Review Article

Fixed-Dose Combination of Dipeptidyl Peptidase-4 Inhibitors Plus Metformin in Patients with Type 2 Diabetes: A Review on Safety and Efficacy

Abstract

There is a significant increase noted in the incidence and prevalence of Type 2 diabetes mellitus (T2DM). The global number of diabetic patients is projected by the International Diabetes Federation (IDF) to reach 552 million. T2DM disease has chronic and progressive nature. More than fifty percent of patients do not attain adequate glycemic control despite initial sufficient monotherapy. To maintain target glycated hemoglobin (HbA1c) levels (<7%), dose adjustment and adoption of several diabetes therapies become necessary in many cases. Compared to monotherapy, a fixed drug combination of oral agents and metformin has proven to be more efficacious to maintain levels of blood glucose and HbA1c. The combination of dipeptidyl peptidase-4 inhibitors (DDPIs) and metformin has been explicated to effectively decrease HbA1c to a relatively higher degree compared to the use of either agent individually. This combination addresses various pathophysiological processes involved in T2DM pathogenesis. Additionally, the concerned combination is safe and associated with a lower risk of hypoglycemia. Moreover, it is well-tolerated and prescribed as an easy-to-use single pill to improve patient compliance. This review provides an overview of the pharmacology, efficacy, and safety of fixed drug combinations of DDPIs and metformin according to current practice.

Keywords: Metformin, DDP-4, T2DM, Fixed-Dose, Monotherapy

Introduction:

An ideal glycemic control is the main objective in order to delay the advancement as well as complications of T2DM. A single antihyperglycemic agent fails in most cases in treatment to attain and/or maintain long term glycemic control among patients with type 2 diabetes (T2DM). Therefore, many patients need combinational therapeutic strategies that consisting of several antihyperglycemic medications with complementary action mechanisms [1]. When the glycemic goal is no longer attained by metformin as a monotherapy strategy, sulfonylurea and insulin are put to use [2-4]. Improper use of the combination therapy, likely linked to pill burden (higher amount of pills and frequency of dosage administration) and poor tolerability, can result in suboptimal clinical outcomes [5, 6]. The use of fixed-dose combinations of antihyperglycemic agents simplifies regimen of treatment via decreasing the pill burden in contrast to the same combination used as individual pills [5].

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) have recommended important guidelines which constitute the traditional stepwise approach to manage T2DM. This approach involves a lifestyle change, medical nutritional therapy, and physical exercise. Additionally, in case the hemoglobin A1c (HbA1c) levels exceed the target level of 7.0%, metformin monotherapy is recommended [6]. However, fewer than 50% of T2DM patients achieve suggested HbA1c targets. This failure to attain sufficient glycaemic control has two reasons, the first is the progressive nature of T2DM, and the second is constraints present in present therapies, which involve poor adherence and tolerability [6-8]. To treat type 2 diabetes patients, monotherapy with metformin or sulphonylurea remains a common initial oral hypoglycaemic agent (OHA) regimen [9].

An enzyme, Dipeptidyl peptidase-4 (DPP-4), is “implicated in the deterioration of the intact (active) incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) to inactive metabolites”. Responding to a meal intake, the intestines discharge GLP-1 and GIP into the circulation, and both hormones enhance glucose-dependent insulin secretion. Furthermore, GLP-1 inhibits glucagon release. By suppressing the degradation of active incretin and incretin metabolites, sitagliptin enables an increase in active incretin concentrations, leading to enhancing their glucoregulatory effects [10-12]. In the year 2006, Dipeptidyl peptidase-4 (DPP-4) inhibitors were presented as a diabetes medications, first with sitagliptin, and then followed by vildagliptin and saxagliptin [13].

This narrative review aims to shed light on the up-to-date clinical utilization of the fixed-dose combination approach of DPP-4 inhibitors plus metformin in the treatment of type 2 diabetes.

Pharmacology of Metformin

Metformin:

Metformin is administered as a hydrochloride salt (IUPAC nomenclature: *N*, *N*-dimethylimidodicarbinimidic diamide hydrochloride). It is a derivative of guanidine and has a molecular formula of $C_4H_{11}N_5HCl$ (figure 1. Chemical structure of metformin) [14]. Metformin is among biguanide class that work mainly by reducing glucose production from the liver and can also decrease insulin resistance [15]. Other probable effects of metformin involve increments in glucose uptake, insulin signalling, and fatty acid β-oxidation while a decrement in fatty acid and triglyceride synthesis. Metformin can also enhance glucose utilization in peripheral tissues and potentially reduce the meal intake and intestinal glucose absorption. Since metformin does not stimulate endogenous insulin secretion, it leads to no hypoglycemia or hyperinsulinemia, which are usually seen as side effects linked to other antidiabetic drugs [16].

