Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 5, Issue 2, 2013

Research Article

US FDA APPROVED NEW DRUG ALOGLIPTIN: A DPP-4 INHIBITOR FOR TREATMENT OF PATIENTS WITH TYPE 2 DIABETES

DILIPKUMAR PAL[1,*], TANMOY DE[2], ARIJIT BARAL[2], ARVIND KUMAR[2]

Received: 15 March 2013, Revised and Accepted: 31 March 2013

[1]Department of Pharmaceutical Sciences, Guru Ghasidash Vishwavidyalya (A Central University) Koni, Bilaspur-495 009, C.G., India, [2]School of Pharmaceutical Sciences, IFTM University, Lodhipur, Rajput, Moradabad, UP, 244 001, India. Email: drdilip71@gmail.com

Received: 12 March 2013, Revised and Accepted: 28 March 2013

ABSTRACT

Rates of type 2 diabetes have increased markedly over the last 50 years in parallel with obesity. In 2010, approximately 285 million people suffered from diabetes. Alogliptin is a new dipeptidyl peptidase (DPP-4) inhibitor and it is used for treatment of type 2 diabetes either alone or in combination with other antidiabetic drugs. In 2013 Takeda receives FDA approval for three new type 2 diabetes therapies, nesina (alogliptin) and fixed-dose combinations oseni (alogliptin and pioglitazone) and kazano (alogliptin and metformin HCL). A double blind placebo-controlled study was performed to evaluate the efficacy and safety with inadequately controlled type 2 diabetes to four arms: 25 mg alogliptin (A25) q.d. monotherapy, 30 mg pioglitazone (P30) q.d. monotherapy, or 12.5 (A12.5) or 25 mg alogliptin q.d. plus pioglitazone (P30) q.d. combination therapy. Primary efficacy was A1C change from baseline with the high-dose combination (A25 + P30) versus each monotherapy. Alogliptin is well tolerated drug. In clinical trials, it has not been found any dose limiting toxicity (DLT).

Keywords: Alogliptin; Dipeptidyl peptidase-4 inhibitor; Glycemic control; Type 2 diabetes, Incretins; GLP-1; GIP; HbA_{1c}

INTRODUCTION

Type-2 diabetes is the most common form of diabetes (non-insulin dependent diabetes). Rates of type 2 diabetes have increased markedly over the last 50 years in parallel with obesity. In the year 1985, 30 million people suffered from diabetes worldwide. In 2010, approximately 285 million people suffered from diabetes[1,2].

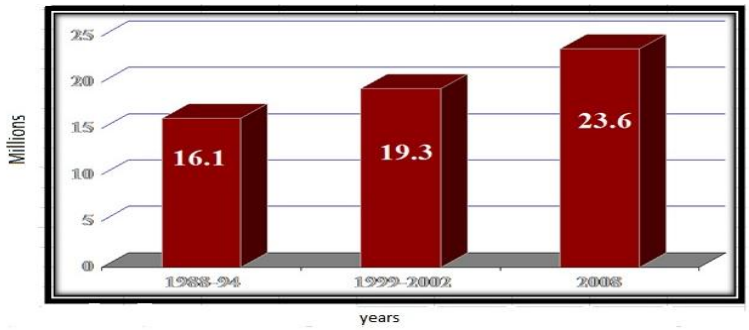

Fig. 1: Prevalence of diabetes in united states Source- http://www.cdc.gov/media/Pressrel/2008/r080624.htm.

Fig. 2: Schematic blood glucose level in diabetic and Non-diabetic patients [1,2,3,4]

Dipeptidyl Peptidase-4 inhibitor (DPP-4 inhibitor) inhibits DPP-4 enzyme. Mechanismically, DPP-4 inhibitors degrades incretin hormones (GLP-1 & GIP) leading to inhibits glucagon release from pancreatic α-cells, increase insulin secretion from pancreatic β-cells, decrease gastric emptying and decrease blood glucose levels. These DPP-4 inhibitors are orally active, do not require a dose-finding period and two of the three types currently available only have to be taken once a day. DPP-4 inhibitors can significantly reduce HbA1c, FPG and PPG[5,6].

