

## IMPROVED GLYCAEMIC CONTROL AND LESS HYPOGLYCAEMIA WITH NOVORAPID® FLEXPEN® (INSULIN ASPART) IN FILIPINO PATIENTS WITH ACUTE HYPERGLYCAEMIA

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### ABSTRACT

**Background:** Insulin aspart, an insulin analogue, approved for diabetes management is rapidly absorbed and has a faster and more effective glucose-lowering action, with superior control of postprandial hyperglycaemia compared with human soluble insulin. Insulin aspart can be used in continuous subcutaneous infusion and offers a valuable treatment options in basal-bolus treatment.

**Objective:** This study assessed the efficacy and safety of NovoRapid® (insulin aspart) from patients admitted to hospitals and clinics and who experienced acute hyperglycaemia as a result of type 1 or type 2 diabetes or any other illness. The study is a prospective, open-labeled, non-controlled, observational study carried out at 40 centres in the Philippines between June 2007 and December 2007 to assess the efficacy and safety of NovoRapid® FlexPen® (insulin aspart) for the treatment of acute hyperglycemia. NovoRapid® FlexPen® (insulin aspart) was initiated and dose was adjusted at the physician's discretion, reflecting everyday practice. Efficacy was assessed by change in fasting plasma glucose (FPG) and change in post-prandial plasma glucose (PPG) following 3½ weeks of treatment. Hypoglycaemic events and other adverse events were also recorded.

**Results:** Statistically significant ( $p < 0.001$ ) decrease in FPG and 2-h PPG during treatment with insulin aspart was observed. Mean FPG decreased by 3.5 mmol/L from baseline to end of treatment, a clinically significant decrease corresponding to an almost 30% reduction. Statistically significant ( $p < 0.001$ ) decrease in 2-hour PPG during treatment with insulin aspart was achieved. Mean 2-hour PPG decreased by 5.3 mmol/L

from baseline to end of treatment, a clinically significant decrease corresponding to an almost 40% decrease in 2-hour PPG. The incidence of hypoglycaemic episodes was low before and during the study. At baseline the incidence was 0.18 episodes/subject, in the last week of study the incidence was slightly lower (0.11 episodes/subject). Small but not statistically significant increase in weight (mean increase of 0.2 kg) during treatment with insulin aspart was observed. No other adverse events were observed during the entire study period.

**Conclusion:** Treatment with insulin aspart was efficacious and safe. This study demonstrates that administration of insulin aspart to patients with acute hyperglycaemia is associated with a statistically significant lowering of fasting plasma glucose and 2-hour postprandial glucose with non-significant increase in weight and lower incidence of hypoglycaemia relative to baseline.

**Keywords:** Diabetes Mellitus, Insulin aspart, NovoRapid® FlexPen®, Hyperglycaemia.

### INTRODUCTION

The effective management of diabetes mellitus poses an increasingly serious challenge to the Philippines healthcare system. When blood glucose levels are poorly controlled, diabetes is known to contribute to a considerable morbidity in the form of metabolic complications, including ocular disorders, peripheral and autonomic neuropathy, kidney disease, peripheral vascular disease, wound infections, amputations, heart disease, stroke, digestive disorders, oral disease, and depression.

In the Philippines, type 2 diabetes is currently the leading cause of adult blindness, kidney failure and non-traumatic limb loss. The disease is also the ninth leading cause of death in the country, with one in twenty five Filipinos affected by the disease.<sup>1</sup> The onset of the modern technological innovations has created a big change in the lifestyle of the Filipinos. The remote control fast-paced lifestyle is another risk factor.

It is thought that by the year 2025, up to 8

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million Filipinos will be affected by the disease (more than double the amount now). It has been reported that since 1993, annual cases of diabetes in the country have gone up by 2.5%.<sup>1</sup> More often than not, developing countries like the Philippines are severely affected by the disease because of high cost of maintenance drugs, diagnostics and other treatment modalities.

Several studies have assessed rapid-acting insulin as an add-on therapy to oral glucose-lowering drugs. Insulin aspart (NovoRapid®) is a rapid-acting insulin analogue designed for improving subcutaneous absorption.<sup>2</sup> Till date, there is little published data exploring the use of NovoRapid® FlexPen® (insulin aspart) in routine clinical practice in the Philippines. It is widely accepted that observational studies can play an important role in investigating treatment outcomes, particularly in large, heterogenous patient populations with complex, chronic diseases. Insulin therapy in patients with type 1 and type 2 diabetes mellitus is a good example of the use of observational studies in this context.

