Saxagliptin: A New Drug for the Treatment of Type 2 Diabetes

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Abstract: Saxagliptin (**BMS-477118**), a recently FDA approved drug for the management of T2DM, has been developed by Bristol-Myers Squibb and AstraZeneca under the trade name Onglyza™. Saxagliptin is a nitrile-containing selective, potent, reversible and durable DPP IV inhibitor developed as an alternative second-line to Metformin in place of a sulphonylurea. Saxagliptin increases and prolongs the action of incretin hormones by inhibiting the DPP IV enzyme that inactivates incretins usually within minutes. Saxagliptin is well absorbed and has low plasma protein binding and displays slow-binding properties to DPP IV. Saxagliptin is metabolized *in vivo* to form an active metabolite (BMS-510849), which is twofold less potent than the parent molecule. The X-ray crystallography revealed that Saxagliptin is covalently bound to the DPP IV active site. In drug-naive patients with T2DM and inadequate glycemic control, once-daily Saxagliptin monotherapy for 24 wks demonstrated clinically meaningful with no weight gain and was generally well tolerated.

Keywords: Diabetes, DPP IV, incretin, gliptin, onglyza.

INTRODUCTION

Saxagliptin (BMS-477118) is a recently U.S. Food and Drug Administration (FDA) approved drug for the management of type 2 diabetes mellitus (T2DM) [1]. Saxagliptin has been developed by Bristol-Myers Squibb Company (NYSE: BMY) and AstraZeneca (NYSE: AZN) and marketed under the trade name Onglyza™. The FDA approved Onglyza (Saxagliptin) on July 31, 2009 [2]. Chemically Saxagliptin is a nitrile-containing selective, potent, reversible and durable dipeptidyl peptidase IV (DPP IV) inhibitor [3]. A number of DPP IV inhibitors have entered clinical development that mainly include Januvia™ (Sitagliptin) and Vildagliptin and are now available for the treatment of T2DM. Alogliptin is awaiting regulatory approval, and others *e.g.* Linagliptin (aka BI-1356) are in phase 3 clinical trials [4]. Saxagliptin is the most recent DPP IV inhibitor developed as an alternative second-line adds on to Metformin in place of a sulphonylurea (SU) in cases of a significant concern regarding hypoglycaemia, when control of blood glucose remains inadequate despite maximal tolerated Metformin monotherapy [5]. Saxagliptin competitively inhibits DPP IV by activating incretin hormones, thereby increasing their blood stream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner.

Dipeptidyl peptidase IV (DPP IV, EC 3.4.14.5) is a non-classical, sequence-specific serine protease [6, 7] that catalyzes the cleavage of dipeptides from the N-terminus of proteins. It is a protein that modulates the biological activity of specific circulating peptide hormones, chemokines, cytokines and neuropeptides by specifically cleaving two nitrogen terminal amino acids protein [8]. It is known under different names depending upon location such as Dipeptidyl peptidase IV (DPP IV), CD26, adenosine deaminase complexing protein 2 (ADCP2), T-cell activation TP103 antigen. DPP IV is imbedded on the epithelial brush boarder mucosal membrane of the intestinal tract lining [9]. It is encoded by the DPP IV gene which is responsible for the initial rapid degradation of glucagon like peptide 1 (GLP 1) and glucose dependent insulinotropic polypeptide (GIP). DPP IV inhibitors are a class of oral hypoglycemics that work by affecting the action of natural hormones in the body called incretins [10]. The incretin pathway, in particular GLP 1 and, to a lesser extent, GIP, plays an important role in modulating islet cell function, gastric emptying and satiety [11]. DPP IV is also responsible for the initial rapid degradation of both GLP 1 and GIP 3. Increased concentrations of the incretin hormones such as GLP 1 and GIP are released into the blood stream from the small intestine in response to meals. Incretins are rapidly degraded by the enzyme DPP IV by cleaving the active peptide at the position 2 alanine (N-terminal) resulting in inactive peptide [12]. DPP IV is widely expressed in human tissues including the brain, lungs, kidneys, adrenals, pancreas, intestine, and lymphocytes. DPP IV has effects beyond its proteolytic action, including T-cell proliferation. In addition, many neuropeptides, growth factors, cytokines, and chemokines have been identified as potential DPP IV substrates. In 1993, Mentlein *et al.* reported degradation of GIP and GLP 1 by DPP in dipeptidyl peptidase IV hydrolyses gastric inhibitory polypeptide, glucagon-like peptide-1 (7-36) amide, peptide histidine methionine and is responsible for their degradation in human serum [13]. Thus the main role of DPP IV enzyme is to cleave the N-terminal 2 amino acids of active GLP 1 to give the inactive GLP 1 amide. Degradation of GLP 1 leads to decrease in insulin