Metformin undergoes saturable and partial oral bioavailability in the range of 40–60%. Food already present delays and reduces absorption. The distribution of metformin occurs without binding to plasma proteins and mainly undergoes renal excretion without any change, with the remaining 20–30% obtained in the faeces. For patients with renal impairment, an appreciable increase in plasma half-life is noticed, and it is not indicated to treat patients with an approximated glomerular filtration rate of less than 30 mL/min/1.73 m. The mean plasma half-life has been projected to be in the range of 4–8.7 hours [12, 14, 17, 18].

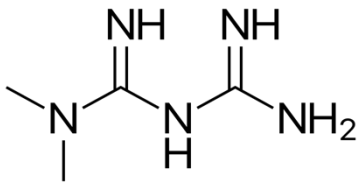

Figure 1. Chemical structure of metformin

Pharmacology of DDP-4 inhibitors:

Sitagliptin

Sitagliptin (Januvia®, Merck Pharmaceuticals) is a dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) that has been approved recently for the therapy of type 2 diabetes. Sitagliptin; IUPAC nomenclature: (2R)-4-Oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine (Figure 2. Chemical structure of Sitagliptin). Sitagliptin works by enhancing the two hormones, endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are produced as a result of food intake. GLP-1 and GIP enhancements result in insulin secretion by pancreatic *β*-cells, a decrease in glucagon secretion, and a decrease in glucose production by the liver. The excretion, as well as elimination, are primarily renal with 75% of an oral doses are presented in the urine as an unchanged drug and the remaining portion is metabolized by the cytochromes CYP 3A4 and CYP 2C8. Under sitagliptin therapy in clinical studies, the drug–drug interactions were not observed. In particular, no interactions of this nature were noticed with other antihyperglycemic agents in type 2 diabetic patients [19-22].

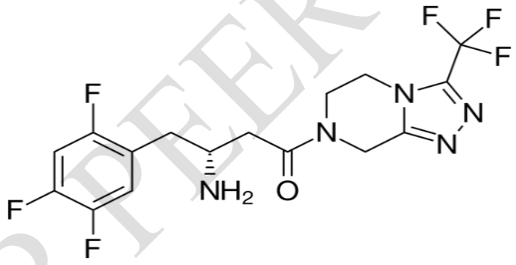

Figure 2. Chemical structure of sitagliptin

Vildagliptin:

Vildagliptin, (2*S*)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile (figure 3. Chemical structure of vildagliptin), is a dipeptidyl peptidase-4 inhibitor that the European Agency approved in the year 2008 for T2DM treatment. The enzymatic degradation of glucagon-like peptide 1 (GLP-1) is evaded by this inhibitor. The intestinal L-cells secrete GLP-1. GLP-1 can stimulate insulin secretion from the pancreatic β-cells into the blood in response to the intake of glucose, reduce glucagon secretion from pancreatic α-cells, delay gastric emptying and suppress appetite. It can also guard pancreatic β-cells against apoptosis and enhance

β-cell proliferation [23-25]. In addition, recent results suggest the anti-sclerotic, vasculoprotective, anti-inflammatory, and antihyperlipidemic effects of vildagliptin [26,27].

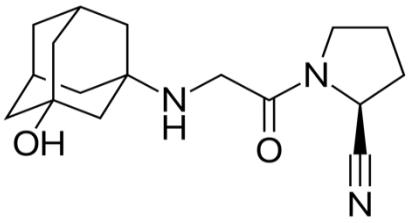

Figure 3. Chemical structure of vildagliptin

Saxagliptin:

Saxagliptin (figure 4. Chemical structure of saxagliptin) is a potent and selective DPP-4 inhibitor which the US Food and Drug Administration (FDA) approved in the year 2009 as an adjunct to diet and exercise to enhance glycemic control in adults suffering from T2DM. Saxagliptin appreciably boosts glycemic control, as shown by decreases in HbA1c, fasting plasma glucose (FPG), and postprandial glucose (PPG) [28,29]. Saxagliptin working as an add-on therapy to glyburide, a thiazolidinedione, or metformin, or in initial combination with metformin, is associated with a lower risk of hypoglycemia and higher reduction in HbA1c [30].

