Pharmacokinetic, pharmacodynamic and clinical evaluation of saxagliptin in type 2 diabetes

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Abstract

Introduction: Dipeptide peptidase-4 (DPP-4) inhibitors such as saxagliptin are established and efficacious oral therapies in the management of type 2 diabetes. These agents have the potential to confer significant benefits in glycaemic control without the risk of weight gain and hypoglycaemia, which may be associated with other medications used to treat type 2 diabetes.

Areas covered: This review examines the pharmacokinetics, efficacy and tolerability of saxagliptin for the management of type 2 diabetes.

Expert opinion: Saxagliptin is routinely used in the management of type 2 diabetes as monotherapy, and in combination with other oral agents and insulin. Robust clinical trials have shown consistent improvements in glycated haemoglobin, fasting and postprandial glucose levels, with few adverse effects. The agent is well tolerated with low rates of hypoglycaemia in the absence of insulin or sulphonylurea therapy.

Keywords: DPP-4; Saxagliptin; Glucagon-like peptide 1.

1. Introduction

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, which prevents the catabolism of endogenous glucagon-like peptide-1 (GLP-1) and subsequently potentiates glucose-dependent insulin secretion and inhibits glucagon secretion. Saxagliptin is a well-established treatment for type 2 diabetes (for reviews see [1, 2]) and along with other DPP-4 inhibitors, offers significant benefits with minimal unwanted effects. Studies have shown that saxagliptin significantly improves glycaemic control when used as monotherapy [3], as add-on therapy to metformin [4, 5], in fixed dose combination with metformin [6], and as add-on to thiazolidinedione [7], sulphonurea [8] and insulin [9] therapies. The addition of saxagliptin to other therapies is well tolerated and not frequently associated with hypoglycaemia [4, 5, 7, 9]. Rosenstock and colleagues have recently published a study examining the efficacy and safety of simultaneously adding saxagliptin to the sodium glucose co-transporter 2 (SGLT2) inhibitor, dapagliflozin in patients with poorly controlled type 2 diabetes mellitus on metformin monotherapy [10].

2. Body of review

2.1 Overview of the market

As described above saxagliptin is a DPP-4 inhibitor licensed for the management of type 2 diabetes, alone or in combination with other glucose lowering medicines. Other DPP-4 inhibitors available for use in the UK and US include sitagliptin, linagliptin, vildagliptin and alogliptin. These agents vary in the dosage, dose frequency and metabolism.

2.2 Introduction to the compound

Saxagliptin (BMS-477118) was originally developed by Bristol-Myers-Squibb, and then a merger occurred with Astra Zeneca in 2007 to bring the product to market. In the UK,

saxagliptin was launched in October 2009 and in the US in July 2013. Further information relating to the chemistry, pharmacokinetics and pharmacodynamic properties of the compound will be discussed below.

2.3 Chemistry of saxagliptin

Saxagliptin (See box 1) has the molecular formula $C_{18}H_{25}N_3O_2$. The systematic name is 1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxy-1-adamantyl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile [11]. Saxagliptin is a potent, selective and competitive, cyanopyrrolidine-based, orally bioavailable inhibitor of DPP-4 and is metabolized into a less potent, active mono-hydroxy metabolite (5-hydroxy saxagliptin). Saxagliptin is available as a 2.5mg and 5mg tablet and administered once a day.

2.4 Mechanism of action

In vivo, pancreatic beta-cell insulin release differs in response to glucose, depending on whether glucose is administered as an enteral or parenteral load. This response is termed the 'incretin effect' and occurs due to the release of incretin gut hormones predominantly glucagon-like peptide 1 (GLP-1). GLP-1 is released from enteroendocrine ileal L-cells in response to nutrients. In response to oral glucose, incretin hormones augment insulin release from pancreatic beta-cells, which facilitates the uptake of glucose into the peripheral tissues including the liver, skeletal muscle and adipose tissue. In addition GLP-1 suppresses pancreatic alpha-cell release of glucagon, which reduces hepatic glucose output. GLP-1 also has effects to promote postprandial satiety and delayed gastric emptying. In patients with type 2 diabetes there is a reduction in the incretin response such that GLP-1 release is lower in response to nutrient ingestion.