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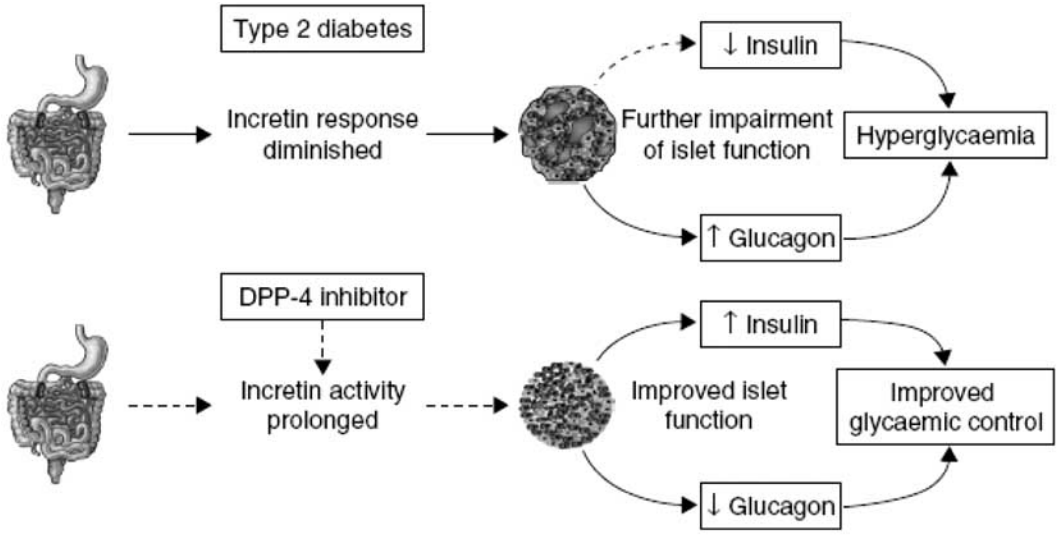


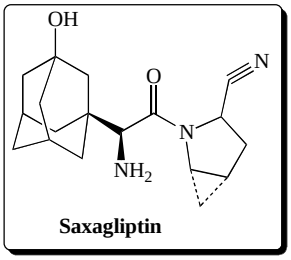
Fig. (1). Mechanism of DPP-4 Inhibitors [15].

secretion and biosynthesis. DPP IV inhibitors are oral hypoglycaemic agents that result in around a four-fold increase in plasma GLP 1 levels. Due to the glucose-dependent effects of GLP 1, DPP IV inhibitors are associated with low risk of hypoglycaemia [14, 15].

Saxagliptin increases and prolongs the action of incretin hormones by inhibiting the DPP IV enzyme that inactivates incretins usually within minutes (Fig. **1**). The inhibition of the DPP IV enzyme by Saxagliptin results in an increase in the production of insulin and a decrease in the production of glucagon by the pancreas. These effects are glucose dependent and enhance the body's natural response to food to reduce blood sugar levels before and after meals. In addition to stimulating insulin secretion, Saxagliptin upgrades all steps in the insulin biosynthesis and is associated with improvement in β-cell function. Preclinical studies have indicated that Saxagliptin is β-cell protective, increases differentiation, proliferation and reduces apoptosis in animal models. This has been associated with increase in β-cell mass [10,12].

CHEMISTRY

Chemically Saxagliptin is (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile. Saxagliptin is a small drug molecule (molecular weight of 315.4 $g.mol^{-1}$ and 334.43 $g.mol^{-1}$ for the Saxagliptin monohydrate dosed ingredient), and having low aqueous solubility. It contains a number of interesting functional groups and the molecule resembles a dipeptide in its 2-D structure. The functional group nitrile (-CN) is essential for inhibitory activity and is found in several other 'gliptins'. This functional group forms a reversible, covalent bond with amino acid residue Ser 630 (S630) of DPP IV. The bulky, hydrophobic adamantane group is a 3D cage like portion of the molecule. Within the 'gliptins' the large bulky adamantyl group blocks an intramolecular cyclisation which would otherwise have inactivated the inhibitor. These nitrile and adamantyl groups are linked *via* an amide bond, and an unusual 5, 3 fused ring system pyrollidine (which resembles the amino-acid proline, found in the corresponding position of natural substrates) [16].