Fig. 3: Schematic mechanism of DPP-4 inhibitors

GIP is secreted from the k cells of the gut. It stimulates insulin secretion. GIP has various activities include modulation of fatty acid synthesis, stimulation of lipoprotein lipase activity, incorporation of fatty acids into triglycerides and promotion of β-cell proliferation and survival. GLP-1 is secreted from L cells of the distal gut into the capillaries and then it reaches into the blood stream. The biologically active forms of GLP-1 are: GLP-1-(7-37) and GLP-1-(7-36) NH2. GLP-1 is converted to active GLP-1 after metabolized by DPP-4 enzyme. It stimulates insulin secretion after reaching to the pancreatic β-cell and decrease glucagon secretion, slowing gastric emptying time. The release of GLP-1 after 2 hours taking meal is about 25% to 30% lower in patients with type 2 diabetes[7,8,9,10].

The U.S. Food and Drug administration (FDA) has been approved alogliptin on 2013 in three formulations:

a) Brand name Nesina
b) Combined with metformin the name Kazono and
c) Combined with Pioglitazone the name Oseni

Alogliptin is an anti-diabetic drug and it is administered orally. It is developed by Takada Pharmaceutical Company. It is a DPP-4 inhibitor[11,12,13].

CHEMICAL STRUCTURE

The chemical name of alogliptin is (R)-2-((3-aminopiperidin-1-yl)-3-methyl-2,4-dioxo-3,4-dihydropirimidin-1(2H)-yl)methyl)benzonitrile.

Its chemical formula is $C_{18}H_{21}N_5O_2$ and molecular weight is 339.39 [14].

Fig. 4: Chemical structure of alogliptin

MECHANISM OF ACTION: ALOGLIPTIN

Alogliptin is an oral administered DPP-4 inhibitor and it inhibit DPP-4 enzyme. DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin (H_bA_1c). There are two types of incretin hormones (GLP-1 & GIP). They act by reduce blood glucose by increasing release of insulin and reducing the secreation of glucagon from the pancrease. Alogliptin degrades incretin hormones. There is a reduction in the secretion of GLP-1 and a reduction in the pancreatic response to GIP. Fortunately, the insulinotropic response to GLP-1 is preserved, making modulation of GLP-1 activity a potential therapeutic target [11,15].

Fig. 5: Schematic mechanism of alogliptin

PHARMACOKINETICS [16,17,18,19]

In pharmacokinetic study, 25 to 800 mg of alogliptin were administered to healthy male volunteers (N=36) in aduit patients with type 2 diabetes in one trial. Alogliptin was rapidly absorbed and reaches maximum plasma concentration (Tmax) in approximately 1-2 h. It has a mean half-life of 12 to 24 h. Alogliptin was metabolized minimally. Primarily the drug is eliminated through kidney. 60% to 70% of drug was excreted unchanged in urine. Mean area under the curve $(AUC)_{0-8}$, 1,327-49,595 ng h/mL. The mean volume of distribution of alogliptin was 60.9L, greater than the body water (42L), indicating that it is well distributed in all tissues.

Table 1: Pharmacokinetic information of alogliptin

Property	Alogliptin
Tmax	1-2 h.
$[AUC]_{0-8}$	1327-49595 ng h/mL
$t_{1/2}$	12-21 h.
Protein binding	20%
Bioavailability	100%
Metabolism	Limited, hepatic (CYP2D6 and 3A4- mediated
Excretion	Renal (major) and fetal (minor)

MONOTHERAPY

Monotherapy and combination therapy of alogliptin is used for treatment of type-2 diabetes patients with HbA_{1c} between 7% and 10%. In the placebo-controlled study, patients were allocated alogliptin and alogliptin plus placebo respectively. 329 patients were randomly subjected to alogliptin (n=133), alogliptin (n=131) plus placebo (n=65) for once daily for 26weeks. Monotherapy of alogliptin has been studied for treatment-native patients with type 2 DM for 26 weeks. The level of HbA_{1c} is decreased significantly with 12.5 mg (-0.56) and 25 mg (-0.59%) compared with placebo (-0.02%) [20].

COMBINATION THERAPY

(1) Add-on combination therapy with metformin

A double blind placebo-controlled study was performed to evaluate the efficacy and safety of a combination therapy of alogliptin and metformin in patients having in sufficient controlled type 2 diabetes. 527 patients were allocated to receive 12.5mg alogliptin (n=213) plus metformin (1847 mg/d) once daily, alogliptin 25 mg (n=210), or placebo (n=104) once daily for 26 weeks in addition to metformin (mean dose, 1,847 mg/d). Mean HbA1c reductions noted with placebo, alogliptin 12.5 mg and 25 mg were −0.1%, −0.6% and −0.6% respectively ($P > 0.001$) [21].