DPP-4 is an endothelial transmembrane enzyme expressed on the surface endothelial cells. This enzyme degrades a number of circulating polypeptides, predominately GLP-1. The result is that circulating GLP-1 has a half-life of approximately two minutes. Inhibitors of DPP-4 therefore prevent the metabolism of GLP-1 and increase endogenous GLP-1 levels resulting in enhanced glucose-dependent insulin secretion by prolongation of incretin action, and subsequently improve glycaemic control without the risk of hypoglycaemia.

Saxagliptin has an effect to reduce both fasting and postprandial plasma glucose excursions. Despite its effects on insulin secretion and glucagon suppression, this form of incretin therapy has not been found to decrease gastric transit times or signal increased satiety like injectable exogenous GLP-1 agonists such as liraglutide and exenatide. Therefore these agents are not typically associated with weight loss, but with weight neutrality. Saxagliptin along with other DPP-4 inhibitors have potential benefits compared to other incretin based therapies, such as GLP-1 analogues, in that DPP-4 inhibitors are orally active and administered once daily, which facilitate ease of use without injection site complications. With its ease of use and reduced propensity to cause hypoglycaemia it is an ideal anti-hyperglycaemic agent in groups of patients deemed to be at high-risk of hypoglycaemia, such as the elderly and those with an erratic eating pattern.

2.5 Pharmacokinetics

Saxagliptin has an methanoproline-nitrile structure [12] which, unlike other DPP-4 inhibitors forms a reversible covalent inhibitor complex at the Ser630 residue located within the active centre of DDP-4 molecule, resulting in both slow rates of binding and disassociation [13]. This prolongs the action and half-life of DPP-4 such that therapeutic effects are observed even after elimination of the free drug. Within the class of DDP-4 inhibitors, saxagliptin requires the lowest concentration of 0.5nmol/L to produce 50% inhibition of DDP-4 (IC50)

and is thus one of the most potent DDP-4 inhibitors [13]. Saxagliptin has a very high selectivity for DPP-4 with in vitro concentrations for blocking DPP-8 and DPP-9, 400- and 75-fold higherr respectively, although the clinical relevance of this remains uncertain. Despite this it has one of the lowest levels of DDP-4 selectivity of the class [14, 15].

Saxagliptin is recommended as a once daily dose, and has been shown to inhibit DPP-4 for twenty-four hours. Following an oral glucose load saxagliptin results in a 3-fold increase in GLP-1 and increased glucose-dependant insulin release. A molar concentration of 30nM of saxagliptin results in 50% inhibition of DPP-4 and at a dosage concentration of 0.5μmol/kg effective DPP-4 inhibition is achieved at 6 hours in 50% of subjects. Thus a dose of 5mg has sufficient activity to allow once-daily administration.

Saxagliptin, as with all as other DPP-4 inhibitors, is readily absorbed in the small intestine following oral administration [14]. At the standard dose of 5mg it has an oral bioavailability of 75%, which is similar to other members of the class. The oral bioavailability suggests it has some aspect of hepatic metabolism, unlike sitagliptin, which has an oral bioavailability of around 86-87% [16]. Peak concentrations (Cmax 25.7ng/mL) following a 5mg dose are reached within 1.5 hours. This is within the average time range (Tmax) for the DPP-4 inhibitor class, but is observed at a relatively lower plasma concentration and thus is one of the more potent DPP-4 inhibitors. Despite the variability in oral bioavailability and potency across the class, the effects on endogenous active GLP-1 levels are comparable (1.8-3 fold increase).

The rate of absorption of all DPP-4 inhibitors in the small intestine is slightly increased with concomitant intake of a high-fat meal. For saxagliptin the area under the curve (AUC) is increased by 27% [13]. This however does not result in a clinically significant difference and there is no requirement for guidance in relation to the administration of the medication in relation to food. The total exposure (as measured by the AUC) of a 5mg dose

of saxagliptin has been shown to range between 78ng.h/mL-215ng.h/mL compared to 7.9µg.h.mL for sitagliptin at a dose of 100mg per day. Thus, saxagliptin has a lower maximum concentration and a smaller total bioavailability than sitagliptin. Saxagliptin has a modest volume of distribution of 151L, which is similar to that of sitagliptin and is strongly influenced by both protein binding and lipophilicity. Since the action of saxagliptin is mainly on endothelial membranes, the volume of distribution is limited. It has <10% protein binding, unlike linagliptin, which can be bound to protein 99% of the time, depending on the concentration [13].