Saxagliptin

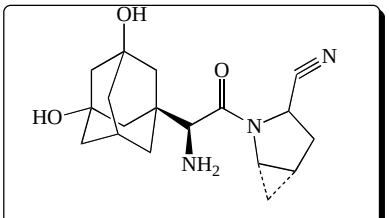
(1*S*,3*S*,5*S*)-2-[(2*S*)-2-amino-2-(3-hydroxy-1-adamantyl) acetyl]-2-azabicyclo[3.1.0] hexane-3-carbonitrile; (1S,3S,5S)-2-[(2S)-2-Amino-2-(3hydroxytricyclo[3.3.1.1]dec-1-yl)acetyl]-2-aza bicyclo [3.1.0]hexane-3-carbonitrile; (*S*)-3-hydroxy adamantylglycine-*cis*-4,5-methanoprolinenitrile

Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400) [16].

PHARMACOKINETICS

Saxagliptin is well absorbed and has low plasma protein binding (<30%),>ca. 15.8 μmol) [16]. It is a potent inhibitor of DPP IV that displays slow-binding properties [17, 18]. The inhibition of DPP IV by Saxagliptin is a two-step process, which involves formation of reversible covalent enzyme inhibitor complex. It starts with slow onset of inhibition and a slow rate of inhibitor dissociation that result in enzyme slowly equilibrating between the active and inactive forms [19]. The inhibition constant (Ki) of Saxagliptin (1.3±0.3nM) for DPP IV inhibition at 37°C suggests that it is 10-fold more potent than either Vildagliptin (13±3nM) or Sitagliptin (18±2nM). Saxagliptin is cleared by both metabolism and renal excretion [20]. Saxagliptin is metabolized *in vivo* to form an active metabolite (BMS-510849), which is two fold less potent than the parent molecule. It is believed

that this metabolism is largely mediated *via* the cytochrome CYP3A in the liver. This is further proved in studies on subjects with liver failure where plasma concentrations of the metabolite are reduced (7%- 33% lower) with increasing severity of hepatic impairment, while at the same time exposure to the parent drug increases (10%-77% higher) [21].



BMS 510849 (Metabolite of Saxagliptin)

Saxagliptin demonstrates greater specificity for DPP IV than for either the DPP VIII or DPP IX enzymes. Saxagliptin and its metabolite are potent inhibitors of DPP IV activity *in vitro* [17]. Both are selective for DPP IV versus DPP VIII (400-fold and 950-fold, respectively) and DPP IX enzymes (75-fold and 160-fold, respectively) and do not inhibit any other members of the DPP IV family (> 4000-fold selectivity) [22]. The t½ of dissociation of Saxagliptin and its metabolite from DPP IV is found to be 50 and 23 minutes, respectively as compared to Sitagliptin and Vildagliptin having t½ 1 and 1.7 hours, respectively [22]. Slow dissociation of Saxagliptin from DPP IV has not been observed with any other enzymes tested, including DPP VIII and DPP IX [17, 18].

MECHANISM OF DPP IV INHIBITION BY SAXAGLIPTIN

The inhibition of DPP IV by Saxagliptin has been proposed to occur through formation of a covalent but reversible complex. DPP IV is a prototypic serine protease whose substrate cleavage is driven by activation of a Ser-His-Asp triad [23]. DPP IV largely contains two active pockets namely S1and S2. In general, the inhibitors of the DPP IV occupy the S1–S2 pocket at the DPP IV active site and make extensive hydrophobic, van der Waals, and hydrogen-bonding interactions with residues lining this pocket. Mechanism-based enzyme inhibitor complex is formed between DPP IV and Saxagliptin. Initial inhibitor binding is followed by serine addition to the inhibitor nitrile carbon, catalyzed by histidine [23]. The three-dimensional structure of the DPP IV-Saxagliptin complex was determined by X-ray crystallography (Fig. **2**).