(2) Add-on combination therapy with sulfonylurea

A double blind, placebo-controlled study was performed to evaluate the efficacy of alogliptin in combination with sulfonylurea (SU). In this study, a total of 500 patients with type-2 diabetes participated for 26 weeks. 500 patients were allocated to receive 12.5mg alogliptin (n=203) plus sulfonylurea (12 mg/d) once daily, alogliptin 25 mg (n=198), or placebo (n=99) once daily for 26 weeks in addition to sulfonylurea (12 mg/d). Mean HbA_{1c} reductions across increasing doses of alogliptin: −0.39% with 12.5 mg and −0.53% with 25 mg compared with placebo (+0.01%) [22].

(3) Add-on combination therapy with pioglitazone

A double blind placebo-controlled study was performed to evaluate the efficacy and safety of a combination therapy of alogliptin and pioglitazone in patients having in sufficient controlled type 2 diabetes. 493 patients were allocated to receive 12.5mg alogliptin (n=197), alogliptin 25 mg (n=199), or placebo (n=97) in addition to pioglitazone (mean dose, 35 mg/d). Reductions in HbA_{1c} were: −0.19%, −0.66% and −0.80% for placebo, 12.5 mg and 25 mg of alogliptin respectively ($P < 0.001$) [23].

(4) Add-on combination therapy with insulin

A double blind placebo-controlled study was performed to evaluate the efficacy and safety of a combination therapy of alogliptin and insulin in patients having in sufficient controlled type 2 diabetes. 490 patients were allocated to receive 12.5mg alogliptin (n=131), alogliptin 25 mg (n=129), or placebo (n=130) in addition to insulin (>100units/day). The addition of alogliptin resulted in HbA_{1c} reduction of −0.51% and −0.59% and was significant ($P <$ 0.001 for both doses [24].

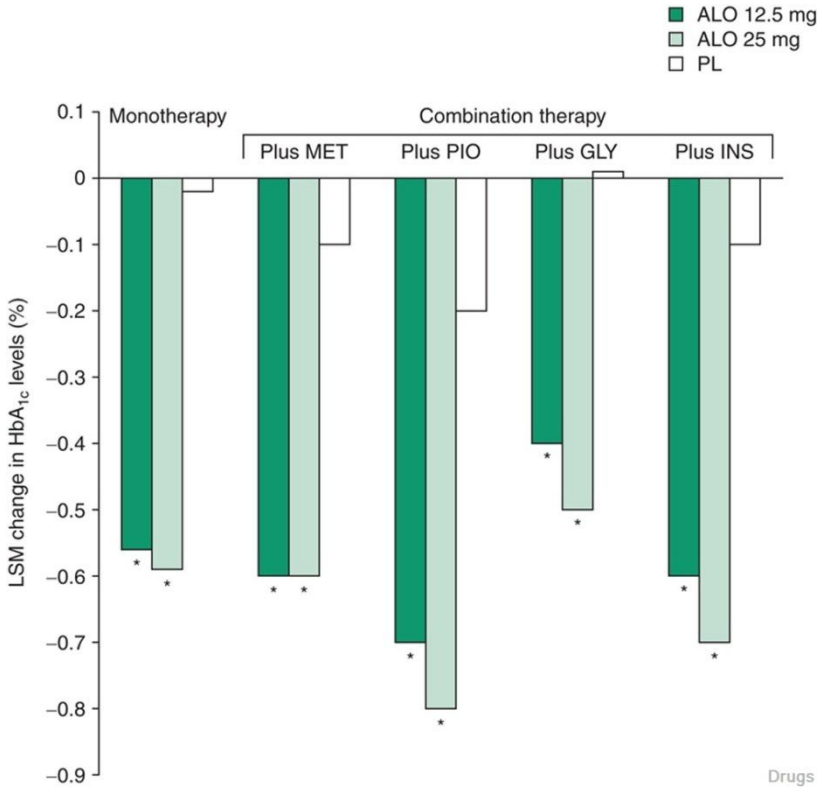

Fig. 5: LSM change in HbA_{1c} levels (%) in monotherapy and in combination therapy (Source- Drugs 2010:70(15):2051-2072)

ADVERSE REACTIONS [12,14,17,18,25]

Alogliptin is well tolerated drug. In clinical trials, it has not been found any dose limiting toxicity (DLT). The most common adverse reactions are-

(1) **Hypoglycemia (Plasma glucose ≤ 60mg/dL)**

The most common adverse reaction is hypoglycemia. Hypoglycemia was reported more in patients treated with the combination of alogliptin and sulfonylurea than in patients treated with the combination of placebo and sulfonylurea.