Saxagliptin can be co-administered with metformin, glyburide or pioglitazone without a need for dose adjustment of either saxagliptin or these oral agents. Co-administration with these products does not result in clinically meaningful alterations in the pharmacokinetics of saxagliptin or its metabolite, 5-hydroxy saxagliptin [17]. Saxagliptin is the only DPP-4 inhibitor to undergo major hepatic metabolism by the CYP3A4/5 enzyme complex [13, 18]. The enzyme metabolises approximately 50% of saxagliptin into its primary metabolite, 5-hydroxy saxagliptin (BMS510849). This active metabolite reaches a maximum concentration at 4 hours, and retains 50% the potency of its parent molecule but has 50% greater selectivity [19]. The mean plasma AUC for metabolite is 214 ng.h/mL and the half-life is 3-7.5hrs, independent of the saxagliptin dose. This unique metabolism, in addition to its slow enzyme binding and dissociation allows saxagliptin to be administered once daily, despite its relatively short half-life. As a consequence of hepatic metabolism, saxaglitpin has the potential for drug-drug interactions with other medications that induce or inhibit the CYP3A4/5 enzyme complex [13]. The potent CYP3A4/5 inhibitor ketoconazole increases the Cmax for saxagliptin by 62% and the AUC by 145% [11]. For 5-hydroxy saxagliptin the Cmax and AUC were decreased by 95% and 88% respectively. Therefore, dose adjustments are required when co-administered with the cytochrome inhibitors. However, although the

concomitant administration of diltiazem, a moderate inhibitor of CYP3A4/5, increased the AUC by 109%, this was not considered to be clinically significant [11, 13, 20]. A similar, clinically insignificant change was found with mild CYP3A4/5 inhibitors and inducers, indicating no dose adjustment is necessary. Saxagliptin expresses no CYP3A4 inhibition itself and so dose adjustment of concomitant drugs won't be required [11, 13, 20].

Unlike other DDP-4 inhibitors, saxagliptin shows rapid excretion through both hepatic and renal pathways [13, 16, 21]. Approximately 25% of the dose undergoes renal excretion and approximately 22% is excreted in the faeces. 5-hydroxy saxagliptin mostly undergoes active renal excretion [14] with the mean renal clearance greater than the standard estimated glomerular filtration rate (eGFR) [13]. In the setting of renal impairment, the total of bioavailability of saxagliptin increases. The AUC was 16%, 41% and 108% higher in mild, moderate and severe renal impairment, respectively [18]. The AUC for the 5-hydroxy saxagliptin was also significantly raised, up to 4.5-fold higher in severe renal impairment. When the lower recommended dose of 2.5mg saxagliptin was given to patients with an eGFR <60 mL/min, there was no increase in adverse effects compared to placebo [22]. There was no further increased risk of cardiovascular events in renally impaired patients prescribed saxagliptin [23]. A further two studies has also shown that saxagliptin 2.5mg once daily is a well-tolerated treatment option for patients with inadequately controlled type 2 diabetes and renal impairment [24, 25].

2.6 Clinical evaluation

2.6.1 Efficacy

Saxagliptin is an oral therapy for type 2 diabetes in adults and is approved as an adjunct to exercise, diet and other antihyperglycaemic medication to improve glycemic. Evidence has shown saxagliptin produces significant clinical and statistical reductions in HbA1c, fasting

plasma glucose (FPG), and postprandial glucose (PPG) levels when used as either a monotherapy [3] or as an adjunct to other oral hypoglycaemic agents (metformin [4, 5], thiazolidinedione [7], sulphonurea [8]) and insulin [9, 26]. The approved dosages of saxagliptin are 2.5mg and 5mg per day. The 10mg dosage of saxagliptin did not provide greater efficacy than the 5mg dosage [13] and is therefore not used in routine clinical practice. The DPP-4 inhibitors have a substantial evidence base to support their pancreatic beta-cell preserving properties, which might the delay the progression of type 2 diabetes [27].

The effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes was examined by Rosenstock et al [3] in 401 patients with a baseline HbA1c between 7-10%. Mean HbA1c changes from baseline (mean 7.9%) to week 24 were -0.43%, -0.46%, -0.54% for saxagliptin 2.5, 5, and 10mg, respectively.

The efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes with inadequate glycemic control with metformin alone, has been assessed in a 24-week trial [4]. This was a randomized, double-blind, placebo-controlled study of saxagliptin (2.5, 5, or 10mg once daily) or placebo plus a stable dose of metformin (1.500–2.500g) in 743 patients (baseline HbA1c: 7.0-10.0%). Saxagliptin (2.5, 5, and 10mg) plus metformin demonstrated statistically significant mean decreases from baseline to week 24 compared to placebo in HbA1c (-0.59%, -0.69%, and -0.58% vs. +0.13%), FPG (-14.31, -22.03, and -20.50 vs. +1.24 mg/dL), and PPG AUC (-8,891, -9,586, and -8,137 vs. -3,291 mg.min/dL). More than twice as many patients achieved a HbA1c <7.0% with 2.5, 5, and 10mg of saxagliptin versus placebo (37%, 44%, and 44% vs. 17%). Beta-cell function and postprandial C-peptide, insulin, and glucagon AUCs improved in all saxagliptin treated groups at week 24. The incidence of hypoglycemia and weight reductions, were similar to those with placebo. Another two studies has also shown that saxagliptin added to metformin therapy was effective in improving glycaemic control in patients with type 2 diabetes mellitus

inadequately controlled by metformin alone and that saxagliptin plus metformin was non-inferior to sitagliptin plus metformin [28, 29]. Saxagliptin combined with metformin in a fixed dose combination is also available with proven efficacy [30].

The long-term efficacy and safety of saxagliptin has also been examined in patients with type 2 diabetes mellitus inadequately controlled on sulphonylurea monotherapy [8]. Chacra and colleagues, examined 768 patients who were randomized to saxagliptin 2.5 or 5mg in combination with glyburide 7.5mg versus placebo, added to up-titrated glyburide over 76 weeks. At 76 weeks, mean changes from baseline HbA1c for saxagliptin 2.5mg, saxagliptin 5mg, and up-titrated glyburide were 0.11% (95% confidence interval-CI: -0.05, 0.27), 0.03% (-0.14, 0.19), and 0.69% (0.47, 0.92), respectively. Adverse effects were not dissimilar in the groups. Another non-inferiority study examined HbA1c reduction between saxagliptin and glipizide in patients with type 2 diabetes inadequately controlled on metformin alone [31] in 858 subjects with a baseline HbA1c 6.5-10.0%. Saxagliptin plus metformin was well tolerated, provided a sustained HbA1c reduction over 52 weeks, and was non-inferior to glipizide plus metformin (mean changes from baseline HbA1c were -0.74% vs. -0.80% respectively). Treatment with saxagliptin was associated with less hypoglycaemic events (3.0% vs. 36.3%) and a reduced body weight.

Saxagliptin can also be used with insulin therapy [9, 32]. This was demonstrated in a randomized, double-blind, parallel-group trial of saxagliptin 5mg once daily versus placebo as add-on therapy to open-label insulin or insulin plus metformin therapy over 52 weeks in patients with type 2 diabetes, aged 18-78 years with a baseline HbA1c 7.5–11 % on a stable insulin regimen (30–150 units/day with or without metformin). Mean change from baseline HbA1c at week 52 was greater with saxagliptin (-0.75 %) versus placebo (-0.38 %). At week 52, a greater proportion of patients receiving saxagliptin achieved a HbA1c <7 % compared

to those receiving placebo (21.3 vs. 8.7 %). No increase in adverse effects was observed in the saxagliptin group.