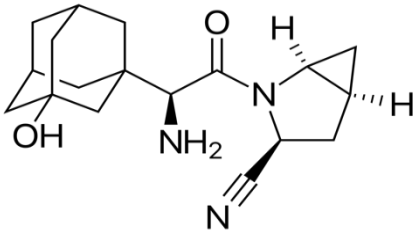

Figure 4. Chemical structure of saxagliptin

A fixed-dose combination approach in the treatment of Diabetes mellitus type 2:

T2DM patients, with concurrent hypertension, dyslipidemia and other comorbidities, face a frequent issue of polypharmacy. To attain optimal therapeutic benefits and decrease pill burden, the employment of FDCs is a rational approach. Pharmacotherapy with fixed-dose combination drugs is being more and more prevalent in the treatment of type 2 diabetes mellitus (T2DM) as evidence-based clinical guidelines have advocated the use of several therapeutic agents in complex regimens. Fixed-dose combination is understood as combinations of two or over active drugs within one dosage formulation (usually pills) [31-33].

Metformin is present as one of the component drugs in many fixed-dose combinations. But the standard immediate-release (IR) formulation of metformin may require two doses per day and may result in tolerability issues related to adverse gastrointestinal (GI) effects. Also, other formulations such as the XR formulations of metformin can be given as one dose per day and have been linked with a decrease in instances of GI effects frequently seen otherwise with metformin IR. As a result, they can possibly have compelling advantages to include in fixed-dose combinations. The long-term cost-effectiveness of a fixed-dose combinations needs to be thoroughly determined. As with all oral hypoglycemic agents (OHAs), monotherapy using a sulphonylurea may be not resulting in or maintaining adequate glycemic control. This necessitates novel, useful, and highly tolerable therapies that can be included in a sulphonylurea agent. In a similar manner, dual-combinational therapy with a sulphonylurea agent and metformin may not maintain or lead to glycemic control [5,34]. Even though insulin is often used as the next therapeutic approach and it needs parenteral administration found troublesome by a lot of patients, and the inclusion of a thiazolidinedione can result in edema and an increment in body weight, additional OHA options are required for inclusion in the dual combination of other OHAs and metformin to evade switching to insulin [35].

Efficacy and safety of DDP-4 inhibitors and metformin as fixed-dose combination:

Previous studies presented that the DPP-4 inhibitors with metformin as the initial combination therapy were linked with a higher reduction in HbA1c level, higher reduction in FPG level, and lower weight loss compared to metformin monotherapy. Furthermore, DPP-4 inhibitors with metformin acting as initial combinational therapy were not linked with a further decrease in adverse cardiovascular events nor the higher risk of hypoglycemia, nor the prolonged risk of gastrointestinal AEs when compared with metformin monotherapy [36, 37]. On the other hand, an increased risk of hypoglycemia and weight gain is present with the

sulfonylurea combinations. FDCs with thiazohdinedione bear warnings of an appreciably higher risk of edema and heart failure relative to placebo and also a higher risk of bone loss and fracture [38-40].

As with DPP-4 monotherapy, the fixed-dose combinations coupling a DPP-4 inhibitor with metformin XR (saxagliptin with metformin XR and sitagliptin with metformin XR) or with metformin immediate-release (sitagliptin with metformin immediate-release and alogliptin with metformin immediate-release) bear caution for pancreatitis and major hypersensitivity reactions. Likewise, in other metformin-containing fixed-dose combinations, tolerability considerations include gastrointestinal effects as possible adverse effects. For the reduction of GI side effects, patients should take fixed-dose combination therapy with a meal, and in most cases, with a progressive escalation of doses. Moreover, fixed-dose combinations of metformin with DDPI-4 inhibitors were found to promote patient adherence by decreasing the number of pills required, making the dosing regimen less complex, and reducing dosing frequency [40-43].

Cost-effectiveness of fixed-dose combination therapy:

The price of a fixed-dose combination formulation, in most cases, matches or is lesser when compared with the overall price of the separate components. The data mainly dealing with the effects of antihyperglycemic single-pill fixed-dose combinations in relation to costs of healthcare are limited. Some of the cost-effectiveness analyses have ascertained the clinical benefits of fixed-dose combinations in terms of a smaller number of healthcare resources and reduced direct monthly healthcare costs related to clinical trials, translating into cost reduction and higher life expectancy. A previous retrospective study revealed that fixed-dose combination therapies present a compliance benefit compared to loose-pill therapies, that can possibly lead to decreases in utilization of healthcare and expenditures [44].

