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# The Most Effective and Safer Answer to Diabetes Mellitus: Alogliptin Benzoate

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## ABSTRACT

Type 2 Diabetes Mellitus is the most prevalent disease, affecting majority of the world's population. There are plenty of antidiabetics available in the market helping in achieving glycaemia control. The use of DPP-4 inhibitor is one the effective approach for treating the disease. Alogliptin is the latest analogue to the DPP-4 inhibitor class, approved in 2013. It is a highly selective, oral inhibitor of DPP-4 enzyme. Along with Alogliptin, FDA approved the fixed dose combinations of Alogliptin with Metformin and Pioglitazone, in the same year. Clinical data demonstrate that administering Alogliptin alone or in combination, leads to reduction in mean HbA1c and Fasting Plasma Glucose (FPG) level. Mean reduction of HbA1c is about 0.5% to 0.6% with Alogliptin alone and on combination with Metformin and Pioglitazone, the mean HbA1c reduce approximately by 0.6% and 1.8% respectively. The drug also reduces the Fasting Plasma Glucose (FPG) level by 10mg/dl to 20mg/dl and in combination with Metformin and Pioglitazone, the FPG level reduce by 20mg/dl and 50mg/dl respectively. Alogliptin is a drug with suitable tolerance and high safety profile. The drug shows no incidence of hypoglycemia and is weight neutral. Hence, Alogliptin benzoate is the preferred choice of the drug to treat type 2 diabetes mellitus.

**Keywords:** Type 2 Diabetes mellitus; Alogliptin; DPP-4 inhibitors; Incretin based therapy.

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## INTRODUCTION

Diabetes mellitus is recognized as the major health problem affecting large number of population worldwide. It is a chronic disease affecting both developed and developing nations at an alarming rate. According to recent estimate from International Diabetes Federation (IDF), the worldwide diabetes cases met a new record of 382 millions in year 2013 and the value is expected to rise to 592 million by 2035. According to IDF, India is ranked second with around 65.1 million people diagnosed with diabetes in year 2013 and the value is expected to increase to 109 million by 2035[1]. A chart showing top 10 countries with number of people with diabetes in year 2013 and 2035 is shown in figure 1. According to IDF, diabetes caused 5.1 million deaths in year 2013. Every six seconds a person dies from diabetes.

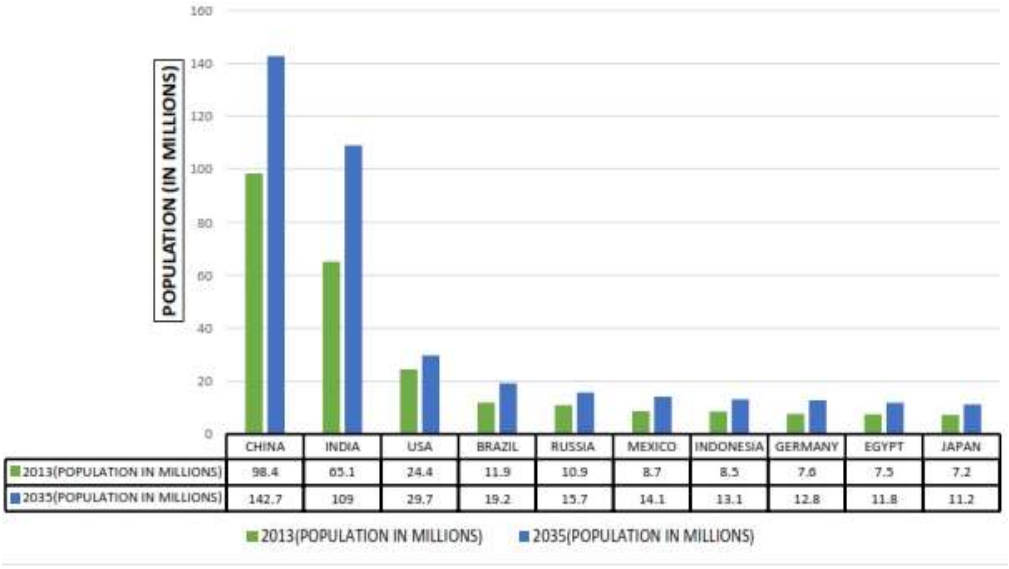


**Figure 1: Top 10 countries with no. of people having diabetes.**

Type 2 diabetes is a chronic metabolic disorder characterized by insulin resistance and abnormal functioning of pancreatic Beta cell. It is also associated with hyperglycemia, glycosuria, hyperlipaemia and negative nitrogen balance. The disease predisposes to micro and macro vascular problems like diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, cardiovascular disease, kidney failure, lower limb amputations and increased risk of morbidity and mortality. The risk of T2DM increases with the age, obesity and physical inactivity. T2DM shows strong familial aggregation, that is, the person with a parent or sibling with the disease is at an increased risk. It acts as a lifelong disease and decreases the quality of life. Diagnosis of diabetes mellitus is usually on the basis of elevated fasting plasma (FPG) and 2-hour post prandial (PPG) levels in the blood. The FPG and PPG levels in the diabetic patients are found to be more than 7mmol/L (126mg/dl) and 11.1mmol/L (200mg/dl) respectively. Another parameter suggested by

American Diabetes Association (ADA) for the assessment of diabetes is the increase in Glycated Haemoglobin (HbA1c) level from 5.7% (110mg/dl) to more than 6.5%(140mg/dl) [6-8]. An effective treatment schedule consists of treating patients with oral hypoglycaemic agents alone or in combination as an adjunct to exercise and diet. Therapy with multiple medications is often required by patients to achieve glycaemic control. Selection of an effective antidiabetic depends upon patients profile and the pharmacological profile of the medication. An appropriate diet and exercise (if possible) will help in reducing glucose levels. Diabetes Mellitus is treated with antihyperglycemic agents like Sulphonylureas, Biguanide, Meglitinides, alpha-glycosidase inhibitors, Thiazolidinedione, glucagon- like peptide – 1 (GLP-1) receptor agonists and Insulin. The currently used antidiabetics shows loss of efficacy, poor tolerability and low compliance due to adverse effects including hypoglycaemia, weight gain, oedema, nausea and gastrointestinal complications. The purpose of the article is to show that DPP4 Inhibitors are suitable alternative for treating T2DM. The study aims to compare all the DPP4 inhibitors available in the market. The article focuses on evaluating clinical efficacy and safety profile of Alogliptin in diabetic patients. The ultimate goal of the article is to prove that Alogliptin is the most effective and safer answer for treatment of Diabetes Mellitus.