Studies are also underway examining the combination of saxagliptin with the SGLT2 inhibitor, dapagliflozin (for review see [33]). Rosenstock and colleagues [10] undertook a 24-week, multicentre, randomized, double-blind phase 3 trial of adults with type 2 diabetic patients with a baseline HbA1c 8.0-12.0% and a body mass index (BMI) <45.0kg/m^2 who were treated with a stable dose of metformin treatment for ≥8 weeks. Following a 4-week lead-in, 534 patients were randomized to receive saxagliptin (5mg/day) and placebo; dapagliflozin and placebo (10mg/day); or saxagliptin and dapagliflozin with background extended release metformin at a dose ≥1500mg/day. At week 24, the addition of both saxagliptin and dapagliflozin achieved the greatest mean reduction in HbA1c of 1.47% compared to 0.88% in those taking saxagliptin only and 1.20% in those taking dapagliflozin only. The improvement in HbA1c was greatest for patients with a baseline HbA1c >9.0%, with a reduction of 2.03% for those taking saxagliptin and dapagliflozin, 1.32% in the saxagliptin group and 1.87% in the dapagliflozin group. The difference was more marked in patients <65 years old with a difference of -0.63% in those taking saxagliptin and dapagliflozin compared with a difference of -0.26% in those taking saxagliptin or dapagliflozin alone. In participants >65 years old, the difference in those on saxagliptin and dapagliflozin was -0.37% compared to -0.35% in those taking either saxagliptin or dapagliflozin alone. The mean proportion of patients with HbA1c <7.0% in those taking dapagliflozin and saxagliptin was 41% compared with 18% taking saxagliptin and 22% taking dapagliflozin. Participants receiving dual add-on therapy had the greatest reduction in FPG of 38mg/dL compared to 14mg/dL in the saxagliptin group and 32mg/dL in the dapagliflozin group. Dual add-on also resulted in greater reductions in PPG with a reduction of 80mg/dL compared with 36mg/dL in the saxagliptin group and 70mg/dL in participants

taking dapagliflozin. This study suggests that the combination of saxagliptin and dapagliflozin is associated with clinically significant reductions in HbA1c, FPG and PPG in patients with a baseline HbA1c >8%. Furthermore, greater efficacy in HbA1c reduction is observed in subjects with poorer glycaemic control with a HbA1c > 9%.

2.6.2 Predictors of response

In a study of 191 patients with type 2 diabetes [34], it was observed that the greatest HbA1c reduction was seen in subjects who had a lower body mass index (BMI) and those without co-existing coronary heart disease. This may be related to the observation that glucose-insulin homeostasis in subjects with a lower BMI is associated with a greater contribution from beta-cell dysfunction and lower insulin release, which is improved by GLP-1, and conversely in subjects with a higher BMI, insulin resistance may be more of a contributory factor to impaired glucose tolerance. Furthermore, it has been observed that the 3 month response to saxaglipitin was predictive of the 12-month reduction in HbA1c, so the efficacy of saxagliptin for an individual patient might be predicted at 3 month [34]. Indeed, a meta-analysis of 98 randomized clinical trials lasting a minimum of 3 months each, provided interesting information on the prediction of effect [35]. The authors demonstrated that most inter-trial variance was explained by baseline HbA1c, to some extent FPG, and the type of DPP-4 inhibitor. Although the study didn't compare directly the efficacy of each inhibitor, it allowed a nomogram to be created in which a clinician can predict the glycaemic response of an individual patient depending on which inhibitor the clinician has chosen.

2.7 Safety and tolerability

Clearly all of the currently available oral antihyperglycaemic therapies are associated with clinically significant reductions in HbA1c, but differ considerably in their untoward effects. In a meta-analysis examining the efficacy of various antihyperglycaemic agents as add-on

treatments to metformin and sulfonylureas, Gross et al reported that compared with placebo, the drug classes did not differ in their effect on HbA1c [36]. However, compared to other medications, DPP-4 inhibitors had the benefits of weight neutrality and lower episodes of hypoglycaemia when compared to other agents such as sulphonylures, thiazolidinedione and insulin. A recent study also demonstrated that saxagliptin was associated with a significant reduction in hypoglycaemia compared to glimepiride in patients aged ≥75 years [37]. The lower risk of hypoglycaemia is related to its glucose-dependant mechanism of action. Pooled data from six phase 3 clinical trials reported no significant increase in confirmed hypoglycemic events for both 2.5 and 5mg of saxagliptin compared to placebo, 0.8%, 0.5% and 0.4% respectively [38]. As an add-on therapy over 24 weeks, similar results were demonstrated [38]. The frequency of confirmed hypoglycemic events was 0% for initial combination therapy with metformin compared to 0.3% with metformin alone. The risk of hypoglycaemia in patients on a combination of metformin and sulfonylureas, compared to metformin and saxagliptin is considerably higher with the percentage of patients having one or more hypoglycaemic event over 52 weeks being 36% versus 3% respectively [38].