Conclusion:

Polypharmacy is considered a serious issue for diabetic patients. The use of fixed-dose combination formulations is a sound approach to obtain excellent clinical outcomes meanwhile reducing the heavy pill burden for the patients. Due to the difficulty of providing complete bioavailability and bioequivalence profiles for fixed-dose combination formulations, there is a dearth of prospective, randomized controlled trials mainly comparing fixed-dose combination formulations with their component drugs given as individual pills. This

should not be taken as a constraint to their use. The treatment with DDP-4 inhibitors as a fixed-dose combination with metformin leads to clinically relevant decrease in HbA_{1c}, fasting glucose, and PPG than monotherapy with metformin alone. Overall, treatment with DDP-4 inhibitors as a fixed-dose combination is well tolerated and results in fewer adverse events.

Ethical Consideration:

Not applicable

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

References:

1- American Diabetes Association: Glycemic targets: standards of medical care in diabetes-2018. *Diabetes Care*. 2018; 41:55-64.

2- Li CJ, Zhang JY, Yu DM, Zhang QM: Adding glimepiride to current insulin therapy increases high-molecular weight adiponectin levels to improve glycemic control in poorly controlled type 2 diabetes. *Diabetol Metab Syndr*. 2014; 6:41.

3- Arya DS, Chowdhury S, Chawla R, et al.: Clinical benefits of fixed dose combinations translated to improved patient compliance. *J Assoc Physicians India*. 2019; 67:58-64.

4- American Diabetes Association: Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019; 42:90-102.

5- Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; 281: 2005–2012.

6- Hermansen, K., Kipnes, M., Luo, E., Fanurik, D., Khatami, H., Stein, P. et al., Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. *Diabetes, Obesity and Metabolism.* 2007; 9: 733-745.

7- Nathan DM, Buse JB, Davidson MB *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32: 193–203.

8- Gerich J. Dpp-4 inhibitors: what may be the clinical differentiators? *Diabetes Res Clin Pract.* 2010; 90: 131–140.

9- Doar JW, Thompson ME, Wilde CE, Sewell PF. Diet and oral antidiabetic drugs and plasma sugar and insulin levels in patients with maturity-onset diabetes mellitus. *Br Med J* 1976; 1: 498–500.

10- Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998; 47: 1663–1670.

11- Deacon CF, Ahren B, Holst JJ. Inhibitors of dipeptidyl peptidase IV: a novel approach for the prevention and treatment of Type 2 diabetes? *Expert Opin Investig Drugs* 2004; 13: 1091–1102.

12- Herman GA, Stevens C, Van Dyck K *et al*. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. *Clin Pharmacol Ther* 2005; 78: 675–688.

13- Gallwitz B. Sitagliptin: profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes (update). *Drugs Today (Barc)* 2007; 43: 801–814.

14- National Center for Biotechnology Information. PubChem Compound Database; CID=4091. Available from: http://pubchem.ncbi.nlm.nih.gov/compound/4091. Accessed October 2021.

15- Hundal RS, Krssak M, Dufour S *et al*. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 2000; 49: 2063–2069.

16- Gong L, Goswami S, Giacomini KM, Altman RB, Klein TE. Metformin pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics*. 2012;22(11):820-827.

17- American Diabetes Association. Standards of medical care in diabetes – 2016. *Diabetes Care*. 2016;39(suppl 1):S1–S106.

18- Papanas N, Maltezis E. Metformin: a review of its use in the treatment of type 2 diabetes. *Clin Med Ther*. 2009;1:1367–1381.

19- Gupta R, Walunj SS, Tokala RK et al. Emerging drug candidates of dipeptidyl peptidase IV (DPP IV) inhibitor class for the treatment of Type 2 Diabetes. *Curr Drug Targets* 2009; 10: 71–87.

20- Gallwitz B. Review of sitagliptin phosphate: a novel treatment for type 2 diabetes. *Vasc Health Risk Manag*. 2007;3(2):203-210.

21- Kim D, Wang L, Beconi M, et al. (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl) butan-2-amine: a potent, orally active dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes. *J Med Chem*. 2005;48:141–51.

22- Herman GA, Bergman A, Yi B, et al. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase–4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Curr Med Res Opin*. 2006a;22:1939–47.

23- National Center for Biotechnology Information. PubChem Compound Database; CID=4091. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Galvus. Accessed October 2021.

24- Croxtall J.D., Keam S.J. Vildagliptin: A Review of its Use in the Management of Type 2 Diabetes Mellitus. *Drugs*. 2008;68:2387–2409.