**Dipeptidyl Peptidase (Dpp-4) Inhibitors**

Dipeptidyl peptidase (DPP-4) inhibitors are the novel class of orally available antidiabetics, commonly called as gliptins, used for the treatment of T2DM. There are five DPP-4 inhibitors available in the market namely Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Alogliptin. Merck, United Stated launched Sitagliptin in year 2006 followed by Vildagliptin in year 2008 by Novartis, India. Saxagliptin was brought into the market in year 2009 by Bristol-Myers Squibb, New York and Astra Zeneca, United Kingdom. Boehringer-Ingelheim, Germany introduced Linagliptin in year 2011.The most recently added DPP-4inhibitor is Alogliptin in year 2013 by Takeda Pharmaceuticals, Japan[9-12]. They potentially reduce blood glucose levels and lower HbA1c by 0.5% to 1.1%. All the agents of the class are safe and well tolerated. The most potential advantage of these drugs is low incidence of hypoglycaemia and are usually weight neutral. The most effective and safer analogue of this class is Alogliptin benzoate. The US FDA also gave approval for Alogliptin fixed dose combination with Metformin and Pioglitazone in the same year for achieving better glycemic control.

**Comparison**

Comparison of five DPP-4 inhibitors: Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin and Alogliptin is shown in Table 1[15-40].

**Table 1: comparison of DPP-4 Inhibitors**

| S.no | Parameters | Sitagliptin | Saxagliptin | Linagliptin | Vildagliptin | Alogliptin |
|---|---|---|---|---|---|---|
| | PHARMACOKINETICS | | | | | |
| 1. | Bioavailability | 87% | 67% | 30% | 85% | 100% |
| 2. | Tmax | 1-4 hours | 2hours | 1.5hours | 1.75hours | 1-2hours |
| 3. | Half-life $t^{1/2}$ | 8-14hours | 2.5hours | 180hours | 1.5-4.5hours | 21hours |
| 4. | Volume of distribution(Vd) | 198L | 151L | 1110L | 71L | 417L |
| | PHARMACODYNAMICS | | | | | |
| 5. | Affinity for DPP-4 than DPP-8 and DPP-9 | High | Moderate | Moderate | Moderate | Moderate |
| 6. | % DPP-4 inhibition | ≥80% | ≥80% | ≥86.1% | ≥90% | ≥95% |
| 7. | Decrease in FPG level | 12mg/dl | 15 mg/dl | 9 mg/dl | 10.8 mg/dl | 10-16 mg/dl |
| 8. | Decrease in HbA1c level | 0.7% | 0.45% | 0.69% | 0.5% | 0.5-0.6% |
| 9. | IC 50 | 19 nM | 50 nM | 1 nM | 62 nM | 24nM |
| | 0THER FACTORS | | | | | |
| 10. | Dose | 100mg once a day | 2.5 or 5mg once a day | 5mg once a day | 100mg once a day | 25mg once a day |
| 11. | Drug Drug Interactions | Low potential for interaction with digoxin | Low potential for interaction with ketoconazole | Low potential for interaction with rifampicin | Low | Low |
| 12 | Adverse effects | Hypoglycemia Headache Nasopharyngitis Upper respiratory tract infection | Hypoglycemia Headache Nasopharyngitis Upper respiratory tract infection Urinary tract infection Peripheral oedema | Hypoglycemia Nasopharyngitis | Hypoglycemia Headache Nasopharyngitis Upper respiratory tract infection | Headache Nasopharyngitis Upper respiratory tract infection |

**Alogliptin Benzoate**

Alogliptin is the newest member and the most effective and safer analogue of the DPP-4 Inhibitor class The US FDA gave approval for Alogliptin monotherapy as well as fixed dose combination with Metformin and Pioglitazone in the year 2013 to Takeda Pharmaceuticals, Japan.

Alogliptin is a selective, orally bioavailable inhibitor of Dipeptidyl peptidase-4 (DPP-4). Chemically, Alogliptin is prepared as a benzoate salt, which is identified as 2-({6-[(3R)-3-aminopiperidin-1-yl]-3-methyl-2,4-dioxo-3,4dihydropyrimidin-1(2H)yl}methyl)benzonitirle monobenzoate[17-22,27]. It has a Molecular formula of $C_{18}H_{21}N_5O_2 \bullet C_7H_6O_2$ & Molecular weight of 461.51 Daltons. The structural formula of alogliptin benzoate is shown in (figure 2).

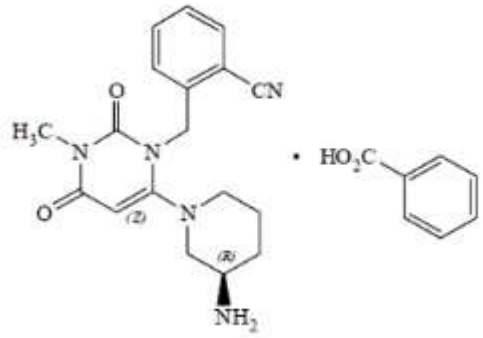


**Figure 2: Alogliptin Benzoate**

It is white to off-white, crystalline powder, containing one asymmetric carbon in the aminopiperidine moiety. It is soluble in dimethyl sulfoxide, sparingly soluble in water and methanol, slightly soluble in ethanol, and very slightly soluble in octanol and isopropyl acetate. The partition coefficient ($C_{1\text{-octanol}}/C_{aqueous}$) of alogliptin benzoate at 25°C and pH 7.4 is -0.5. The pKa is 8.5.

**Pharmacology**

**Mechanism of action of alogliptin**

DPP-4 is a serine protease widely expressed in many tissues, rapidly degrades incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) secreted by enteroendocrine L and K cells respectively. Both incretins are released from small intestine into the vasculature during the meal. The elevated incretins stimulate the release of insulin from pancreatic beta cells after a meal leading to indirect glycaemic control. In T2DM patients, the concentration of GLP-1 is decreased while the insulin response to GLP-1 remains unchanged. DPP-4 inhibitors stimulate the release of insulin in a glucose-dependent manner. DPP-4 inhibition targets the diminished incretin effect by increasing circulating blood levels of endogenous incretins which in turn increase insulin levels and decrease glucagon levels in a

glucose-dependent manner. The increase in insulin levels enhances glucose uptake by tissues and the decrease in glucagon levels reduces hepatic glucose production leading to improved glycaemic control as depicted in figure 3[41-44,48,49]. Alogliptin is around 10,000-fold more selective for DPP-4 than other related enzymes including DPP-8 and DPP-9.

