who had received at least one dose of insulin glulisine, did not have any major protocol violations, and had a baseline and at least one post-baseline HbA1c data available.

Baseline patient demographics (sex, age, weight, height and blood pressure) of the safety population were tabulated and summarized using frequencies, percentages, means and ranges. Safety and tolerability were based on the incidence and severity of hypoglycemia. Other adverse events were described using frequencies and percentages. Changes from baseline HbA1c, FBG and PPBG levels were compared using a 5.0% level of significance. Frequencies and percentages were used to describe the results of patient satisfaction questionnaires on using the insulin glulisine pen.

Results

Patient disposition

A total of 2,292 patients were screened and deemed eligible for inclusion in the study, of which 2,246 received at least one dose of Insulin glulisine. One thousand eight hundred five (1,805) patients were included in the safety population, while 1,714 patients comprised the effectiveness population (Figure 1). Six hundred fifty-two (652) patients (36.1%) did not complete the study; the most common reasons were lost to follow-up (n=382) and unspecified (n=181).

Baseline characteristics

Females comprised the majority of the safety population (54.0%). The mean age was 54.0 ± 11.5 years. Despite previous diabetes treatments, glycemic control was poor at baseline with less than 5% of patients with HbA1c $<7\%$ and/or fasting blood glucose <110 mg/dL. Hypertension and dyslipidemia were present in 62.0% and 65.0% of patients, respectively. Other baseline patient characteristics and concomitant medications for hypertension and dyslipidemia are described in Table I.

In the safety population, 84.7% of patients had been previously diagnosed with diabetes, most of whom had diabetes for five or more years. The most common diabetes complications were neuropathies (40.4%), microalbuminuria (31.4%) and proteinuria (27.6%, Table II). Previous insulin treatment included long-acting insulin (insulin glargine, 24.0%), intermediate-acting combined with fast-acting insulin (insulin human, 11.5%) and intermediate-acting insulin (insulin isophane, 3.2%, Table III). Previous use of OADs such as metformin (51.9%), glimepiride (15.2%) and gliclazide (11.3%) prior to the study was also

reported in some patients.

Duration and dose of insulin glulisine and concomitant antidiabetes treatment

The median duration of study treatment was 170 days with range of five to 512 days. Metformin was the most commonly prescribed OAD at baseline (46.3%), at three months (41.9%) and at six months (24.2%). Insulin glargine was the most common concomitantly prescribed insulin both at baseline and during follow-up visits, with 1,217 (67.4%) patients receiving this medication (Table III). From a mean baseline total dose of 22.0 IU/day, the average total daily dose was noted to increase to 29.30 IU at 2nd visit and then decrease to 25.20 IU at 3rd visit (Table IV).

Table I: Baseline patient characteristics

	Value
Sex [n(%)]	
Male	827 (45.8%)
Female	975 (54.0%)
Not specified	3 (0.2%)
Age [Mean±SD (range)]	54.0±11.5 (18.0-74.0) years
Weight [Mean±SD (range)]	65.4±11.7 (33.0-118.0) kg
Height [Mean±SD (range)]	162.2±7.8 (121.9-195.6) cm
BMI [Mean±SD (range)]	24.8±3.8 (12.5-41.6) kg/m ²
Systolic BP [Mean±SD (range)]	128.3±15.6 (90.0-220.0) mmHg
Diastolic BP [Mean±SD (range)]	80.5±9.3 (50.0-120.0) mmHg
Hypertension	1,120 (62.0%)
Hypertension with treatment	1,041 (57.7%)
Beta-blockers	184 (10.2%)
Calcium channel blockers	469 (26.0%)
ACE inhibitors	282 (15.6%)
ARB	648 (35.9%)
Diuretics	119 (6.6%)
Others	6 (0.3%)
Dyslipidemia	1,173 (65.0%)
Dyslipidemia with treatment	1,093 (60.6%)
Statins	1,032 (57.2%)
Fibrates	163 (9.0%)
Others	10 (0.6%)
Current smoker	194 (10.7%)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; SD, standard deviation.

