e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(10); 1311-1316

Original Research Article

A Comparative Study of the Efficacy of Pioglitazone versus Vildagliptin as Add-on Therapies for Type 2 Diabetic Patients Who Had Poor Glycemic Control with Metformin and Sulfonylureas: A Prospective Study

Ashish Ranjan[1], Deepak Kumar[2]

[1]Tutor, Department of Pharmacology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India

[2]Professor & Head of Department, Department of Pharmacology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India

Received: 19-08-2023 / Revised: 18-09-2023 / Accepted: 15-10-2023

Corresponding Author: Dr. Ashish Ranjan

Conflict of interest: Nil

Abstract

Background: Vildagliptin has recently received approval in Europe as an adjunctive therapy to metformin, Sulfonylurea, or thiazolidinedione. Vildagliptin offered an additional HbA1c decrease in comparison to metformin alone and was comparable to pioglitazone, the only one to cause weight gain.

Aims and Objectives: A comparative study of the efficacy of pioglitazone versus vildagliptin as add-on therapies for Type 2 diabetic patients who had poor glycemic control with metformin and sulfonylureas**.**

Materials & Methods: The present prospective observational study consisted of 80 poorly controlled Type 2 DM patients with metformin and sulfonylureas of both genders attaining out-patient departments or emergency care at the Department of Medicine in collaboration with the Department of Pharmacology.

Results: The Mean age of patients in the Pioglitazone group was 52.48±10.26 years and in the Vildagliptin group were 56.80±9.79 years, respectively. The mean HbA1c levels at the beginning of the study were 10.02±1.60% and 11.50±0.08% in the pioglitazone and vildagliptin groups, respectively. At the end of the study, HbA1c levels were reduced from baseline by 1.60% in the pioglitazone group and by 1.25% in the vildagliptin group ($p < 0.002$ for both groups).

Conclusion: The results show that pioglitazone is slightly more efficacious than Vildagliptin, but the cost of Vildagliptin can be a limiting factor for its wider use in India.

Keywords: Type 2 DM, Metformin, Sulfonylureas, Pioglitazone and Vildagliptin.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0) and the Budapest Open Access Initiative (http://www.budapestopenaccessinitiative.org/read), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Vildagliptin has recently received approval in Europe as an adjunctive therapy to metformin, sulphonylurea, or thiazolidinedione. Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor that improves glycemic control in patients with type 2 diabetes mellitus by increasing pancreatic beta- and alpha-cell responsiveness to glucose. In large-scale clinical trials, vildagliptin (as monotherapy or in combination with other oral antidiabetic agents) has been shown to lower blood glucose levels [1,2], and significantly reduce HbA1c while being well tolerated [3–5]. While Type 2 DM poses a huge financial burden on all nations, developing countries bear the highest burden, as more than 80% of cases occur in these countries. Prevalence estimates of diabeties mellitus and impaired glucose tolerance (IGT) are high in all Asian countries and are expected to grow further in the next two decades. Urbanization and socio-economic progress are important factors in the increase in the prevalence of DM in the last two or three decades. The current trend indicates that more than 60% of the world's total population with type 2 DM will live in Asia [6]. By 2025, approximately 57.2 million Indians will be affected by this disease [7]. After 12 weeks of treatment with metformin, sulfonylureas, and pioglitazone or, vildagliptin, there was a statistically significant reduction in HbA1c levels in both groups [8]. Vildagliptin shows favourable safety and tolerability over a year when used with metformin. Vildagliptin offered an additional HbA1c decrease in comparison to metformin alone and was comparable to pioglitazone, the only one to cause weight gain [9].

Aims and objectives

A comparative study of the efficacy of pioglitazone versus vildagliptin as add-on therapies for Type 2

diabetic patients who had poor glycemic control with metformin and sulfonylureas**.**

Methods and Materials

The present prospective observational study consisted of 80 poorly controlled Type 2 DM patients with metformin and sulfonylureas of both genders attaining out-patient departments (OPD) at the Department of Medicine in collaboration with the Department of Pharmacology at Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India, for a period of one years (February 2019–January 2020). The Institutional Ethics Committee gave the study its approval. A written informed consent was obtained from all the patients prior to the beginning of the study. Keeping power (1-beta error) at 80% and confidence interval (1-alpha error) at 95%, the minimum sample size required was 60 patients; therefore, we included 80 (More than the minimum required number of cases) patients in present study.