(2) **Weight gain**

In combination therapy of alogliptin, the weight of type-2 diabetic patients increased when alogliptin was added to the background of sulfonylurea: −0.2 kg placebo, +0.6 kg alogliptin 12.5 mg (P = 0.018) and +0.68 kg for alogliptin 25 mg (P = 0.010). There is no change in weight when alogliptin added to metformin. Mean differences in weight relative to placebo were 0.0 kg and −0.3 kg for 12.5 mg and 25 mg respectively.

(3) Headache

(4) Dizziness and

(5) Constipation

(6) Back pain

(7) muscle or joint pain

DOSE AND ROUTE OF ADMINISTRATION

Alogliptin is orally administered to adults once daily as 12.5 to 25mg for 26 weeks. It has no fixed dosage regimen[12,25].

DRUG-DRUG INTERACTION

Alogliptin has no significant drug-drug interactions when it administered with metformin, sulfonylurea, and pioglitazone in healthy volunteers. It has been found that alogliptin has no effect on the pharmacokinetic or pharmacodynamic profile of warfarin administered once daily in a 7-day study in healthy volunteers [13,14,26].

EFFECTS ON LIPIDS

The patients randomly received 12.5–25 mg/day alogliptin (n = 25) or severe low calorie traditional Japanese diet (n = 26). In these clinical trials, atherogenic lipids, such as, total cholesterol, non-high density lipoprotein cholesterol, and low density lipoprotein cholesterol levels significantly decreased in both groups. Changes in LDL were −3.2 mg/dL compared with placebo and +3.9 mg/dL (P = 0.044) in monotherapy and in combination therapy with glyburide. It has been no significant effects on lipid profiles, when alogliptin were given to type 2 diabetic patients with metformin [27,28].

MARKET ACCESS HISTORY OF ALOGLIPTIN

After positive results from phase III clinical trials, Takeda submitted a new Drug application for alogliptin to the United State Food and Drug Administration in December 2007. Takeda also submitted alogliptin for approval in japan in September 2008 and winnig approval in April 2008. The first USFDA NDA failed to gain approval and was followed by a pair of NDAs (one for alogliptin and a second for a combination of alogliptin and pioglitazone) in July 2011. The FDA is expected to make a decision on whether or not to approve both alogliptin and the combination pill by April 25, 2012. In 2012, Takeda received a negative response from the USFDA on both of these NDAs, citing a need for additional data. In 2013 Takeda receives FDA approval for three new type 2 diabetes therapies, nesina (alogliptin) and fixed-dose combinations oseni (alogliptin and pioglitazone) and kazano (alogliptin and metformin HCL) [11,12,29].

CONCLUSIONS

Alogliptin is a well tolerated drug. In clinical trials alogliptin alone or in combination with other antidiabetic drugs (metformin, sulfonylurea, pioglitazone etc.) has shown a significant reduction in HbA1c and FPG level in patients with type 2 diabetes. However, its consistent efficacy for longer duration of therapy needs further investigation.