The aim of this observational study was to collect the efficacy and safety data from patients admitted to hospitals and clinics in the Philippines and who have experienced acute hyperglycaemia as a result of type 1 or type 2 diabetes or any other illness.

## MATERIALS AND METHODS

### *Study Design*

The study was a prospective, open-labeled, non-controlled, observational study carried out at 40 centres in the Philippines between June 2007 and December 2007. Study procedures complied with local regulations and practice governing observational studies that were applicable to health authority approval.

### *Patient Population*

Filipino patients with acute hyperglycaemia as a result of type 1 or type 2 diabetes or any other illnesses seen in out-patient clinics or admitted to a hospital were eligible for this study unless with known hypersensitivity to NovoRapid® FlexPen® (insulin aspart) or any of its excipients. The intention-to-treat (ITT) population included all patients who entered this study and prescribed with NovoRapid® FlexPen® (insulin aspart) by physician during routine clinical evaluation. The starting dose and frequency of injection as well as subsequent dose adjustments

were individualized and were at the discretion of the physician. Insulin aspart (NovoRapid® FlexPen®) was provided at a concentration of 100 U/mL in a 3 mL pre-filled pen and was administered subcutaneously. The mean duration of treatment was approximately 3½ weeks (23.5 days). No study-specific investigations were carried out except the collection of data. No comparator group was included in this non-interventional study and patients acted as their own control.

### *Assessment and Outcome Measures*

Patients visited the clinic for screening and assessment (Visit 1), for NovoRapid® FlexPen® (insulin aspart) treatment initiation (Visit 2) and final visit (visit 3). At visit 1, investigators collected demographic data and detailed medical histories. The safety endpoints were adverse events other than hypoglycaemia between visit 2 and visit 3. The efficacy endpoints were change in fasting plasma glucose (FPG), 2-hour post prandial plasma glucose (PPG) and weight from visit 2 to visit 3. Data on the efficacy endpoints were collected during the week before start of treatment (Visit 2) and during the last week before final visit (Visit 3) according to the routine procedure.

### *Statistical Analysis*

Descriptive statistics were used to summarize the baseline characteristics and safety outcomes. Mean and SDs were prepared for continuous variables, and frequencies and percentages for categorical variables. All statistical testing were performed on the ITT population at the 5% level. Tests for mean difference were performed for efficacy endpoints between data collected at Visit 2 and Visit 3. Statistical testing (comparison of before and after insulin aspart therapy) for safety end points were performed with paired t-tests for continuous variables and with chi-square statistics for discrete variables.

## RESULTS

A total of 334 patients were enrolled into this study of which 330 were included in the safety analysis. Of 334 patients, 213 (63.8%) were females. The mean age of patients was 49.4±17.9 years with mean BMI of 25.0±4.9 kg/m<sup>2</sup> and mean diabetic duration of 6.7±6.4 years. The major reasons for hyperglycaemia were Type 2 Diabetes Mellitus (T2DM) (71.0%) followed by gestational DM (GDM) (13.2%). The baseline characteristics of the trial population are shown in Table I. Of the 334 patients enrolled, 280 (84%) completed the study. The most

common reasons for withdrawal from the study were choice of another treatment regimen (35 patients, 10.5%) or control achieved without NovoRapid® FlexPen® (insulin aspart) (10 patients, 3%).

### Glycaemic Control and Insulin Dose

Treatment with NovoRapid® FlexPen® (insulin aspart) was associated with significant improvement in glycaemic control. The analysis of FPG showed a decrease in mean FPG from baseline to end-of-trial by 3.5 mmol/L, an almost 30% reduction in mean fasting blood glucose and a reduction which was clinically and statistically significant ( $p < 0.0001$ ).

The analysis of FPG change in the insulin-naïve patients and those already in insulin treatment indicated that the insulin-naïve patients were less controlled at baseline than those already on insulin treatment (FPG of 11.3 mmol/L versus 9.9 mmol/L) (Table II). The effect of addition of NovoRapid® FlexPen® (insulin aspart) on FPG was most pronounced in the insulin-naïve group (decrease of 4.4 mmol/L versus 2.6 mmol/L).