Inclusion criteria

1. Patients aged > 30 and ≤ 60 years of either gender
2. Patients taking a combination of metformin and sulfonylurea (Glibenclamide, Glipizide, Gliclazide, or Glimepride) for at least 3 months with uncontrolled hyperglycemia, i.e., HbA1c >7% or ≤11% and
3. Body Mass Index (BMI) >25 kg/m2.

Exclusion criteria

1. Pregnant and lactating females,
2. patients on insulin therapy with a history of type 1 DM,
3. Signs of diabetic complications (nephropathy, neuropathy, and retinopathy), and
4. Patients with clinical signs and symptoms of any chronic diseases were excluded.

Randomly, the patients are divided into two groups equally (n = 40).The patients received either pioglitazone or vildagliptin. The patients in the first group (n = 40) received pioglitazone (30 mg once daily), and those in the second group (n = 40) received vildagliptin (50 mg twice daily) in addition to the earlier treatment with metformin (500 mg daily) and sulfonylurea (1.5–12 mg/dl daily). The patients were advised to continue with the lifestyle modifications, including daily moderate exercise and a controlled diet. The efficacy of pioglitazone and vildagliptin was assessed by measuring the change in HbA1c and fasting plasma glucose (FPG) levels after 12 weeks of treatment. Fasting plasma glucose and HbA1c levels were measured at baseline and at 12 weeks. The primary end point was the change in HbA1c levels at 12 weeks as compared to the baseline levels in both groups. The secondary end points were the change in FPG levels at 12 weeks as compared to baseline levels and the percentage of patients with HbA1c <7% at 12 weeks. Along with the serum creatinine, HbA1c, Aspartate transaminase, Alanine amino transaminase, and alkaline phosphatase levels, they were measured both at baseline and after 12 weeks. The patients were instructed to report any adverse events that they appreciated.

Statistical Analysis

The data was analysed using an unpaired t test and Microsoft Excel (2016). The statistical analysis was done by the software Statistical Package for the Social Sciences (SPSS), version 21.0. When the difference's p value was less than 0.05, it was considered significant.

Results

The present study consists of 80 patients of both genders. The patients (n = 80) were equally divided into two groups with similar gender distribution. The patients in the group I (n = 40) received pioglitazone (30 mg once daily) include males 16, females 24 and those in the group II (n = 40) received vildagliptin (50 mg twice daily) include18 and females 22 in addition to the earlier treatment with metformin (500 mg daily) and sulfonylurea (1.5–12 mg/dl daily) (Figure 1).