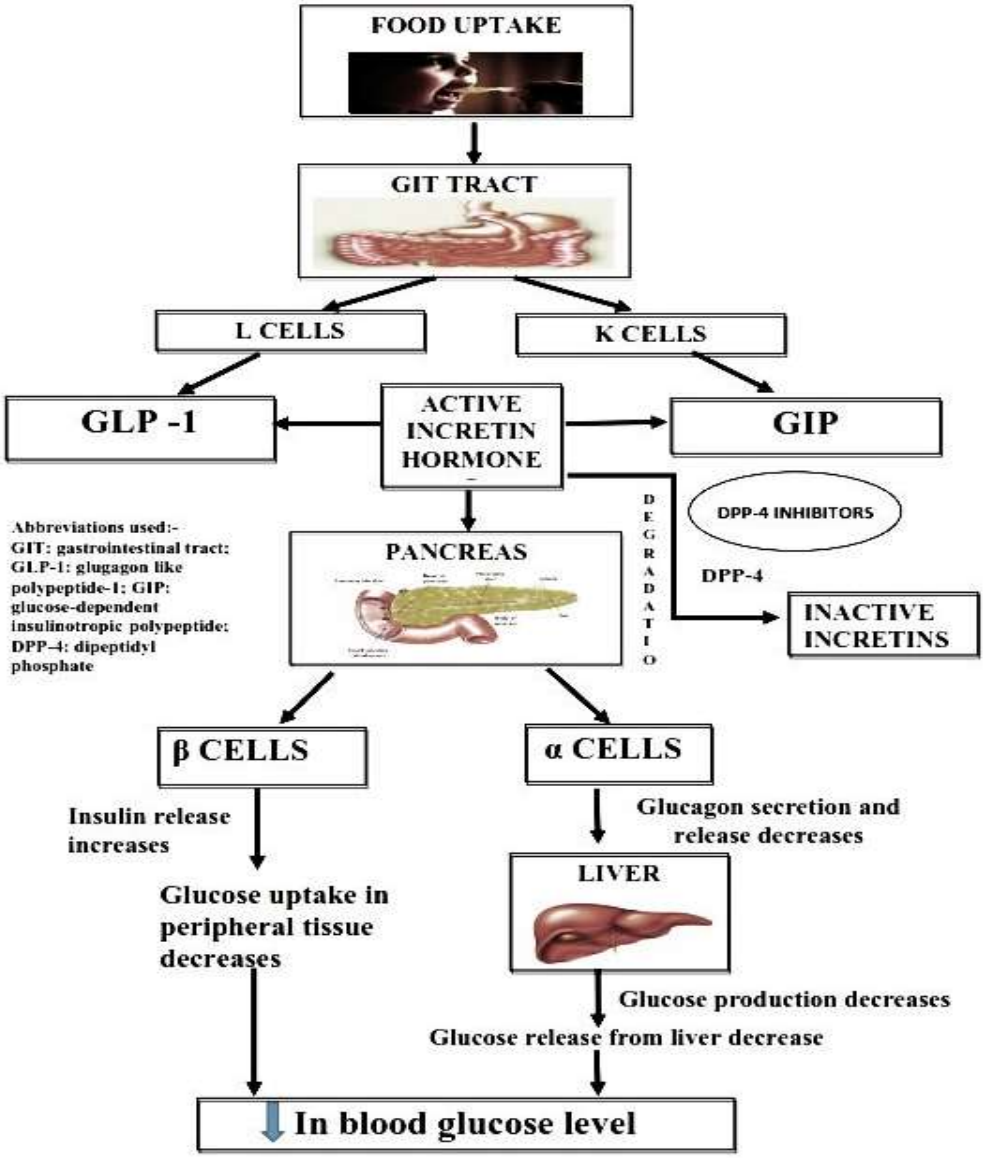


**Figure 3: Mechanism of Action of DPP-4 Inhibitors**

**Mechanism of action of alogliptin in fixed dose combination**

**With Metformin**:

Alogliptin is combined with biguanide, such as Metformin, to achieve better glycemic control. Mechanism of both ALG and MET are different but complementary to each other. Alogliptin improves insulin availability by increasing levels of incretin hormones. Metformin helps in overcoming insulin resistance and presence of insulin is essential for its action. Metformin acts by

suppressing hepatic gluconeogenesis and glucose output by the liver which is responsible for lowering blood glucose levels. Molecular mechanism of Metformin involves activation of enzyme AMP-activated protein kinase (AMPK) which reduce serum lipids and blood glucose concentrations. AMPK-dependent inhibitory phosphorylation of acetyl-CoA carboxylases Acc1 and Acc2 suppresses lipogenesis and lowers cellular fatty acid synthesis in liver and muscles, which in turn improves insulin sensitivity. It also decreases the intestinal absorption of glucose and increases intestinal glucose utilization. Thus, Alogliptin and Metformin together increase the insulin availability and insulin sensitivity and shows improved glycemic control.

**With Pioglitazone:**

Alogliptin when combined with thiazolidinediones, such as Pioglitazone, improves glycemic control in T2DM patients. The mechanism of action of both ALG and PIO is synergistic. Pioglitazone is a potent insulin sensitizer which binds to specific nuclear receptor, peroxisome proliferator activated receptor gamma (PPARγ) to increase insulin sensitivity of liver, fat and skeletal muscle cells and results in decreasing plasma glucose levels. It enhances the transcription of several insulin responsive genes and decreases the insulin resistance by by enhancing GLUT4 expression and translocation. It binds to peroxisome proliferator activated receptor alpha (PPARα) in the adipocytes to promote adipogenesis and fatty acid uptake which causes reduction in fatty acid concentrations and lipid availability. Pioglitazone also suppresses hepatic glucose output and increase peripheral glucose utilization. Pioglitazone, like metformin, causes increase in insulin sensitivity which results in improved glycemic control when given in combination with Alogliptin[19-21].

**Pharmacokinetics**

The Pharmacokinetics of Alogliptin has been studied in patients with type 2 diabetes mellitus. The Pharmacokinetics parameters of Alogliptin are shown in table 2[16,17, 21,22].