The X-ray crystallography revealed that Saxagliptin is covalently bound to the DPP IV active site, with the nitrile forming a covalent imidate adduct with the hydroxyl of the active-site serine 630 (S630) resulting in a stable trigonal complex. The 4, 5-methanopyrrolidine ring is buried in the hydrophobic S1 pocket near catalytic serine, where it forms van der Waals interactions with the side-chain residues that form the pocket. In the complex with DPP IV, the nitrile carbon of Saxagliptin adopts sp^2 geometry as it forms a covalent bond with the serine hydroxyl. However, unable to form a covalent interaction in DPP IV S630A, the nitrile carbon retains its sp character. In this hybridization geometry, the nitrile of Saxagliptin causes a large steric clash with the Ala630 side chain of DPP IV S630A. The enhanced nucleophilicity of S630A by the basicity of H740 is an essential component of the mechanism by which Saxagliptin covalently binds to DPP IV. In the S2 pocket, the side-chain NH_2 of N710 hydrogen bonds with the carbonyl oxygen of Saxagliptin. The adamantane ring extends into the S2 pocket, enabling two hydrogen bonds with the side-chain hydroxyl of Y547: one with the adamantane hydroxyl and the second with the imidate nitrogen [24].

PRECLINICAL STUDIES

Preclinical studies suggest that Saxagliptin shows a high sensitivity for DPP IV (IC_{50} = 3.5, 18, and 26 nM for Vildagliptin, Sitagliptin, and Saxagliptin, respectively). Conversely, Saxagliptin demonstrates a low affinity for DPP VIII and DPP IX (IC_{50} for DPP VIII = IX and > 50 nM for Vildagliptin and Sitagliptin, respectively; IC_{50} for DPP IX ≥ 50 nM for Sitagliptin). Saxagliptin dose-dependently inhibits plasma DPP IV activity in Han-Wistar rats, by ~70% at 7 hours postdose with 1 mg/kg and by ~90% at 7 hours postdose with 10 mg/kg. At 24 hours postdose, ~20% and 70% inhibition, respectively, remained. In C57BL/6J mice, Saxagliptin at a dose of 1 mg/kg, suppressed the glucose excursion by ~50% compared with the control when given 45 minutes before the glucose challenge, but the effect was lost when the glucose challenge was given 16 hours postdose. However, consistent with the effect on plasma DPP IV activity, when the dose was increased to 10 mg/kg, the glucose-lowering effect was evident 16 hours postdose [25]. In Zucker fatty rats, maximal reductions in the glucose excursion following oral glucose (2 g/kg) were attained when plasma DPP IV activity was inhibited by ~60%, with no further increase in efficacy with greater inhibition. Single doses of Saxagliptin (0.3, 1, and 3 μmol/kg) given 4 hours prior to an oral glucose tolerance test dose-dependently reduced the glucose excursion by ~30 up to ~60% in this model. In experiments in the *ob/ob* mouse, the oral glucose tolerance test (OGTT) was performed 1 h after oral administration of Saxagliptin 1, 3 or 10 μmol/kg. Dose-dependent elevations in plasma insulin were seen, with a significant effect noted at 15 min post-OGTT, along with improvement in glucose clearance curves 60 min after the OGTT. These results support the role of potentiating GLP-1-induced insulin secretion in the antihyperglycemic activity of Saxagliptin [17].

CLINICAL STUDIES

In a monotherapy trial with Saxagliptin on a total number of 766 subjects with type II diabetes inadequately controlled on diet and exercise participated in two 24-week, double-blind, placebo-controlled trials were taken. In a 2-week single-blind diet, exercise, and placebo lead-in period, 401 subjects were randomized to 2.5 mg, 5 mg, or 10 mg of Saxagliptin or placebo. Treatment with Saxagliptin provided significant improvements in A1C, FPG, and PPG compared to placebo. The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the Saxagliptin 2.5 mg treatment group, 20% in the Saxagliptin 5 mg treatment group, and 26% in the placebo group.