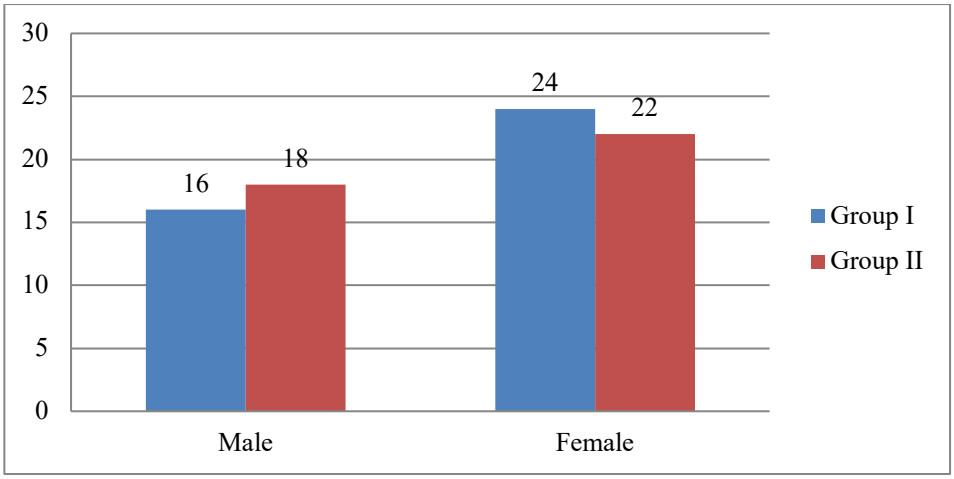

Figure 1: Gender wise distribution of patients

The two groups' baseline characteristics were comparable. The HbA1c, fasting blood sugar (FBS), and postprandial blood sugar (PPBS) levels were not statistically different between the two groups as the p value was greater than 0.05. The Mean age of patients in the Pioglitazone group was 52.48±10.26 years and in the Vildagliptin group were 56.80±9.79 years, respectively. The mean HbA1c levels at the beginning of the study were 10.02±1.60% and 11.50±0.08% in the pioglitazone and vildagliptin groups, respectively (Table 1, Figure 2).

Table 1: Baseline parameters of patients at beginning of study

Parameters	**Pioglitazone (Group I)**	**Vildagliptin (Group II)**	**P value**
	Mean±SD		
Mean age of patient (years)	52.48±10.26	56.80±9.79	
Fasting blood sugar(mg/dl)	220.65±25.90	230.46±28.52	0.15
Postprandial blood sugar(mg/dl)	305.27±35.60	315.76±32.50	
HbA1c (%)	10.02±1.60	11.50±0.08	
Aspartate transaminase(AST) in U/L	12.50±1.20	11.25±1.41	0.83
Alanine amino transaminase (ALT) in IU/L	11.65±1.58	11.90±1.98	
Alkaline phosphatase (ALP) in U/L	9.42±1.97	9.86±1.76	