**Table 2: Pharmacokinetics of Alogliptin Benzoate**

| Parameters | Alogliptin 12.5mg/25mg |
|---|---|
| Bioavailability | 100% |
| T max | 1-2 hours |
| Volume of distribution(Vd) | 417 L |
| Protein binding | 20% |
| Half-life t1/2 | 21 hours |
| Primary route of elimination | Renal as unchanged drug |
| Metabolism | CYP2D6 ,CYP3A4 |
| Active metabolites | M-I(N-demethylated metabolite),active, M-II(N-acetylated) |
| Percentage excreted unchanged in urine | 60-80% |

**Pharmacodynamics**

Alogliptin is the most selective and potent inhibitor of DPP-4 enzyme as compared to other gliptins available in the market. Administration of ALG 25mg to the patients with type 2 diabetes mellitus showed peak inhibition of DPP-4 within 1 to 2 hours[21,22]. Single dose of ALG shows more than 95% DPP-4 inhibition and the value remains more than 81% after 24 hours indicating once daily administration. It has two enantiomeric forms of which R-isomer is 1000 times more active than S-isomer. The N-demethylated metabolite, M-I, is the active metabolite, showing significant DPP-4 inhibition.

**Clinical Pharmacology**

Clinical trials were conducted to study the safety and efficacy of Alogliptin. Clinical studies were carried out using Alogliptin as monotherapy and in combination with several type 2 diabetes mellitus medication, including insulin. The results demonstrate significant reduction in mean HbA1c levels and FPG levels[15-18]. Table 3. Shows the clinical data obtained from the clinical trials.

**Table 3: Clinical Effectiveness of Alogliptin and Its Combination Therapy**

| Study (year) | Duration | Total number of Patients involved [N] | Drug{dose (mg)}[no. of patients] | Mean HbA1c% | Reduction of HbA1c% | Reduction in FPG level (mg/dl) Mean=≥126mg/dl |
|---|---|---|---|---|---|---|
| Defronzo et al (2008) | 26 weeks | 329 | ALOGLIPTIN MONOTHERAPY | | | |
| | | | Placebo [64] | 7.9 | 0.02 | +11.3 |
| | | | Alogliptin(12.5) [133] | 7.9 | 0.56 | 10.3 |
| | | | Alogliptin(25) [131] | 7.9 | 0.59 | 16.4 |
| Rosen stock et.al (2010) | 26 weeks | 655 | ALOGLIPTIN IN COMBINATION WITH PIOGLITAZONE | | | |
| | | | Alogliptin(25) [164] | 8.80 | 0.96 | 25.2 |
| | | | Pioglitazone(30) [163] | 8.76 | 1.15 | 37.8 |
| | | | Alogliptin(12.5) +pioglitazone (30) [164] | 8.85 | 1.56 | 48.6 |
| | | | Alogliptin(25) + Pioglitazone(30) [164] | 8.80 | 1.71 | 50.6 |
| Seino et.al | 26 weeks | 288 | ALOGLIPTIN IN COMBINATION WITH METFORMIN | | | |
| | | | Placebo + Metformin(500) | 8.5 | +0.21 | 0.80 |
| | | | Alogliptin(12.5) + Metformin(500) | 8.4 | 0.54 | 19.0 |
| | | | Alogliptin(25)+ Metformin(500) | 8.5 | 0.64 | 23.1 |
| Nauck et.al (2009) | 26 weeks | 527 | IN PATIENTS RECEIVING METFORMIN | | | |
| | | | Placebo + Metformin(500) [104] | 8.0 | 0.1 | 0 |
| | | | Alogliptin(12.5)+ Metformin(500) [213] | 7.9 | 0.6 | 19 |
| | | | Alogliptin(25)+ Metformin(500) [210] | 7.9 | 0.6 | 17 |
| Pratley et.al (2009) | 26 weeks | 493 | IN PATIENTS RECEIVING PIOGLITAZONE | | | |
| | | | Placebo + Pioglitazone (30/45) [97] | 8.0 | 0.19 | 5.7 |
| | | | Alogliptin(12.5) + Pioglitazone (30/45) [197] | 8.1 | 0.66 | 19.7 |
| | | | Alogliptin(25) + Pioglitazone (30/45) [199] | 8.0 | 0.80 | 19.9 |
| Pratley et.al (2009) | 26 weeks | 500 | IN PATIENTS RECEIVING SULPHONYUREAS | | | |
| | | | Placebo +Glyburide [99] | 8.1 | +0.01 | +22 |
| | | | Alogliptin(12.5) +Glyburide[203] | 8.1 | 0.39 | 4.7 |
| | | | Alogliptin(25) +Glyburide[198] | 8.1 | 0.53 | 8.4 |
| Rosen stock et.al (2009) | 26 weeks | 390 | IN PATIENTS RECEIVING INSULIN | | | |
| | | | Insulin +placebo ± Metformin [130] | 9.3 | 0.13 | +5.8 |
| | | | Insulin + Alogliptin(12.5) ± Metformin[131] | 9.3 | 0.63 | +2.3 |
| | | | Insulin + Alogliptin(25) ± Metformin [129] | 9.3 | 0.71 | 11.7 |

**Alogliptin versus Placebo**

A 26 week, double blind, placebo controlled study, was conducted by Defronzo et al. in year 2008 to study the effect of alogliptin and alogliptin plus placebo on patients with type 2 diabetes mellitus. A total of 329 patients with a mean age of 53.4 years were randomized to receive once-daily dosing of alogliptin 12.5mg, alogliptin 25mg, or placebo. At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.56% with 12.5mg of ALG and 0.59% with 25 mg of ALG compared with 0.02% reduction in case of placebo. There was also reduction in FPG level, the level reduce by 10.3mg/dl with 12.5mg of ALG and 16.4mg/dl with 25mg of ALG compared to placebo with an increase of 11.3mg/dl.

**Combination Therapy**

**Alogliptin in Combination with Metformin**

A 26 week, double blind, placebo-controlled study was performed by Seino et al. to evaluate the efficacy and safety of alogliptin in combination with metformin. A total of 288 patients were randomized to receive once-daily dosing of Metformin (500mg) plus placebo, Alogliptin 12.5mg plus metformin (500mg), Alogliptin 25mg plus metformin (500mg). At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.54% with 12.5mg ALG plus metformin (500mg) and 0.64% with 25 mg of ALG plus metformin (500mg) compared with 0.21% with Metformin (500mg) plus placebo. There was also reduction in FPG level, the level reduce by 19mg/dl with 12.5mg of ALG plus metformin (500mg) and 23.1mg/dl with 25mg of ALG plus metformin (500mg) compared to 0.80mg/dl reduction with placebo plus metformin (500mg).

