**Treatment evaluation**

# Metformin plus saxagliptin for type 2 diabetes

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**SUMMARY**

Metformin is considered as the first-line drug therapy for the management of type 2 diabetes. Dipeptidyl peptidase-4 (DPP-4) inhibitors, by promoting insulin secretion and reducing glucagon secretion in a glucose-dependent manner, offer new opportunities for oral therapy after failure of metformin. Saxagliptin, a DPP-4 inhibitor, and metformin may be administered together, separately or in fixed-dose combination (FDC), either as saxagliptin added to metformin or as initial combination in drug-naive patients. Both compounds exert complementary pharmacodynamic actions leading to better improvement in blood glucose control (fasting plasma glucose, postprandial glucose, HbA1c) than either compound separately. Adding saxagliptin to metformin monthotherapy results in a consistent, sustained and safe reduction in HbA1c levels. Tolerance is excellent without hypoglycemia or weight gain. The combination saxaglitpin plus metformin may be used as first-line or second-line therapy in the management of type 2 diabetes, especially as a valuable alternative to the classical metformin-sulfonylurea combination.

Key-words : DPP-4 inhibitor – Fixed-dose combination - Metformin – Saxagliptin - Type 2 diabetes mellitus

## 1. Introduction

Clinical practice recommends lifestyle interventions together with starting metformin once type 2 diabetes mellitus (T2DM) is diagnosed [1,2]. Metformin is considered as the first-line or reference drug because of its favourable overall profile, including its glucose-lowering activity, no weight gain or even slight weight loss, low risk of hypoglycemia and reduction in cardiovascular events [3]. Once metformin fails to maintain glycemic control, there is, however, no consensus about the next pharmacological strategy [1,4]. The addition of a sulfonylurea, a thiazolidinedione (TZD, pioglitazone), a basal insulin regimen or a glucagon-like peptide-1 (GLP-1) agonist has been considered in the algorithm proposed by the American Diabetes Association (ADA) - European Association for the Study of Diabetes (EASD) experts [1]. In this regard, dipeptidyl peptidase-4 (DPP-4) inhibitors, by inhibiting the enzymatic degradation of endogenous GLP-1 secreted in response to meal, and thereby promoting insulin secretion (incretin effect) and inhibiting glucagon secretion in a glucose-dependent manner, offer new options for oral combined pharmacological therapy in the management of T2DM [5,6]. Although they are not proposed in the ADA-EASD consensus statement, they are considered as a valuable option in the algorithm for glycemic control according to the American Association of Clinical Endocrinologists/American College of Endocrinology [4] and the updated UK NICE (National Institute for Health and Clinical Excellence) [7] guidelines. Indeed, the addition of a DPP-4 inhibitor to metformin may be a logical option because of the almost similar effect on glycated hemoglobin (HbA1c) compared to the addition of a sulfonylurea or TZD, and because this incretin-based intervention is associated with a excellent tolerance profile, neutral effects on body weight, an absence of hypoglycemic risk and possible positive effects on beta-cell function [3,8]. Furthermore, preliminary data suggested that DPP-4 inhibitors may be associated with a reduced rate of cardiovascular events [9], an effect that is currently tested in several prospective clinical trials [6]. Fixed-dose combinations (FDC) combining metformin plus sitagliptin and metformin plus vildagliptin are already commercialized, and a metformin extended-release (XR) plus saxagliptin FDC is already on the market in the US (Kombiglyze®). [10-12]. A saxagliptin/metformin immediate release FDC will also be available in Europe very soon (Komboglyze®). Saxagliptin/metformin XR 5? mg/500? mg and saxagliptin/metformin XR 5? mg/1000? mg FDCs were shown to be bioequivalent to individual tablets of saxagliptin and metformin of the same strengths [13]. Of note, however,

this study did not assess saxagliptin 2.5 mg/metformin 1000 mg FDC to demonstrate its bioequivalence with corresponding doses of individual ounds. FDC can offer convenience, reduce the pill burden and simplify administration regimens for the patient [11,14].

The present paper provides a treatment evaluation of the saxagliptin plus metformin combination, considering the evidence-based clinical data that support its approved use and comparing this dual therapy with other options currently used in a highly competitive environment.

## 2. Approved use

The clinical efficacy and safety of the combination metformin plus saxagliptin has been demonstrated in several placebo-controlled randomized clinical trials (Table 1). In patients with T2DM inadequately controlled on metformin alone (≥ 1500 mg/day), saxagliptin 5 mg added to metformin provided sustained clinically meaningful glycemic improvements (reductions in HbA1c, fasting – FPG – and postprandial – PPG – plasma glucose levels) after 24 weeks [15,16], which were sustained over 102 weeks [17]. Combination therapy was generally well tolerated with no increase in hypoglycemia or body weight. Several trials (only reported as abstracts) also demonstrated that the addition of saxagliptin 5 mg once daily to metformin 1500 mg/day provides better glucose control than uptitrating metformin doses (up to 2000 or 2500 mg/day), without inducing adverse events (in contrast a better gastrointestinal tolerance was noticed with the combination therapy because of the lower daily dosage of metformin) [18,19] . Finally, saxagliptin plus metformin as initial therapy led to statistically significant improvements compared with either treatment alone across key glycemic parameters (HbA1c, FPG, PPG) with a tolerability profile similar to the monotherapy components and no increase in hypoglycemic episodes (Table 2) [20,21].