*Percentages were based on the safety population (n=1,805)

Insulin glulisine was started at an average dose of 0.32±0.16 IU/kg per day and remained stable throughout the evaluation period, with mean total daily doses of 0.29±0.18 IU/kg and 0.33±0.44 IU/kg at three months and six months, respectively.

It seems patients on basal insulin are not fully optimized prior to initiation of insulin glulisine; at 6th month, patients on insulin glargine were on the average receiving 25.20 units per day, with an insulin glulisine average dose of 20.3 ± 12.8 units per day (Table IV, V).

Table II: Diabetes history and complications

	Value
Newly diagnosed DM	183 (10.1%)
Previously diagnosed DM	1528 (84.7%)
Period from first diagnosis:	
< 5 years	552 (30.6%)
5-10 years	644 (35.7%)
> 10 years	332 (18.4%)
Unknown	80 (4.4%)
Glycemic control at baseline:	
HbA1c < 7%	84 (4.7%)
Fasting blood glucose < 110 mg/dL	74 (4.1%)
DM complications:	
Retinopathy	358 (19.8%)
Neuropathy	729 (40.4%)
Microalbuminuria	567 (31.4%)
Proteinuria	499 (27.6%)
Past or present foot ulcer	110 (6.1%)
Amputation	23 (1.3%)
Angina	284 (15.7%)
Myocardial infarction	117 (6.5%)
Heart failure	84 (4.7%)
Stroke	121 (6.7%)
Peripheral vascular diseases	298 (16.5%)
Erectile dysfunction	109 (6.0%)

DM, diabetes mellitus

*Percentages were based on the safety population (n=1,805)

Hypoglycemic adverse events

Among the 1,805 patients in the safety population, 132 (7.31%) experienced hypoglycemia. The classification of the hypoglycemic adverse events and their corresponding computed event rates per patient-year are summarized in Table VI.

Non-hypoglycemic adverse events

The overall incidence of patients experiencing non-hypoglycemic adverse events was 0.78%, with 17 non-hypoglycemic adverse events observed in 14 patients (see Table VII). These included acute tonsillitis, nasopharyngitis, pneumonia, upper respiratory tract infections, urinary tract infections, headache and cough. None resulted in the permanent discontinuation of the study treatment. Weight and BMI were relatively unchanged during follow-up.

Six (0.33%) patients in the safety population were reported to have experienced serious adverse events. Pulmonary congestion secondary to hypertensive atherosclerotic cardiovascular disease was reported in one patient, and five of the patients died due to natural causes, accidental electrocution, liver cirrhosis, road traffic accident, or cerebrovascular accident. An independent study coordinator together with the pharmacovigilance manager assessed the adverse events. They conducted a series of interviews with the attending physician and examined the patients to ascertain that the events were not attributed to the study drug.

139.4 mg/dL at third months and 121.1 mg/dL at sixth months of treatment. Mean PPBG decreased

Table VI: Summary of hypoglycemic events

	N (number of patients) Number of events	Percent (%) Event rate (per patient-year)
Suffered hypoglycemia	132	7.31%
Severe hypoglycemia	23	3.39
Documented symptomatic hypoglycemia	137	20.17
Asymptomatic hypoglycemia	46	6.77
Probable symptomatic hypoglycemia	106	15.60
Relative hypoglycemia	97	14.28

*Percentages were based on the safety population (n=1,805)

Table III: Concomitant medications (insulin)

Anatomical Group	Generic Name	Baseline		Visit 2		Visit 3	
		Average Total Daily dose	N (%)	Average Total Daily dose	N (%)	Average Total Daily dose	N (%)
Insulins and analogues for injection, intermediate-acting combined with fast-acting	Insulin Aspart	38.90	7 (0.4)	36.40	5 (0.3)	43.80	5 (0.3)
Insulins and analogues for injection, long-acting	Insulin Detemir	29.80	18 (1.0)	34.40	14 (0.7)	40.60	9 (0.5)
Insulins and analogues for injection, long-acting	Insulin Glargine	22.00	1217 (67.4)	29.30	1134 (62.9)	25.20	797 (44.2)
Insulins and analogues for injection, intermediate-acting combined with fast-acting	Insulin Human	35.00	67 (3.7)	42.60	52 (2.9)	48.20	35 (1.9)
Insulins and analogues for injection, intermediate-acting	Insulin Isophane	71.40	21 (1.2)	50.60	16 (0.9)	53.40	13 (0.7)
Insulins and analogues for injection, fast-acting	Insulin Lispro	53.80	6 (0.3)	37.00	4 (0.2)	58.00	1 (0.1)

*The denominator used in the computation of percentages is the safety population.