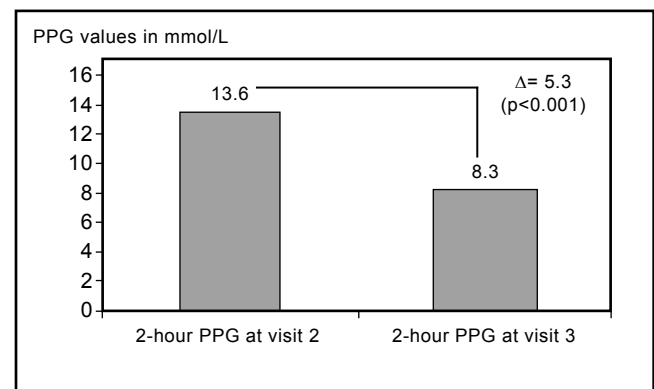
**Table I. The Baseline Characteristics of ITT Population**

Age, years	
N	334
Mean (SD)	49.4 (17.9)
Sex, N (%)	
Female	213 (63.8%)
Male	121 (36.2%)
Weight, kg	
N	334
Mean (SD)	63.0 (14.3)
Height, m	
N	334
Mean (SD)	1.58 (0.1)
BMI, kg/m <sup>2</sup>	
N	334
Mean (SD)	25.0 (4.9)
Duration of Diabetes, years	
N	334
Mean (SD)	6.7 (6.4)
Reasons for Hyperglycaemia, N (%)	
Type 1 DM	37 (11.1%)
Type 1 DM & Others†	3 (0.9%)
Type 2 DM	237 (71.0%)
Type 2 DM & Others†	13 (3.9%)
Gestational DM	44 (13.2%)
Number of patients with hypoglycaemic episodes noted for the past 1 week prior to visit 1	
N	30 (9.0%)
Hypoglycaemic episodes	
N	30
Mean (SD)††	2.0 (1.4)
† Others can be nephropathy, sepsis, stroke, community-acquired pneumonia, steroid-induced hyperglycaemia, septicæmia secondary to liver abscess, missed insulin, urinary tract infection, diabetic ketoacidosis, diabetic foot gangrene, pulmonary Tb, attending physician gave only OAD because of fear etc.	
†† Mean is mean number of episodes per patient per week	

**Table II: FPG Levels in Insulin-Naïve and Non-Insulin Naïve Patients During Treatment**

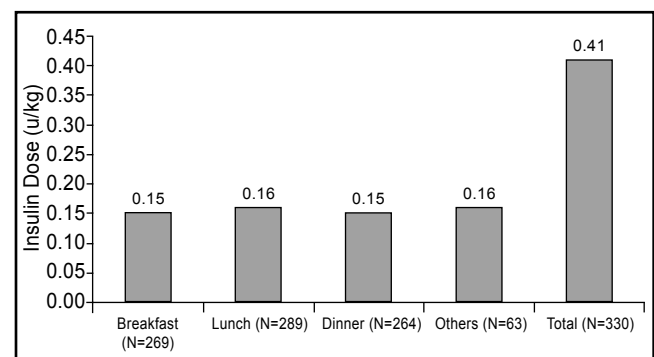
Variable	Insulin-Naïve Patients at Baseline (N=157)	Non-insulin Naïve Patients at Baseline (N=151)
FPG at visit 2	11.3±5.3	9.9±3.8
FPG at visit 3	6.9±1.8	7.3±2.2
Absolute change in FPG	-4.4±4.9	-2.6±3.4
(p<0.0001)		

The 2-hour PPG was decreased by 39% (a decrease of 5.3 mmol/L, from 13.6 mmol/L at Visit 2 to 8.3 mmol/L at Visit 3) as shown in Figure 1. The change was clinically and statistically significant (p value < 0.0001).



**Figure 1: 2-Hour PPG Levels in Study Population**

The statistical and clinically significant reduction in FPG and 2h-PPG after using NovoRapid® FlexPen® (insulin aspart) clearly indicate that there is an overall improvement in glycaemic control of patients with hyperglycaemia. The mean total NovoRapid® FlexPen® (insulin aspart) dose was 0.41 U/kg. The insulin doses used at different main course of meals are shown in Figure 2.



**Figure 2: Insulin Doses Taken at Different Courses of Meal**

### *Adverse events and other safety measures*

Hypoglycaemic episodes were recorded for the week preceding Visit 2 and the week preceding visit 3. A total of 59 episodes were reported corresponding to 0.18 episodes/patient. Hypoglycaemic episodes were reported by only 30 patients during the week prior to Visit 2. A total of 31 episodes were reported prior to Visit 3 (0.11 episodes/patient). The data proved that the frequency of hypoglycaemic episodes both prior to and during treatment with NovoRapid® FlexPen® (insulin aspart) were very low and non-serious.

The mean weight of patients was changed from 63.1±14.2 kg at visit 2 to 63.3±14.0 kg after the treatment with NovoRapid® FlexPen® (insulin aspart). The absolute weight increased slightly by 0.2 ±2.1 kg, which was not statistically significant.