REFERENCES

1. Vijan S. Type 2 diabetes. Annals of Internal Medicine.2010; 152 (5): ITC31-15.
2. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB. Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk. Circulation 2010; 121 (11):1356-64.
3. Centers for Disease Control and Prevention. National diabetes fact sheet, 2007. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2007.pdf. Accessed August 15, 2008.
4. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care. 2008; 31:S12–S54.
5. Barnett A. DPP-4 inhibitors and their potential role in the management of type 2 diabetes. Int J Clin Pract. 2006; 60:1454–1470.
6. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. Drugs. 2011, 71:1441-1467.
7. 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 Suppl 1:S16-29.
8. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nat Rev Endocrinol. 2009; 5:262-269.
9. Russell-Jones D, Gough S. Recent advances in incretin-based therapies. Clin Endocrinol (Oxf). 2012; 77:489-499.
10. Neumiller JJ. Clinical pharmacology of incretin therapies for type2 diabetes mellitus: implications for treatment. Clin Ther. 2011;33:528-576.
11. Takeda Submits New Drug Application for Alogliptin (SYR-322) in the U.S. Takeda Pharmaceutical Company (Press release). January 4, 2008. Retrieved January 9, 2008.
12. Grogan K. FDA wants yet more data on Takeda diabetes drug alogliptin. PharmaTimes(PharmaTimes): PharmaTimes online. 2012.
13. Eiji K, Yasuhiro U. Alogliptin as an initial therapy in patients with newly diagnosed, drug naïve type 2 diabetes: a randomized, control trial (abstract only). Endocrine. 2012.
14. Abdelghany S, Glode A. Alogliptin: A dipeptidyl peptidase-IV inhibitor for treatment of type 2 diabetes. Formulary Journal-Modern Medicine. 2008. Available at: http://www.cdc.gov/diabetes/Pubs/ /ndfs_2007. Accessed August 15, 2008.
15. Deacon CF. Alogliptin, a potent and selective dipeptidyl peptidase-IV inhibitor for the treatment of type 2 diabetes. Curr Opin Investig Drugs. 2008;9:402–413.
16. Covington P, Christopher R, Davenport M, et al. Pharmacokinetic, pharmacodynamic, and tolerability profiles of the dipeptidyl peptidase-4 inhibitor alogliptin: A randomized, double-blind, placebo-controlled, multiple-dose study in adult patients with type 2 diabetes. *Clin Ther*. 2008;30:499–512.
17. Christopher R, Covington P, Davenport M, et al. Pharmacokinetics, pharmacodynamics, and tolerability of single increasing doses of the dipeptidyl peptidase-4 inhibitor alogliptin in healthy male subjects. *Clin Ther*. 2008; 30:513–527.
18. Karim A, Fleck P, Hetman L, et al. Single-dose pharmacokinetics of the dipeptidyl peptidase-4 inhibitor alogliptin in subjects with renal impairment [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008; 538-P.
19. Karim A, Fleck P, Dorsey D, et al. Single-dose pharmacokinetics of alogliptin benzoate (SYR-322), a highly selective dipeptidyl peptidase-4 inhibitor, in subjects with moderate hepatic impairment [abstract]. Presented at: American College of Clinical Pharmacology 36th Annual Meeting; San Francisco, CA. September 9-11, 2007; 107-P.

20. Defronzo R, Fleck P, Wilson C, et al. Alogliptin monotherapy improves glycemic control in patients with type 2 diabetes [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008;446-P.
21. Nauck M, Ellis G, Fleck P, et al. Efficacy and safety of alogliptin added to metformin therapy in patients with type 2 diabetes [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008; 477-P.
22. Pratley R, Kipnes M, Fleck P, et al. Alogliptin added to sulfonylurea therapy in patients with type 2 diabetes reduces HbA1c without increasing hypoglycemia [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008; 445-P.
23. Pratley R, Reusch J, Fleck P, et al. Efficacy and safety of alogliptin added to pioglitazone therapy in patients with type 2 diabetes [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008; 478-P.
24. Rosenstock J, Rendel M, Gross J, et al. Alogliptin added to insulin therapy in patients with type 2 diabetes reduces HbA1c without increasing weight gain or hypoglycemia [abstract]. Presented at: American Diabetes Association 68th Annual Scientific Sessions; San Francisco, CA. June 6–10, 2008; 444-P.
25. Bosi E, Ellis G.C, Wilson C.A.; Fleck P.R. 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, Obesity and Metabolism.2011; 13 (12):1088–1096.
26. Kutoh E, Ukai Y. Kutoh E, Ukai Y. Alogliptin as an initial therapy in patients with newly diagnosed, drug naive type 2 diabetes: a randomized, control trial. Endocrine. 2012; 41:435-441.
27. Yutaka S, Tetsuya F, Shinzo H, Masashi H, Kohei K. 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 (abstract only). Current Medical Research and Opinion. 2011;27 (9): 1781–1792.
28. Andukuri R, Drincic A, Rendell M. Alogliptin: a new addition to the class of DPP-4 inhibitors. Diabetes Metab Syndr Obes. 2009; 2:117-126.
29. Jun F, Zhiyuan Z, Michael B.W, Jeffrey A.S, Stephen W.K, Daniel B.K, Marc N, Lihong S, et al. Discovery of alogliptin: a potent, selective, bioavailable, and efficacious inhibitor of dipeptidyl peptidase IV. J. Med. Chem. 2007; 50 (10): 2297–2300.