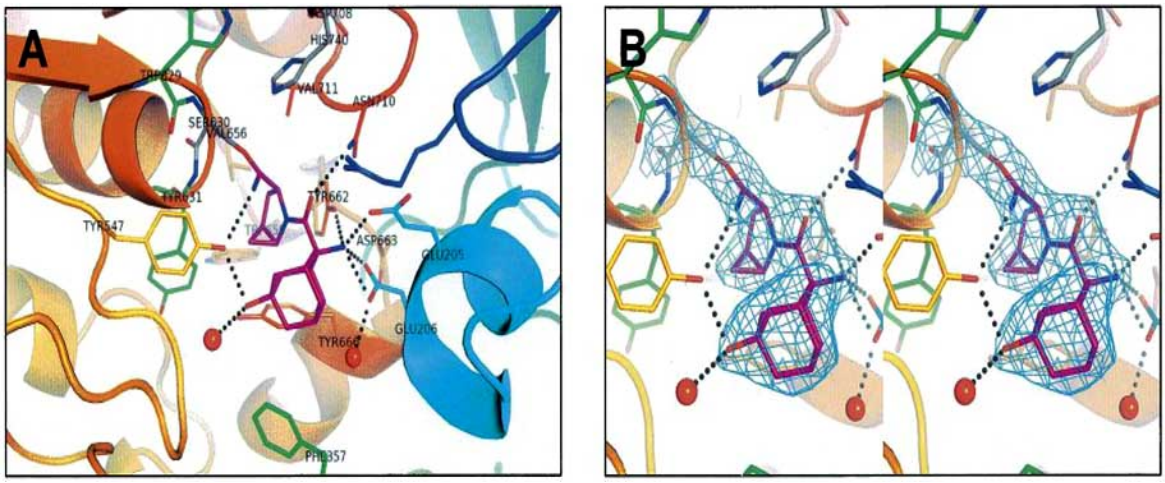


Fig. (2). X-ray co-crystal structure of Saxagliptin (magenta) complexed with DPP IV [23].

In the 24-week monotherapy trial enrolled 365 treatment-naive subjects with inadequately controlled diabetes. Following a 2 week, single-blind diet, exercise, and placebo lead-in period, the subjects were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of Saxagliptin or placebo. Treatment with either Saxagliptin 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of -0.4 % and -0.3%, respectively). Treatment with Saxagliptin 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of 0.4%).

In trials evaluating Saxagliptin in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone), Saxagliptin 2.5 mg and 5 mg plus combination provided significant improvements in A1C, FPG, and PPG compared with placebo plus combination [26,27].

Various studies have revealed that Saxagliptin exposure was slightly increased (less than twofold) in elderly individuals (aged ≥65 years) following a single oral 10 mg dose, compared with younger individuals (aged 18-40 years). A small difference in the pharmacokinetics is also observed between healthy male and female participants. No dosage adjustment for Saxagliptin was necessary on the basis of age or gender [28]. Moreover, hepatic insufficiency does not seem to alter the pharmacokinetics of Saxagliptin [29]. No dose adjustment is required based on gender, race, weight or hepatic impairment. A significant reductions in HbA1c is achieved with Saxagliptin over a dose range 2.5–40mg [30].

In drug-naive patients with T2DM and inadequate glycemic control, once-daily Saxagliptin monotherapy for 24 wks demonstrated clinically meaningful reductions in A1C, FPG, and PPG-AUC with no weight gain, and was generally well tolerated [31, 32]. The general comparative characteristic features of Saxagliptin, Vildagliptin and Sitagliptin have been summarized in Table **1**.

FDA APPROVAL AND MARKET AUTHORIZATION

The FDA approval of Saxagliptin was based on monotherapy trials and in trials combining Saxagliptin with Metformin, Glyburide, and thiazolidinedione (Pioglitazone and Rosiglitazone) therapy. The FDA's action was primarily based on data from eight clinical trials. Results showed that Saxagliptin is superior to placebo for reducing HbA_{1c}, fasting plasma glucose, and postprandial glucose levels in

Table 1.

S. No.	Properties	Saxagliptin	Vildagliptin	Sitagliptin
1.	K_i (nM)	1.3±0.3	13±3	18±2
2.	IC_{50}(nM)	26	18	3.5
3.	$t_{1/2}$	50 min.	1.7 hr	1 hr
4.	Bioavailability	67% (Predicted)75 %(Animal Models)	85%	87%
5.	Protein Binding	30%	9.5%	38%
6.	Excretion	Renal +Hepatic(75%)	Renal(85%)	Renal(80%)
7	Dosage	2.5 or 5 mg/day	100 mg /day(50mgtwice /day)	100 mg / day
8.	Trade Name	Onglyza(Bristol Myers Squibb-Astra Zeneca)	Galvus(Novartis)	Januvia(Merck)

patients with T2DM. Likewise, adding Saxagliptin to Metformin, sulfonylurea, or thiazolidinedione lowered HbA_{1c} levels to a greater extent than either of these standard drugs alone. Throughout the Phase III development program, treatment with Saxagliptin at all doses produced clinically relevant and statistically significant reductions in all three key measures of glucose control studied A1C, fasting plasma glucose (FPG) and post-prandial glucose (PPG) when combined with other commonly used oral anti-diabetic agents or when used as a monotherapy [33].