Table IV: Concomitant insulin average total daily dose (IU) by visit

Generic name	Baseline [n (%)]	Visit 2 [n (%)]	Visit 3 [n (%)]
Insulin aspart	38.90 [7 (0.4)]	36.40 [5 (0.3)]	43.80 [5 (0.3)]
Insulin detemir	29.80 [18 (1.0)]	34.40 [14 (0.7)]	40.60 [9 (0.5)]
Insulin glargine	22.00 [1217 (67.4)]	29.30 [1134 (62.9)]	25.20 [797 (44.2)]
Insulin human	35.00 [67 (3.7)]	42.60 [52 (2.9)]	48.20 [35 (1.9)]
Insulin isophane	71.40 [21 (1.2)]	50.60 [16 (0.9)]	53.40 [13 (0.7)]
Insulin lispro	53.80 [6 (0.3)]	37.00 [4 (0.2)]	58.00 [1 (0.1)]

*The denominator used in the computation of percentages is the safety population.

Table V: Insulin glulisine average total daily dose (IU) by visit

	Baseline	Follow-up Visit 1	Follow-up Visit 2
n	1567 (238)	1687 (117)	1133 (446)
Mean (SD)	20.3 (9.8)	18.5 (11.8)	20.3 (12.8)

Changes in glycemic parameters

HbA1c, FBG and PPBG levels during follow-up visits were significantly lower than baseline levels (all $p < 0.0001$, Table VIII). Mean HbA1c decreased from a baseline value of 9.3% to 7.8% at three months and 7.1% at six months. From a mean baseline FBG of 196.7 mg/dL, mean values decreased to

Table VII: Table for Adverse Events

Adverse Events	Number of Patients (n=14)
Acute Tonsillitis	3
Nasopharyngitis	3
Pneumonia	2
Upper Respiratory Tract Infection	2
Urinary tract infection	2
Headache	1
Cough	1

from 263.9 mg/dL to 177.7 mg/dL at third months and 154.7 mg/dL at sixth months.

Patients' evaluation of Insulin glulisine pen

According to the patients' overall evaluation and ease of learning how to use the Insulin glulisine pen, assessment results were between good to excellent (Table IX). All patients recommended and planned to continue using the Insulin glulisine pen.

Discussion

There is currently limited data on the use of insulin glulisine locally. Furthermore, differences in study populations, methodology, treatment interventions and measured outcomes compound the difficulty in arriving at definitive conclusions. This study was a real-world observational study of patients with type 1 or type 2 diabetes on insulin glulisine who used to be treated with different insulin and OAD regimens.

Table VIII: Mean glycosylated hemoglobin, fasting blood glucose and post-prandial blood glucose at baseline and follow-up visits

	Baseline	Third Month	Sixth Month	p-value
Glycosylated hemoglobin, %				
Number (missing)	1,639 (75)	1,515 (197)	1,065 (457)	
Mean±SD	9.3±1.8	7.8±1.2	7.1±0.9	<0.0001
Fasting blood glucose, mg/dL				
Number (missing)	1,536 (178)	1,476 (236)	982 (540)	
Mean±SD	196.7±67.2	139.4±38.5	121.1±29.8	<0.0001
Post-prandial blood glucose, mg/dL				
Number (missing)	1,115 (599)	1,114 (598)	770 (752)	
Mean±SD	263.9±83.3	177.7±50.2	154.7±37.6	<0.0001

SD, standard deviation

Table IX: Patients' overall evaluation of the Insulin glulisine pen

	Mean value±SD
Ease of learning how to use Glulisine pen	1.5±0.6
Ease of use of Insulin glulisine pen in general	1.5±0.6
Overall assessment of Insulin glulisine pen	1.5±0.6
Plan to continue Insulin glulisine pen	1.0±0.0
Recommend Insulin glulisine pen	1.0±0.0