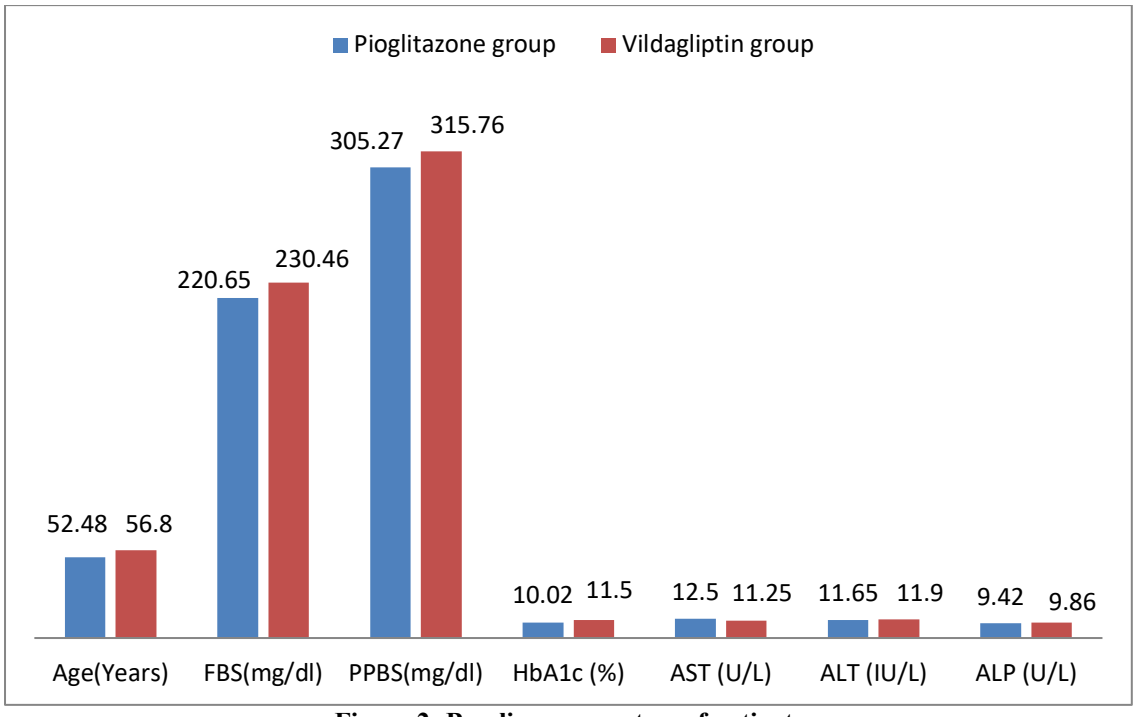

Figure 2: Baseline parameters of patients

At the end of 12 weeks 0f the study, HbA1c levels were reduced from baseline by 1.60% in the pioglitazone group and by 1.25% in the vildagliptin group (p <0.002 for both groups). But this reduction was statistically non-significant between the two groups (p = 0.21). Only 7 patients out of a total of 80 showed HbA1c <7% at 12 weeks, out of which 5 were from the pioglitazone group and 2 from the vildagliptin group.

Fasting plasma sugar and Postprandial blood sugar levels decreased significantly from baseline to the end of the study in both groups by 2.5 mmol/l in pioglitazone group and 1.5mmol/l in vildagliptin (p <0.005), and the reductions were not statistically different in either group (p = 0.085). Also, there was a non-significant difference in mean FBS levels at 12 weeks (p = 0.062). Similarly, the reduction in postprandial blood sugar (PPBS) levels was significant in both groups (p < 0.002), but there was no statistical difference in the decrease in either group (p = 0.30). None of the patients reported any adverse events during the study period. There was a non-significant change in the levels of serum creatinine, AST, ALT, and ALP enzymes in both groups as compared to baseline (Table 2, Figure 3).

Table 2: Glycaemic parameters of patients at the end of study (12week)

Parameters	Pioglitazone (Group I)	Vildagliptin (Group II)	P value
	Mean ± SD		
Fasting blood sugar(mg/dl)	190 ±22.50	211.25±25.73	0.001
Postprandial blood sugar(mg/dl)	262.87±26.40	289.45±30.70	
HbA1c (%)	9.86 ±0.60	11.36±0.09	0.002

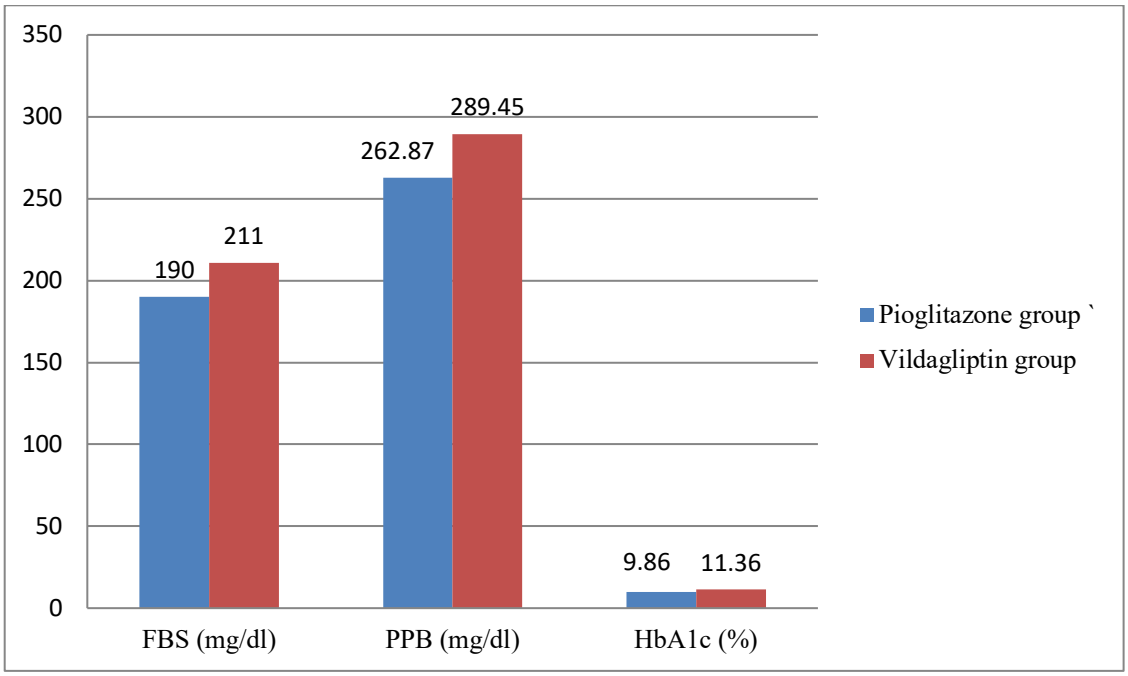

Figure 3: Glycemic parameters of the patients at 12 weeks of study

Discussion

In present study, we evaluated two different add-on therapies among patients with inadequately controlled Type 2 DM even after treatment with dual therapy of metformin and sulfonylurea.