2.7.1 Cardiovasular risk

Saxagliptin has been shown to be neutral with respect to the future risk of cardiovascular disease in both high and low-risk patient populations. This was observed in a published study examining pooled data from 8 clinical trials where saxagliptin was used as monotherapy or in combination with other oral antihyperglycaemic agents [39]. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 trial investigated composite primary endpoints of myocardial infarction, cardiovascular death or ischaemic stroke in patients with multiple cardiovascular risk factors or prior cardiovascular disease in 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events [40]. This trial

observed no increase in risk for all primary (hazard ratio-HR, 1.00 [95% CI: 0.89-1.12]) and broader endpoints (HR, 1.02 [95% CI: 0.94-1.11]). No superiority for any endpoint was found over placebo. Of interest in the SAVOR-TIMI 53, more patients in the saxagliptin group than in the placebo group were hospitalised for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007) [40]. This increase in risk was highest among patients with elevated levels of natriuretic peptides, previous heart failure, or chronic kidney disease [41]. Iqbal et al [42], analysed the incidence of major cardiovascular events in 20 phase 2b and 3b clinical trials of saxagliptin. They investigated the rates of cardiovascular death; any cardiac ischaemia including myocardial infarction; stroke; and heart failure in patients receiving any dose of saxagliptin versus the control group. No increased risk of cardiovascular events were observed with saxagliptin as a monotherapy or add-on therapy (HR, 0.75 [95% CI: 0.46-1.21]) [43]. Although Davidson et al, found a small increased incidence of hypertension and vascular disorders with saxagliptin and metformin compared to metformin monotherapy alone, the number of cardiovascular adverse events was still lower for dual therapy compared to metformin alone [38]. Iqbal et al [42], showed that the incidence rate ratio between those taking saxagliptin and metformin versus those on metformin alone for any adverse cardiovascular event was 0.93 (95% CI: 0.44-1.99) illustrating no increased cardiovascular risk in the 20 trials studied..

Early pharmacodynamic studies have shown that saxagliptin (2.5-400 mg/day for <14 days) or its active metabolite do not prolong the corrected QT interval in patients with type 2 diabetes or healthy volunteers [13].

2.7.2 Pancreatitis

Although preclinical and clinical trial data do not indicate an increased risk of pancreatitis in patients treated with saxagliptin, post-marketing reports suspected an increased risk of pancreatitis and pancreatic cancer, but the complete set of available data appears reassuring

that this is not the case [15, 44]. Reassuringly in the SAVOR-TIMI 53 trial, within 2.1 years of follow-up, the risk for pancreatitis in type 2 diabetic patients treated with saxagliptin was low and apparently similar to placebo, with no sign of increased risk for pancreatic cancer [45, 46].

2.7.3 Other adverse events

Saxagliptin has been shown to have a low rate of adverse events as a monotherapy and add on therapy. The most common being upper respiratory and gastroenterological side effects. However, there is a greater than 1% risk of non-life threatening hypersensitivity reactions and lymphopenia [13]. In a pooled analysis of 6 placebo controlled randomized control trials investigating saxagliptin monotherapy or combined with metformin, Davidson et al [38], showed that saxagliptin had similar adverse events to placebo. As a monotherapy, only 1% of subjects had adverse effects compared to placebo. These included sinusitis, gastroenteritis, abdominal pain and vomiting. All had an incidence of less than 3% in the 882 people studied at saxagliptin doses of 2.5mg and 5mg. Saxagliptin may be associated with headache, upper respiratory tract infection, diarrhea, and nasopharyngitis [47]. In the study by Davidson et al [38], combining 5mg saxagliptin with metformin was associated with a similar rate of headache (7.5%), nasophayngitis (6.9%) and vascular disorders (5.2%) versus 5.2%, 4% and 4.6% of those on metformin monotherapy respectively. There was a 1.5% incidence of hypersensitivity reactions in saxagliptin treated patients compared to 0.4% in placebo treated, however, none required hospitalisation. Lymphopenia occurred in 0.5%, 1.5% and 1% for saxagliptin 2.5mg, 5mg, and placebo arms respectively. Interestingly there was a 5% absolute drop in lymphocyte count also seen in those treated with 5mg but not in those with 2.5mg [30]. The clinical relevance of this remains unclear. The incidence of discontinuation due to adverse events was 2.2%, 3.3% and 1.8% for 2.5, 5mg of saxagliptin and placebo

respectively [38]. The causes of discontinuation included lymphopaenia, rash, increased blood creatinine and increased creatinine kinase.