**Alogliptin in Combination with Pioglitazone**

A 26 week, double blind, placebo-controlled study was performed by Rosenstock et al. in year 2010 to evaluate the efficacy and safety of Alogliptin in combination with Pioglitazone. A total of 655 patients were randomized to receive once-daily dosing of Alogliptin (25mg), Pioglitazone (30mg), Alogliptin 12.5mg plus pioglitazone (30mg), Alogliptin 25mg plus pioglitazone (30mg). At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 1.56% with 12.5mg ALG plus pioglitazone (30mg) and 1.71% with 25 mg of ALG plus pioglitazone (30mg) compared with 0.96% with Alogliptin (25mg) and 1.15% with pioglitazone (30mg). There was also reduction in FPG level, the level reduce by 48.6mg/dl with 12.5mg of ALG plus pioglitazone (30mg) and 50.6mg/dl with 25mg of ALG plus pioglitazone (30mg) compared to 25.2mg/dl reduction with Alogliptin (25mg) and 37.8 mg/dl reduction with pioglitazone (30mg).

**Alogliptin in Combination with Sulfonylurea (Glyburide)**

A 26 week, double blind, placebo-controlled study was performed by Pratley et al. to evaluate the efficacy and safety of alogliptin in combination with glyburide. A total of 500 patients were randomized to receive once-daily dosing of glyburide plus placebo, Alogliptin 12.5mg plus glyburide, Alogliptin 25mg plus glyburide. At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.39 with 12.5mg ALG plus glyburide and 0.53% with 25 mg of ALG plus glyburide compared with 0.01% with glyburide plus placebo. There was also reduction in FPG level, the level reduce by 4.7mg/dl with 12.5mg of ALG plus glyburide and 8.4mg/dl with 25mg of ALG plus glyburide compared to 22mg/dl increase with placebo plus glyburide.

**Alogliptin in Combination with Insulin**

A 26 week, double blind, placebo-controlled study was performed by Rosenstock et al. in year 2009 to evaluate the efficacy and safety of Alogliptin in combination with Insulin alone or combined with metformin. A total of 390 patients were randomized to receive once-daily dosing of placebo, Alogliptin 12.5mg, Alogliptin 25mg in addition to insulin with or without metformin. At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.63% with 12.5mg ALG plus insulin and 0.71% with 25 mg of ALG plus insulin compared with 0.13% with placebo plus insulin. There was also reduction in FPG level, the level reduce by 2.3mg/dl with 12.5mg of ALG plus insulin and 11.7mg/dl with 25mg of ALG plus insulin compared to 5.8mg/dl increase with placebo plus insulin.

**Alogliptin in patients receiving Metformin**

A 26 week, multi center, randomized, double blind, placebo-controlled study was performed by Nauck et al. in year (2009) to evaluate the efficacy and safety of adding Alogliptin to Metformin for treating the patients with inadequate glycemic control. A total of 527 patients were randomized to receive once-daily dosing of placebo plus Metformin (500mg), Alogliptin 12.5mg plus metformin (500mg), Alogliptin 25mg plus metformin (500mg). At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.6% with 12.5mg ALG plus metformin (500mg) and 0.6% with 25 mg of ALG plus metformin (500mg) compared with 0.01% with Metformin (500mg) plus placebo. There was also reduction in FPG level, the level reduce by 19mg/dl with 12.5mg of ALG plus metformin (500mg) and 17mg/dl with 25mg of ALG plus Metformin (500mg) compared to 0 mg/dl reduction with placebo plus metformin (500mg).

**Alogliptin in patients receiving Pioglitazone**

A 26 week, multi center, randomized, double blind, placebo-controlled study was performed by Pratley et al. in year (2009) to evaluate the efficacy and safety of adding Alogliptin to

pioglitazone for treating the patients with inadequate glycemic control. A total of 493 patients were randomized to receive once-daily dosing of placebo plus pioglitazone (30/45mg), Alogliptin 12.5mg plus pioglitazone (30/45mg), Alogliptin 25mg plus pioglitazone (30/45mg). At week 26, the glycosylated haemoglobin (HbA1c) level reduced significantly by 0.66% with 12.5mg ALG plus pioglitazone (30/45mg), and 0.80% with 25 mg of ALG plus pioglitazone (30/45mg), compared with 0.19% with pioglitazone (30/45mg) plus placebo. There was also reduction in FPG level, the level reduce by 19.7mg/dl with 12.5mg of ALG plus pioglitazone (30/45mg) and 19.9mg/dl with 25mg of ALG plus pioglitazone (30/45mg) compared to 0.19 mg/dl reduction with placebo plus pioglitazone (30/45mg).

**Adverse Drug Reactions**

Alogliptin and its combination with metformin and pioglitazone have high safety profile and good tolerance. The common side effects associated with Alogliptin are headache, nasopharyngitis, and Upper respiratory tract infection. Another most common side effect associated with all DPP-4 inhibitors is Pancreatitis[21,22,50,55].

**Hypoglycemia**

No hypoglycaemic episodes are reported in patients on Alogliptin monotherapy. Alogliptin stimulates the release of insulin in proportion to the amount of glucose ingested indicating that chances of excess of insulin release are minimal and thus no hypoglycaemia will be caused[51]. A 12-week study conducted by Defronzo et al showed that there were no drug related hypoglycaemic episodes reported in patients administered with Alogliptin 12.5 or 25 mg whereas a 26-week study conducted Mekki by et al showed moderate hypoglycaemic cases in about 1.5-3.0% of patients[52]. There was no difference in the incidence of hypoglycaemia B/w elderly and younger patients shown in a pool analysis of six randomized trials[53]. Alogliptin given in combination with pioglitazone showed significant number of hypoglycaemic cases. The incidence of hypoglycaemia was highest when Alogliptin was given in combination with Sulphonylureas[54].

**Weight Neutral**

Alogliptin 25mg is weight neutral when administered alone or in combination to both young as well as elderly patients[56-64]. Changes in body weight caused by 25mg Alogliptin ranges from -0.7kg to +1.1kg[63,64]. A study demonstrated that Alogliptin decreases body weight more effectively when compared with glipizide. Changes were -0.62kg with Alogliptin 25mg versus +0.60kg with glipizide after one year in elderly patients ($p<0.001$) [65]

**Warnings and Precautions**

**Lactic Acidosis**

Lactic acidosis is a rare but serious metabolic complication. It is fatal in approximately 50% of cases. The complication results due to metformin accumulation in the body. Lactic acidosis is characterized by elevated blood lactate levels (more than 5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. Metformin plasma levels of more than 5 mcg/mL are generally found in case of lactic acidosis. The patients with renal dysfunction are at higher risk. Elderly patients are more vulnerable because of improper renal functioning. The risk reduces significantly by regular monitoring of renal function in patients taking ALG in combination with MET.