The results suggest that both vildagliptin and pioglitazone led to a significant decrease in HbA1c and FPS levels after 12 weeks of treatment. There was a non-significant difference between the two groups with reference to reductions in HbA1c, FPS, and PPPS levels. More patients (5 out of 7) from the pioglitazone group achieved the target of HbA1c < 7% during the present study period. The evaluation of the primary end point (HbA1c levels) shows no significant difference in the efficacy of both drugs, as there was a non-significant difference in the mean reduction in HbA1c levels. Kaur et al; [8], in 2014 and Bolli G et al; [9], in 2008 found similar results.

After 12 weeks of treatment with metformin, sulfonylureas, and pioglitazone/vildagliptin, there was a statistically significant reduction in HbA1c levels in both groups (p <0.001); however, the difference in the reduction in HbA1c levels at 12 weeks was not statistically significant (p = 0.16). Only four patients—three from the pioglitazone group and one from the vildagliptin group—out of

a total of 50 had HbA1c <7% at 12 weeks. Both groups' random plasma glucose and FPG levels reduced significantly (p <0.001) as well. [10] The patients did not report any negative consequences. Vildagliptin and pioglitazone both provided additional reductions in HbA1c than metformin and sulfonylurea did. Vildagliptin shows comparable efficacy and safety to pioglitazone when used for three months with metformin and sulfonylureas [8].

Bolli G et al; [9], 2008 compared vildagliptin 50 mg twice daily (n = 295) and pioglitazone 30 mg daily (n = 281) among patients with inadequate glycemic control (HbA1c -7.5–11%) receiving a stable dose of metformin ≥1500 mg in a randomised, active-controlled study of 52 weeks duration.

Vildagliptin shows favourable safety and tolerability over a year when used with metformin. Vildagliptin offered an additional HbA1c decrease in comparison to metformin alone and was comparable to pioglitazone, the only one to cause weight gain. The non-inferiority of HbA1c reduction from vildagliptin to pioglitazone over 24 weeks was established at a non-inferiority margin of 0.3% (between-group difference = 0.1%) when added to a stable dose of metformin (mean baseline dose approximately 2 g/day). In both groups, comparable reductions in HbA1c were seen during the course of the following 28 weeks. Vildagliptin provided an additional HbA1c decrease compared to pioglitazone and metformin alone, with pioglitazone being the only one to cause weight gain [9, 10].

The results by Bell DS et al; [12], show that a fixed-dose triple oral diabetes poly pill containing glimepiride, metformin SR (500 mg), and pioglitazone (15 mg) led to lower HbA1c levels as compared to a combination of human insulin 70/30 mix and 500 mg metformin among patients with type 2 DM inadequately controlled on a combination of glimepiride and metformin.

Rodriquez A. et al; [13],conducted an observational cohort clinical study in which patients were started on pioglitazone plus a sulfonylurea, pioglitazone plus metformin, or a sulfonylurea plus metformin due to inadequate control with previous therapy. In all the groups, there was an increase in serum high-density lipoprotein cholesterol (HDL-C) and a decrease in triglyceride levels, and the inter-group differences were significant (p < 0.001 in both parameters). The mean FPG and HbA1c reductions were significantly greater in the pioglitazone cohorts.

Rosenstock J. and Fitchet M; [14], in 2008 also mention a comparison of vildagliptin 50 mg twice daily and pioglitazone 30 mg daily in patients inadequately controlled with ongoing metformin therapy. Compared with add-on pioglitazone, vildagliptin reduced HbA1c by 0.9% vs. 1.0% and was not associated with weight gain (+0.3 kg vs. +1.9 kg) over 24 weeks.