*Patient evaluation based on five-point questionnaire rating scale (1=Excellent; 2=Good; 3=Acceptable; 4=Poor; 5=Very poor)

Glycemic variability from episodes of post-prandial hyperglycemia is believed to play a role in the development of micro- and macrovascular diabetes complications. The efficacy of RAIs in improving glucose control when used in basal plus or basal bolus insulin regimens have been demonstrated in previous studies, and is largely attributed to its unique PK/PD properties that result in appreciable improvements in controlling post-prandial hyperglycemia.⁶ The results of this study showed that an insulin glargine-containing treatment regimen significantly lowered baseline HbA1c and FBG levels, consistent with those of other studies,⁷⁻¹¹ and demonstrated significant reductions in baseline PPBG levels by 33% and 41% at third and sixth months, respectively.⁶ Whether these improvements in

post-prandial glycemic control and glycemic variability potentially lead to a reduction in long-term diabetes complications remains subject to further investigation.

Hypoglycemia was reported in approximately 7% of the safety population in this study. This reported incidence rate was lower compared to that of randomized studies¹²⁻¹⁴ even when adjusted for almost 20% of patients who were not followed-up. A possible explanation for this could be underreporting for both HCP and patient as hypoglycemia is an expected adverse event during insulin use. Another possible explanation is the lower total insulin dosage for these patients, at 0.33-0.44 IU/kg body weight. Patients were mostly on the combination of basal insulin and glulisine, and when patients experience the symptoms of hypoglycemia, they would lower the dose of the glulisine, relieving them of the symptoms. This can explain the lower daily dose of glulisine. Differences in the criteria used to define hypoglycemia, the study population, dosing and method of insulin administration could also lead to significant variability in reported hypoglycemia rates. Additionally, factors such as race, age, obesity and drug interactions have also been known to alter the pharmacokinetic (PK) and pharmacodynamic (PD) activity of insulin analogues.¹⁵

Similar to other studies, the proportion of patients who experienced other adverse events was low at 0.78%.¹⁶ However, unlike other studies on insulin where weight gain was observed, there was no significant increase in weight or BMI observed in this study.^{2,17,18} None of the serious adverse events, including the five deaths reported in the present study, were considered to be related to the use of Insulin glulisine.

The patient satisfaction questionnaire was used to evaluate the patients' experience with the Insulin glulisine pen. The pen was rated as "good" (mean score of 1.6) on most attributes, including ease in selecting and reading the insulin dose. This is relevant especially since as much as 20% of patients in the study had retinopathy and may have had some degree of visual impairment. Moreover, even if only 10% of the respondents were newly diagnosed patients who had not had previous treatment, the glulisine pen was rated as good to excellent for ease of use and learning, thus suggesting that most patients were comfortable with changing their previous regimen with a new method of administration. The good to excellent overall assessment of the Insulin glulisine pen was consistent with similar surveys conducted in other countries and affirms the universal acceptability of the pen among diabetes patients.^{19,20}

Conclusion

This post marketing surveillance study demonstrates the safety and tolerability of insulin glulisine when used as part of insulin regimen in actual clinical setting for the management of diabetes among Filipino patients. The incidence of hypoglycemia and other adverse events was low at 7.31% and 0.78%, respectively. Likewise, evidence of significant reduction in blood glucose levels was observed. Based on the administered standard validated Patient Satisfaction Questionnaire, patients also gave good satisfaction ratings on the attributes of Insulin glulisine. The overall evaluation of patient experience with glulisine pen was good to excellent.

Disclosures

This study was sponsored by Sanofi Philippines, Inc. Dr. Araceli Panelo is a member of the Advisory Board of the following: Astra Zeneca, Eli Lilly, MSD, Novartis Philippines and Sanofi-Aventis. Dr. Maria Pamela Chua, Dr. Raymond Oliva, Marievi Lelis and Pauline Joy Pastor are employees of Sanofi Philippines, Inc. A complete list of the study investigators is available upon request from Sanofi-Aventis.

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