CONGESTIVE HEART FAILURE**:** Thiazolidinedione's, like pioglitazone causes congestive heart failure due to fluid retention in the body. Patients taking pioglitazone should be carefully monitored for symptoms of heart failure which includes excessive and rapid weight gain, dyspnoea, and/or oedema. The patients with symptomatic heart failure are at increased risk and it is advisable not to treat them with ALG and PIO combination.

**SPECIAL POPULATION**

Special population includes patients with renal impairment, cardiovascular disorders and elderly patients. It also includes infants, pregnant women and lactating mothers.

**a) Elderly**

A study was done to evaluate efficacy of Alogliptin in elderly diabetic patients with mean age of 70years and mean HbA1c 7.5%. The patients were randomized to receive Alogliptin 25mg or glipizide 5-10mg for 52weeks. At the end of the study the reduction in HbA1c level was -0.42% with Alogliptin and 0.33%with glipizide[65]. Analysis of six randomized controlled trials of Alogliptin showed a similar improvement in elderly patients (mean age 70years) compared with younger patients[66].

**Renal impairment**

Dose adjustment of Alogliptin needs to be done in patients with renal impairment. A study showed that treatment with 6.25mg/day of Alogliptin as monotherapy or in combination with other antidiabetic agent was effective in patients with type 2 diabetes mellitus who were undergoing haemodialysis[67,68]. In a 24months single arm study, 16 patients with renal impairment were treated with Alogliptin 6.25mg/day showed decreased HbA1c level from 7.1%±0.2% to 5.8%±1.6%. There is also decrease in glycated albumin levels from 22.5%±0.7% to 19.6%±0.6%[68].

**Cardiovascular Disorders**

A pooled analysis of Alogliptin trials with 4168 diabetic patients showed no sign of increased

cardiovascular risk with Alogliptin[69, 70]. No studies are conducted to assess the effect of Alogliptin in pediatrics, pregnant women and lactating mothers.

**Drug Interactions**

Interaction of Alogliptin with drugs like Atorvastatin, Caffeine, Cimetidine, Oral contraceptives, Cyclosporine, Dextromethorphan, Digoxin, Fexofenadine, Metformin, Pioglitazone, warfarin does not affect the peak plasma concentration of the drug.

**Dosage**

The usual dose of Alogliptin is 12.5 mg twice daily or 25mg once a day. Table 4 indicates the dosage schedule of the ALG and its combination. It also contains information regarding dose adjustment required for special population.

**Storage**

Storage of Alogliptin and its combinations is at room temperature between 68°F to 77°F (20°C to 25°) in a tightly closed container.

**Future Aspects**

The DPP-4 inhibitor class is the emerging area of research and have good scope for further development. Prospective trials investigating the effect of Alogliptin as well as other DPP-4 inhibitors on cardiovascular outcomes are ongoing and results are eagerly awaited. More number of DPP-4 analogues will be launching sooner in the market. Clinical trials are being carried out to estimate the efficacy and safety of the upcoming gliptins. Gliptins in development are listed in Table 5.

**Table 4: Dosing Recommendations for Alogliptin and Its Formulations**

| **Parameters** | **Alogliptin 12.5mg/25mg** | **Alogliptin+Metformin 12.5mg/500mg or 12.5mg/1000mg** | **Alogliptin + Pioglitazone 12.5mg/15mg or 12.5mg/30mg or 12.5mg/45mg** |
|---|---|---|---|
| Usual dosage | 25mg once daily | 12.5mg/1000mg twice daily with food | 25/15mg or 25mg/30mg or 25mg/45mg With or without food |
| Food | With or without food | | |
| Quantity limit | 1 tablet a day | 2 tablet a day | 1 tablet a day |
| Dose in special population | | | |
| Renal impairment | CrCl 30 to <60ml/min, 12.5mg once daily; CrCl<30ml/min,6.25mg once daily; not recommended for severe renal impairment | Contraindicated due to risk of lactic acidosis | CrCl 30 to <60ml/min, 12.5mg/15mg;12.5mg/30mg,12.5mg/45mg once daily |
| Hepatic impairment | No Dose Adjustment | | |
| Elderly | No Dose Adjustment | | |
| Drug interaction | No Dose Adjustment | | |
| Patients with chf | No Dose Adjustment | | 25mg/15mg once daily |

**Table 5: Gliptins in Development**

| **Name** | **STATUS** | **Company** |
|---|---|---|
| Dutogliptin | Phase III | Phenomix pharmaceuticals |
| Tenegliptin | Phase III | Mitsubishi pharmacorp |
| Syr472 | Phase III | Takeda |
| Krp104 | Phase II | Kyorin |
| Lc15-0444 | Phase II | Lg life sciences |
| Melogliptin | Phase II | Glenmark |

## CONCLUSION

Use of DPP-4 inhibitor is the recent approach used for treating the Diabetes mellitus. The most effective and safer analogue of the class is Alogliptin benzoate. Clinical studies effectively demonstrate the usefulness of Alogliptin in lowering down plasma glucose levels in the diabetic patients. Alogliptin is a highly selective DPP-4 inhibitor approved by USFDA to treat T2DM as an adjunct to diet and exercise. It is 100% bioavailable and majorly eliminated renally. It has maximum potency and longer duration of action thus administered once daily. It has potential advantage of showing low hyperglycaemic episodes and is weight neutral in both younger as well as elderly patients. Alogliptin is a well-tolerated drug and has high safety profile. Dosage adjustment is required in patients with renal impairment. Fixed dose combination of alogliptin with other anti-diabetics including insulin helps in achieving better glycemic control. Alogliptin is the only DPP-4 inhibitor having fixed dose combination with thiazolidinedione, Pioglitazone. Clinical data demonstrate that fixed dose combination of Alogliptin with Pioglitazone shows greater reduction in FPG Levels as well as HbA1c levels than other combinations and caution should be taken in patients with symptomatic heart failure. Thus, Alogliptin benzoate and its fixed dose combinations with other antidiabetics can be used for treating type 2 diabetes mellitus successfully.