2.8 Regulatory affairs

Saxagliptin was launched in the UK and US in 2009. As a class, different DPP-4 inhibitors differ in their chemical structure and metabolism, however all have the end result of increasing endogenous GLP-1 levels and glucose lowering properties. Saxagliptin in the UK is licensed for use in patients with type 2 diabetes, with the recommended dose being of saxagliptin being 2.5mg or 5mg once daily administered orally without regard for food (https://www.medicines.org.uk/emc/medicine/22315, accessed November 2015). In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min) and in patients with end-stage renal disease requiring haemodialysis, the dosage of saxagliptin should be adjusted to 2.5 mg/day to achieve plasma exposures of saxagliptin that are similar to those in patients with normal renal function; no dosage adjustment is required in patients with mild renal impairment. Saxagliptin dosage should also be adjusted to 2.5 mg/day when the drug is co-administered with strong CYP3A4/5 inhibitors (e.g. ketoconazole, atazanavir or clarithro-mycin). Saxagliptin should not be used for the treatment of type 1 diabetes (https://www.medicines.org.uk/emc/medicine/22315, accessed November 2015).

3. Conclusion

Saxagliptin is a DPP-4 inhibitor that improves glycaemic control by preventing the inactivation of the incretin hormone GLP-1, resulting in increased endogenous GLP-1 levels which stimulates glucose-dependent insulin secretion and reduces postprandial glucagon and glucose levels. There are robust phase 3 clinical trials demonstrating the efficacy of saxagliptin at a dose of 2.5 and 5mg once a day as an oral antihyperglycaemic agent as

monotherapy, dual therapy and in combination with insulin. Saxagliptin as monotherapy or in combination with other oral antihyperglycaemics is well tolerated and most adverse events are of a mild or moderate severity. In clinical trials, the incidence of hypoglycaemic events in patients receiving saxagliptin is similar to placebo or other oral antihyperglycaemic agents apart from sulphonylureas. Treatment with saxagliptin is not associated with an increased risk of cardiovascular events.

4. Expert opinion

In our opinion, saxagliptin is an established DPP-4 inhibitor, which is has a similar efficacy and tolerability profile to other DPP-4 inhibitors. The phase 3 clinical trial programme is robust and the results of the SAVOR-TIMI 53 trial provide reassurance with respect to cardiovascular safety along with the risk of pancreatitis and pancreatic cancer. Saxagliptin appears effective in the elderly, and patients with renal and hepatic disease, but dosage adjustment may be required. Saxagliptin has also been examined in combination with different diabetes therapies and appears to have a desirable safety profile. As with other DPP-4 inhibitors, the risk of hypoglycaemia may be increased when co-administered with sulphonylurea and insulin therapy. Saxagliptin may be used with dapagliflozin and it is anticipated that a fixed dose combination of this product will be available in 2016. This will have the potential of combining the therapeutic advantages of a DPP-4 inhibitor along with an SGLT2 inhibitor. As a consequence of hepatic metabolism, saxaglitpin has the potential for drug-drug interactions with other medications that induce or inhibit the CYP3A4/5 enzyme complex e.g. the calcium channel blocker diltiazem for hypertension, and so these potential interactions should be considered when prescribing alongside other therapies.

Article highlights box

- Saxagliptin is a DPP-4 inhibitor available for the treatment of type 2 diabetes, as monotherapy or in combination with other glucose lowering products including insulin.
- Saxagliptin is available as a 2.5 or 5mg once a day dose.
- Untoward and adverse effects are uncommon and mild.
- Saxagliptin requires dosage adjustment in the setting of renal impairment.

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