## DISCUSSION

The aim of this study was to assess the safety and efficacy of NovoRapid® FlexPen® (insulin aspart) in the treatment of acute hyperglycaemia. Insulin aspart (NovoRapid®) is a clear, sterile aqueous solution (100U/mL) and it is a rapid-acting insulin analogue that can be used to control prandial glucose levels as part of basal-bolus therapy, in continuous subcutaneous insulin infusion or in combination with oral antidiabetic drugs. NovoRapid® (insulin aspart) was first launched in the EU in 1999 and has been used extensively since then in EU, the US and elsewhere. It has been shown to be a safe and effective treatment of diabetes mellitus, both for patients with type 1 and patients with type 2 diabetes mellitus.<sup>3</sup> Compared with exogenous human soluble insulin, NovoRapid® (insulin aspart) has a faster onset of action, a higher peak concentration, and a shorter duration of action and is therefore more comparable to the physiological prandial insulin response.<sup>4</sup> Randomized clinical trials (RCTs) showed improved postprandial glucose control and lower rates of hypoglycaemia with NovoRapid® (insulin aspart).<sup>5-8</sup>

This study showed significant reduction in FPG and 2h-PPG. Similar results were observed in a clinical study in patients with type 2 diabetes.<sup>9</sup> The study by deBoer *et al* (2005)<sup>9</sup> run for a 1-year period and included 58 poorly regulated people with type 2 diabetes (mean HbA1c ~ 10%). NovoRapid® (insulin aspart) was administered at meals (3 times daily), glimepiride in the evening and metformin (continued from pretreatment). After 3 months mean FPG had improved by 3.6 mmol/L and HbA1c had decreased to 7.2%, a decrease of 2.8%. The treatment was

not associated with any nocturnal hypoglycaemic episodes.

The study consisted of 44 (13.2%) GDM patients. Controlling hyperglycaemia is especially important for pregnant women with diabetes, as poor glycaemic control during gestation has been shown to be associated with maternal and fetal complications.<sup>10</sup> Women with GDM are at high risk of developing overt type 2 diabetes months or years postpartum.<sup>11</sup> Adjustment of insulin therapy in gestational diabetes to normalize PPG levels leads to a decreased rate of macrosomia and lower rates of caesarean sections.<sup>12,13</sup> In this study, a 40% overall reduction in the 2h-PPG value was noted signifying better postprandial glycaemic control of GDM patients treated with NovoRapid® FlexPen® (insulin aspart).

The low number of hypoglycaemic episodes recorded before and at the end-of-study period is impressive considering the tremendous improvement of glycaemic control. The most significant barrier to optimizing glycaemic control is the increasing risk of hypoglycaemia associated with reduction in HbA<sub>1c</sub>. However, the more rapid action of NovoRapid® FlexPen® (insulin aspart) makes post-absorptive and hypoglycaemia less of a problem when compared with human soluble insulin.<sup>14,15</sup> NovoRapid® (insulin aspart) provides improved glycaemic control without increasing risk of hypoglycaemia in Type 1 & 2 diabetes patients. In particular, risk of hypoglycaemia is especially reduced in an all-analog regimen using NovoRapid® (insulin aspart).<sup>4</sup>

The data showed, that mean glycaemic control relative to FPG and 2h-PPG improved significantly. Although quality of life was not part of efficacy endpoint, majority of patients (83.8%) chose to continue NovoRapid® FlexPen® (insulin aspart) after the final visit. Successful management of diabetes and adherence to an insulin regimen are dependent not only on treatments that are effective and well tolerated, but also on choice of insulin delivery device. The insulin FlexPen® that is currently available is a robust prefilled/disposable insulin pen.<sup>16</sup> It has been developed to help improve injection-related quality of life issues for people with type 1 or insulin-requiring type 2 diabetes. Several studies have indicated a patient preference for FlexPen® compared with other pen-type injection devices.<sup>17</sup>

## CONCLUSION

This study demonstrated that for Filipino patients with acute hyperglycaemia who are inadequately

controlled on their previous therapy, treatment with NovoRapid® FlexPen® (insulin aspart) offers improvements in glycaemic control and is well-tolerated and well-received by Filipino patients. A statistically significant lowering of both FPG and 2-hour PPG with non-significant increase in weight was achieved. The incidence of hypoglycaemia was slightly lower than at baseline. Majority of subjects chose to continue using NovoRapid® FlexPen® (insulin aspart) even after the final visit and it might indicate that this regimen was assessed as having a positive influence on quality of life.

In general, this study provides a valuable and practical insight for the use of NovoRapid® FlexPen® (insulin aspart) in routine clinical practice in the Philippines.

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