## REFERENCES

1. IDF Diabetes Atlas, 6th ed. International Diabetes Federation, 2013.
2. Ramachandran A, Das AK, Joshi SR, Yajnik CS, Shah S, Kumar KMP. Current status of Diabetes in India and Need for Novel Therapeutic Agents. JAPI 2009; 58: 7-9.
3. Mehta SR, Kashyap AS, Das S. Diabetes Mellitus in India: The Modern Scourge. MJAFI 2009; 65: 50-54
4. Health Care Guidelines- Diagnosis and the Management of type 2 Diabetes Mellitus in Adults. Institute for Clinical System Improvements (ICSI), 16th ed. 2014; 1-30.
5. Kaku K. Pathophysiology of Type 2 Diabetes and Its Treatment Policy. JMAJ 2010; 53: 41-46
6. Harris P, Mann L, Phillips P, Webster C. Diabetes Management in General Practise Guidelines for type 2 Diabetes. Diabetes Australia.18th ed.2012/13.
7. American Diabetes Association. Standards of Medical Care in Diabetes-2009 Diabetes Care 2009; 32: 513-561

8. Sacks DB Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS et al. Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus. Diabetes Care 2011; 34: e61-e99
9. Ganie MA, Kotwal S. Recent Advances in Management of type 2 Diabetes Mellitus. JIMSA 2012; 25: 171-175.
10. Dicker D, DPP-4 inhibitor: Impact on glycemic control and cardiovascular risk factors, Diabetes Care 2011; 34: S276-S278
11. Mkele G. Dipeptidyl Peptidase-4 Inhibitors: their role in the Management of type 2 Diabetes Mellitus. S Afr Farm Pract 2013; 55: 508-510.
12. Mudaliar S. New frontier in the Management of type 2 Diabetes Mellitus. Indian J Med Res, 2007; 125: 275-296.
13. Diabetes. Int j Clin Pract 2006; 60:1454-1470
14. Neumiller JJ. Differential chemistry (structure), mechanism of action, and Pharmacology of GLP-1 receptor agonists and DPP-4 inhibitors. J Am Pharm Assoc.2009; 49:S16-S29.
15. Bohannon N. Overview of the Gliptin class (Dipeptidyl Peptidase-4 Inhibitors) in Clinical Practise. Postgraduatet Medicine 2001; 121: 1-6.
16. Dineen L, Law C, Scher R, Pyon E. Alogliptin (Nesina) for Adults with Type-2 Diabetes, Drug Forecast 2014;39: 192-197.
17. Pal DK, Kumar A, Baral A. De T. US FDA approved new drug alogliptin: a DPP-4 inhibitor for treatment of patients with type 2 diabetes. Int J Curr Pharm Res. 2013; 5: 135-139.
18. Gibbs JP, Fredrickson J, Barbee T, Correa I, Smith B, Lin S, and. Gibbs MA. Quantitative Model of the Relationship between Dipeptidyl Peptidase-4 (DPP-4) Inhibition and Response: Meta-Analysis of Alogliptin, Saxagliptin, Sitagliptin, and Vildagliptin Efficacy Results. J Clin Pharmacol 2012; 52:1494-1505
19. Andukuri R, Drinic A, Rendell M. Alogliptin: a new addition to the class of DPP-4 inhibitors, Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2009, 117-126
20. Cada DJ, Levien TL, Baker DE. Alogliptin. Formulary Drug Reviews 2013; 48: 580-592.
21. Product information for AusPAR alogliptin (as benzoate), NESINA and Vipidia, Takeda Pharmaceuticals Australia Pty Ltd. 2-4 Lyon park Road. Macquarie park NSW 2113, 2013; 1-19.
22. Prescribing information for NESINA, (Alogliptin tablets). Takeda pharmaceuticals America Inc. 2013, 1-34

23. Prescribing information for Trajenta (Linagliptin tablets). Boehringer-Ingelheim Pharmaceuticals 2014, 1-18.
24. Product information for AusPAR Trajenta, Linagliptin Boehringer-Ingelheim Pharmaceuticals Pty Ltd 2014, 1-18
25. Prescribing information for Onglyza (Saxagliptin) tablets. Bristol-Myers Squibb Company, USA and Astra Zeneca Pharmaceuticals, Wilmington 2013, 1-12.
26. Prescribing information for Januvia (Sitagliptin) tablets. Merck and Co, Inc. USA 2010, 1-23.
27. http://www.drug bank.ca/drugs/DB06203.
28. http://www.drug bank.ca/drugs/DB01261.
29. http://www.drug bank.ca/drugs/DB06335.
30. http://www.drug bank.ca/drugs/DB08882
31. http://www.drug bank.ca/drugs/DB04876
32. Kalra S. Emerging Role of Dipeptidyl Peptidase-IV (DPP-4) Inhibitor Vildagliptin in the Management of type 2 Diabetes. JAPI 2011; 59: 237-243.
33. Guedes EP, Hohl A, Melo TG, Lauand F. Linagliptin: farmacology, efficacy and safety in type 2 diabetes treatment. Diabetology & Metabolic Syndrome 2013; 5: 1-7.
34. Sciria BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B et al. Saxagliptin and Cardiovascular Outcomes in Patients with Patients with type 2 Diabetes. N E NGL J MED 2013; 369: 1317-26.
35. Cobble ME, Frederich R. Saxagliptin for the treatment of type 2 diabetes mellitus assessing cardiovascular data. Cardiovascular Diabetology 2012; 11:1-8.
36. Defronzo RA, Hissa MN, Garber AJ, Gross JL, Duan RY, Ravichandran S et al. The Efficacy and Safety of Saxagliptin when Added to Metformin Therapy in Patients With Inadequately Controlled Type 2 Diabetes with Metformin Alone. Diabetes Care 2009; 32: 1649-54.
37. Sitagliptin, vildagliptin and Saxagliptin- Dipeptidyl Peptidase-IV (DPP-4) Inhibitors (‘gliptins’) for add on therapy in type 2 diabetes mellitus. NPS RADAS 2013.
38. Ji LN, Pan CY, Lu JM, Li H, Li Q, Li QF et al. Efficacy and Safety of combination therapy with vildagliptin and metformin versus metformin up titration in Chinese patients with Type 2 Diabetes mellitus: Study design and rationale of the vision study. Cardiovascular Diabetology 2013; 12: 1-9.
39. Babu S. Vildagliptin- A new prospect in management of Type 2 Diabetes mellitus. Indian Journal of Clinical Practise 2012; 22: 377-385.