Onglyza is a trademark of the Bristol-Myers Squibb Company. Bristol-Myers Squibb announced on 27 December 2006 that Otsuka Pharmaceutical Co. has been granted exclusive rights to develop and commercialize the compound in Japan [34]. Under the licensing agreement, Otsuka will be responsible for all development costs, but Bristol-Myers Squibb retains rights to co-promote Saxagliptin with Otsuka in Japan. Further, on 11 January 2007 Bristol-Myers Squibb and AstraZeneca entered into a collaboration to enable the companies to research, develop and commercialize investigational drugs for T2DM. The Bristol-Myers Squibb/ Astra Zeneca diabetes collaboration is dedicated to global patient care, improving patient outcomes and creating a new vision for the treatment of T2DM. Bristol-Myers Squibb and AstraZeneca working together to complete development and subsequent marketing of the Onglyza.

DOSAGE

Onglyza is supplied as a 5 mg and 2.5 mg tablet designed for oral administration. Each film-coated tablet of Onglyza for oral use contains either 2.79 mg Saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg Saxagliptin or 5.58 mg Saxagliptin hydrochloride (anhydrous) equivalent to 5 mg Saxagliptin and the following excepients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides [35]. The recommended initial dose of the drug is 2.5 mg or 5 mg once daily taken regardless of meals. The 2.5 mg daily dosage is recommended for patients with moderate or severe renal impairment or end-stage renal disease and also for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors [26].

Saxagliptin is indicated as an adjunct to diet and exercise to improve blood sugar (glycemic) control in adults for the treatment of T2DM. Saxagliptin once daily can be used in combination with commonly prescribed oral anti-diabetic medications metformin, sulfonylureas or thiazolidinediones (TZD) or as a monotherapy to significantly reduce glycosylated hemoglobin (A1C) levels. Saxagliptin should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis (high levels of certain acids, known as ketones, in the blood or urine) [36].

ADVERSE EFFECTS

Saxagliptin as monotherapy and in combination with other antidiabetic drugs has demonstrated a good safety and tolerability profile. Specifically, DPP IV inhibitors are not associated with nausea or vomiting, which are common adverse events for GLP 1 analogues [37]. Adverse events associated with the use of Saxagliptin may include upper respiratory tract infection, urinary tract infection, headache, nasopharyngitis, acute pancreatitis, toxic skin eruption. Small, reversible, dose dependent reductions in absolute lymphocyte count has been observed that is more apparent at doses $\geq$20 mg, which, however, remained within normal limits [38]. Low blood sugar (hypoglycemia) may become worse in people who already take another medication to treat diabetes such as sulfonylureas [35, 39]. Hypersensitivity-related events (e.g., urticaria, facial edema) were reported more commonly in patients treated with Saxagliptin than in patients treated with placebo. Swelling or fluid retention in hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes [40].

DRUG INTERACTIONS

Pharmacokinetic studies have been conducted to assess the potential interactions between Saxagliptin and Diltiazem, Ketoconazole, Pioglitazone, Metformin and Digoxin. Ketoconazole and Diltiazem, potent inhibitors of CYP3A4/5, might be expected to alter the pharmacokinetics of Saxagliptin. Thus dosage adjustment of Saxagliptin may be required when co-administered with Ketoconazole or Diltiazem [41, 42]. The findings of an open-label evaluation of co-administration of Saxagliptin and Pioglitazone indicated that no dose adjustments are necessary for such combined treatment. The pharmacokinetic effects resulting from co-administration of Saxagliptin and Metformin are not sufficient to warrant dose adjustment for either agent according to the results of an interaction study [43]. Also, Digoxin and Saxagliptin does not affect the pharmacokinetics profile of each other. So, there was a lack of interaction when these two agents were co-administered [44].

CONCLUSION

Saxagliptin in combination with other antidiabetic drugs has exhibited a good safety and tolerability profile evident from the existing clinical data. Saxagliptin could prove to be a new alternative to the currently available antidiabetic medications for the patients with T2DM.

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