25- Thornberry N.A., Gallwitz B. Mechanism of action of inhibitors of dipeptidyl-peptidase-4 (DPP-4) *Best Pract. Res. Clin. Endocrinol. Metab*. 2009;23:479–486.

26- Hausenloy D.J., Whittington H.J., Wynne A.M., Begum S.S., Theodorou L., Riksen N., Mocanu M.M., Yellon D.M. Dipeptidyl peptidase-4 inhibitors and GLP-1 reduce myocardial infarct size in a glucose-dependent manner. *Cardiovasc. Diabetol.* 2013;12:154.

27- Donath M.Y. Multiple benefits of targeting inflammation in the treatment of type 2 diabetes. *Diabetologia.* 2016;59:679–682.

28- US Food and Drug Administration. *NDA Approval* [Onglyza New Drug Approval]. Silver Spring: US Food and Drug Administration; 2009. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022350s000ltr.pdf. Accessed October 2021.

29- Rosenstock J, Aguilar-Salinas C, Klein E, Nepal S, List J, Chen R; CV181-011 Study Investigators. Effect of saxagliptin monotherapy in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin.* 2009;25(10):2401–2411.

30- Karyekar CS, Frederich R, Ravichandran S. Clinically relevant reductions in HbA1c without hypoglycaemia: results across four studies of saxagliptin. *Int J Clin Pract*. 2013;67(8):759-767.

31- World Health Organization. Annex 5, Guidelines for registration of fixed-dose combination medicinal products [WHO Technical Report 2]. 2005. http://www.who.int/medicines/areas/quality_safety/quality_assurance/Guidelines Registration Fixed DoseCombinationTRS929Annex5. pdf. Accessed October 2021.

32- Wertheimer AI. The economics of polypharmacology: fixed dose combinations and drug cocktails. *Curr Med Chem.* 2013; 20:1635-8.

33- Kawalec P, Holko P, Gawin M, Pilc A. Effectiveness of fixed dose combination therapy in hypertension: systematic review and meta-analysis. *Arch Med Sci*. 2018; 14:1125 1136.

34- Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled on metformin alone. *Diabetes Care*2006; **29**: 2638–2643.

35- Wainstein J, Katz L, Engel SS, *et al*. Initial therapy with the fixed-dose combination of sitagliptin and metformin results in greater improvement in glycaemic control compared with pioglitazone monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab*. 2012;14: 409– 418.

36- Wu, D., Li, L. and Liu, C., Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. Diabetes Obes Metab. 2014;16: 30-37.

37- Pfützner A, Paz-Pacheco E, Allen E et al. Initial combination therapy with saxagliptin and metformin provides sustained glycaemic control and is well tolerated for up to 76 weeks. *Diabetes Obes Metab* 2011; 13: 567–576.

38- Rosenstock J, Brazg R, Andryuk P, Lu K, Stein P. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing pioglitazone therapy in patients with type 2 diabetes: a 24-week, multicenter, randomized, double-Blind, placebo-controlled parallel group study. *Clin Ther* 2006; 28: 1556–1568.

39- Charbonnel B, Karasik A, Liu J, Wu M, Meininger G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled on metformin alone. *Diabetes Care*2006; 29: 2638–2643.

40- Roberts VL, Stewart J, Issa M, Lake B, Melis R. Triple therapy with glimepiride in patients with type 2 diabetes mellitus inadequately controlled by metformin and a thiazolidinedione: results of a 30-week, randomized, double-blind, placebo-controlled, parallel-group study. *Clin Ther*2005; 27: 1535–1547.

41- Hutchins V, Zhang B, Fleurence RL, Krishnarajah G, Graham J. A systematic review of adherence, treatment satisfaction and costs, in fixed-dose combination regimens in type 2 diabetes. *Curr Med Res Opin.* 2011;27:1157-1168.

42- Stenlöf K, Raz I, Neutel J, Ravichandran S, Berglind N, Chen R. Saxagliptin and metformin XR combination therapy provides glycémie control over 24 hours in patients with T2DM inadequately controlled with metformin. *Curr Med Res Opin.* 2010; 26: 2355-2363.

43- Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. *Adv Ther*. 2012;29:1-13.

44- Lokhandwala T, Smith N, Sternhufvud C, et al. A retrospective study of persistence, adherence, and health economic outcomes of fixed-dose combination vs. loose-dose combination of oral anti-diabetes drugs. *J Med Econ* 2016; 19:203-12