40. Australian Public Assessment Report for Vildagliptin. Australian Government Department of Health and Ageing Therapeutics Goods Administration. Novartis Pharmaceuticals Australia Pty Ltd 2010. Vella A. Mechanism of action of DPP-4 inhibitors, new insight. J Clin Endocrinol Metab. 2012; 97: 2626-28.
41. Lovshin JA, Drucker DJ. Incretin based therapies for type 2 Diabetes Mellitus. Nat rev Endocrinol 2009; 5:262-269
42. Brunton LL. Goodman & Gilman's. The Pharmacological Basis of Therapeutics, Inc, Chapter-43. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus And Hypoglycaemia, 12th ed. McGraw Hill 2011;1237-1271.
43. Tripathi KD. Essentials of medical pharmacology, 7th edition, Jaypee Brothers medical publishers Pvt. Ltd., New Delhi 2012; 254-274
44. Sweetman SC. Martindale. The Complete Drug Reference. AntiDiabetics. 36th ed. Pharmaceutical Press 2009; 431-464.
45. http://www.fda.gov/ohrms/dachys/02/may02/053102/80047/e6.pdf
46. http://www. drug bank.ca/drugs/DB00331.
47. http://www. drug bank.ca/drugs/DB01132.
48. Holland DQ, Neumiller JJ. Alogliptin in combination with, Metformin and Pioglitazone for the treatment of type 2 diabetes mellitus. Diabetes, Metabolic, Syndrome and Obesity. Targets and Therapy 2004;277-288.
49. Rosenstock J, Inzucchi SE, Seufert J, Fleck PR, Wilson CA, Mekki Q. Initial Combination Therapy with Alogliptin and Pioglitazone in Drug-Naïve Patients with Type 2 Diabetes. Diabetes care 2010; 33: 2406-2408.
50. Barclay L, Tucker M. FDA Approvals: Three new type 2 Diabetes Formulations of Alogliptin. The Metabolomics Innovation Centre (TMIC), Released on 28th February, 2013
51. Seino Y, Fujita T, Hiroi S, et al. Efficacy and safety of alogliptin in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, dose-ranging comparison with placebo, followed by a long-term extension study. Curr Med Res Opin 2011; 27:1781-92
52. Defronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the Dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care 2008;31:2315-17
53. Pratley RE, McCall T, Fleck PR, et al. Alogliptin use in elderly people: a pooled analysis from phase 2 and 3 studies. J Am Geriatr Soc 2009; 57:2011-19

54. 51. Pratley RE, Kipnes MS, Fleck PR, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy. Diabetes Obes Metab2009;11:167-76
55. Ndefo UA ,Okeli O, Erowele G. Alogliptin:A new Dipeptidyl peptidase-4 inhibitor for the management of type 2 diabetes mellitus. Am J Health Syst Pharm 2015;71:103-109
56. Berhan A, Berhan Y. Efficacy of alogliptin in type 2 diabetes treatment: a meta-analysis of randomized double- blind controlled studies. BMC Endocr Disord 2013;13:9 Meta-analysis confirming the antihyperglycemic efficacy of alogliptin alone or in combination with other antidiabetic drugs. 2009;63:46-55
57. DeFronzo RA, Fleck PR, Wilson CA, Mekki Q; Alogliptin Study 010 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes and inadequate glycemic control: a randomized, double-blind, placebo-controlled study. Diabetes Care 2008;31:2315-17
58. Rosenstock J, Rendell MS, Gross JI et al. Alogliptin added to insulin therapy inpatients with the type 2 diabetes reduces HbA(1c) without causing weight gain or increased hypoglycemia. Diabetes Obes.Metab.2009; 11:1145-52.
59. Nauck MA, Ellis GC, Fleck PR, et al. Efficacy and safety of adding the Dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a multicenter, randomized, double-blind, placebo-controlled study. Int J Clin Pract 2009;63: 46-55. Study demonstrating the efficacy and safety of adding alogliptin to metformin for 26 weeks, in patients not adequately controlled on this widely used first-line therapy
60. Seino Y, Hiroi S, Hirayama M, Kaku K. Efficacy and safety of alogliptin added to sulfonylurea in Japanese patients with type 2 diabetes: randomized, double- blind, placebo-controlled trial with an open-label, long-term extension study. J Diabetes Invest 2012;3:517-25
61. Pratley RE, Reusch JE, Fleck PR, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin added to pioglitazone in patients with type 2 diabetes: a randomized, double-blind placebo-controlled study. Curr Med Res Opin 2009;25:2361-2371.
62. Del Prato S, Camisasca R, Wilson C, Fleck P. Durability of the efficacy and safety of alogliptin compared to glipizideover 2 years when used in combinationwith metformin [poster 66-LB]. 73rd Scientific Sessions of the American Diabetes Association.2013 Jun 21-5; Chicago, USA. Available from: http://ada.apprisor.org/epsSearch. cfm?compid=1 [Last

accessed 2 December 2013]Longest study reported for alogliptin to date, showing that its efficacy and good tolerability are maintained for 2 years.

63. Defronzo RA, Burant CF, Fleck P, et al. Efficacy and tolerability of the DPP-4 inhibitor alogliptin combined with pioglitazone, in metformin-treated patients with type 2 diabetes. J Clin Endocrinol Metab 2012;97:1615-22
64. Bosi E, Ellis GC, Wilson CA, Fleck PR. Alogliptin as a third oral antidiabetic drug in patients with type 2 diabetes and inadequate glycaemic control on metformin and pioglitazone: a 52-week, randomized, double-blind, active- controlled, parallel-group study. Diabetes Obes Metab 2011;13:1088-96
65. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. Diabetes Obes Metab 2013;15:906-14
66. Pratley RE, McCall T, Fleck PR, et al. Alogliptin use in elderly people: a pooled analysis from phase 2 and 3 studies. J Am Geriatr Soc 2009;57:2011-19
67. Fujii Y, Abe M, Higuchi T, et al. The dipeptidyl peptidase-4 inhibitor alogliptin improves glycemic control in type 2 diabetic patients undergoing hemodialysis. Expert Opin Pharmacother 2013;14:259-67
68. Nakamura Y, Inagaki M, Shimizu T, et al. Long-term effects of alogliptin benzoate in hemodialysis patients with diabetes: a 2-year study. Nephron Clin Pract 2013;123:46-51
69. Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care. 2014;37:2884–2894.
70. White WB, Pratley R, Fleck P, et al. Cardiovascular safety of the dipetidyl peptidase-4 inhibitor alogliptin in type 2 diabetes mellitus. Diabetes Obes Metab. 2013;15:668–673.