Similarly, the results of our study show that both drugs led to a significant decrease in all the parameters of glycemic control, i.e., HbA1c, FPS, and PPPS levels.

Limitation of Study: The number of patients in the current study was small, and they were only observed for a short period of time.

Conclusions

According to the current study's findings, vildagliptin and pioglitazone both resulted in an additional reduction in HbA1c than was possible with metformin and a sulfonylurea alone. When used with metformin and sulfonylureas for three months, pioglitazone is more efficacious than vildagliptin. The results show that pioglitazone is slightly more efficacious than Vildagliptin, but the cost of Vildagliptin can be a limiting factor for its wider use in India. An economic analysis can help in evaluating these two drugs.

Acknowledgement: The concepts of manuscript ideas, study design, data collection, and analysis were given by Ashish Ranjan. Special thanks to Dr. Deepak Kumar, Professor & Head of Department, Department of Pharmacology, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar India, for their encouragement and, from time to time, valuable suggestions.

Reference

1. Ristic S., Byiers S., Foley J., and Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with type 2 diabetes: vildagliptin (LAF237) dose response Diabetes Obes Metab. 2005; 7: 692–698.
2. Pratley RE, Jauffret-Kamel S, Galbreath E, Holmes. Twelve-week monotherapy with the DPP-4 inhibitor vildagliptin improves glycemic control in subjects with type 2 diabetes. Horm Metab Res. 2006; 38: 423–428.
3. Dejager S, Razac S, Foley JE, Schweizer A. Vildagliptin in drug-naive patients with type 2 diabetes: a 24-week, double-blind, randomised, placebo-controlled, multiple-dose study Horm Metab Res. 2007; 39: 218–223.
4. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care. 2007; 30: 890–895.
5. Rosenstock J, Baron MA, Dejager S, Mills D, Schweizer A. Comparison of vildagliptin and rosiglitazone monotherapy in patients with type 2 diabetes: a 24-week, double-blind, randomised trial Diabetes Care. 2007; 30: 217–223.

6. Ramachandran A, Snehalatha C, Samith Shetty A, and Nanditha A. Trends in the prevalence of diabetes in Asian countries World J Diabetes. 2012;3(6):110–117.
7. Chakdoufi , S., Moumen, A., & Guerboub, A. Dyslipidemia and Diabetic Retinopathy in Moroccans Type 2 Diabetics Patients: A Cross-Sectional Study. Journal of Medical Research and Health Sciences, 2023; 6(3): 2471–2479.
8. Pradeepa R, Deepa R, and Mohan V. Epidemiology of diabetes in India: current perspective and future projections J Indian Med Assoc. 2002; 100(3):144–148.
9. Kaur K, Kaur R, Mittal Naveen, Arora Shalini, and K Sandeep. Comparison of efficacy of add-on therapy of vildagliptin versus pioglitazone among Type 2 diabetes mellitus patients inadequately controlled on dual therapy of metformin plus sulfonylurea. Asian Journal of Medical Sciences. Jul-Sep 2014; 5:3.
10. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab. 2008; 10:82–90.
11. Bolli G, Dotta F, Colin L, Minic B and Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab. 2009;11(6):589-595.
12. Bell DS, Dharmalingam M, Kumar S, and Sawakhande. Triple oral fixed-dose diabetes polypill versus insulin plus metformin efficacy demonstration study in the treatment of advanced type 2 diabetes (TrIED study II). Diabetes Obes Metab. 2011; 13(9):800–805.
13. Rodriquez A, Reviriego J, Polavieja P and Mesa J. Six-month effectiveness and tolerability of pioglitazone in combination with sulfonylureas or metformin for the treatment of type 2 diabetes mellitus. Med Clin (Barc). 2008;131(19):721-730.
14. Rosenstock J. and Fitchet M. Vildagliptin: Clinical Trials Programme in Monotherapy and Combination Therapy for Type 2 Diabetes Int J Clin Pract Suppl. 2008;159:15.