In recently published pooled analyses, clinically pertinent reductions in HbA1c were obtained with saxagliptin as monotherapy or add-on therapy across a wide range of subgroups of T2DM patients when examined either by specific baseline demographic characteristics (age, gender, body mass index, duration of diabetes) or by ß-cell function indices [22]. The elderly population is particularly attractive for using a DPP-4 inhibitor instead of a sulfonylurea in addition to metformin because these older patients are exposed to a greater risk of severe hypoglycemia [23,24].

Saxagliptin got recently the indication for the treatment of T2DM patients with mild, moderate or severe renal impairment (RI), provided that the daily dosage is reduced from 5 mg to 2.5 mg in patients with moderate to severe RI (defined by a creatinine clearance level of <50ml/min), according to previously reported pharmacokinetic data [25]. Saxagliptin 2.5 mg once daily was shown to offer sustained efficacy and good tolerability for patients with T2DM and moderate to severe RI, both after 12 weeks [26] and after 52 weeks [27]. Interestingly, it was also suggested that metformin can be used in such patients with mild to moderate RI provided that the dose is reduced (e.g., by 50% or to half-maximal dose) and that careful monitoring of renal function is done [28]. Even if one might consider that the combination metformin plus saxagliptin could also be used with caution in T2DM patients with mild to moderate RI, this is not an official indication so that this off-label use cannot be recommended yet. Indeed, in the US, the use of metformin is officially contraindicated in case of RI (e.g., serum creatinine levels =1.5 mg/dL for men, =1.4 mg/dL for women, or abnormal creatinine clearance).

In the US, the approved use of metformin extende-release plus saxagliptin (FDC, Kombiglyze XR®) is as adjunct to diet and exercise in T2DM when treatment with both saxagliptin and metformin is appropriate [10,29]. In Europe, Komboglyze® (saxagliptin plus metformin film-coated tablet) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients aged 18 years and older with T2DM inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets [30]. In both the US and in Europe, the maximum daily recommended dose is 5 mg for saxagliptin and 2000 mg for metformin.

Saxagliptin (Onglyza®) is indicated in adult patients aged 18 years and older with T2DM to improve glycaemic control in combination with metformin, when metformin alone, with diet and exercise, does not provide adequate glycaemic control. Other official indications are in combination with a sulphonylurea, when the sulphonylurea alone, with diet and exercise, does not provide adequate glycaemic control ormin is considered inappropriate and in combination with a TZD, when the TZD alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a TZD is considered appropriate (these last two indications are out of the scope of the present paper and will not be considered further). No dose adjustment is recommended for patients with

mild RI. The dose of saxagliptin should be reduced to 2.5 mg once daily in patients with moderate or severe RI. However, the experience in patients with severeRI is very limited. Therefore, saxagliptin should be used with caution in this population. Saxagliptin is not recommended for patients with end-stage renal disease (ESRD) requiring haemodialysis (same restriction for metformin, together with severe RI without dialysis). Currently, the restrictions of use of metformin in case of RI currently contraindicate the prescription of a saxagliptin plus metformin FDC in T2DM patients with chronic kidney disease.

## 3. Competitive environment

After failure of metformin monotherapy, various combination therapies may be considered [1,4] and the efficacy/safety profile of adding saxagliptin should be compared to each of these options. However, in most cases, only indirect comparaisons can be performed because published head-to-head trials are rather scarce in the literature, and even less with saxagliptin than with the first DPP-4 commericialized sitagliptin. We will briefly present the available data comparing the addition of either a DPP-4 inhibitor (here focusing on saxagliptin) or another pharmacological option (either oral or injectable) on top of metformin monotherapy.

### 3.1. Saxagliptin versus a sulfonylurea

A controlled trial randomized 858 T2DM patients with inadequate glycemic control on stable doses = 1500 mg/day of metformin alone to saxagliptin 5 mg/day or glipizide up-titrated as needed from 5 to 20 mg/day for 52 weeks [31]. Non-inferiority of saxagliptin versus glipizide was demonstrated with adjusted mean changes from baseline HbA1c averaging -0.74% versus -0.80%, respectively (between-group difference = 0.06%; 95% confidence interval or CI, -0.05% to 0.16%) (Table 3). Treatment with saxagliptin versus glipizide was associated with a much smaller proportion of patients with hypoglycemic events (combination of reports of either signs or symptoms con oglycemia or reported low glucose levels : 3.0% versus 36.3%; $p < 0.0001$) [difference present across all baseline HbA1c categories] and a divergent impact on body weight. This first part of the study was followed by a 52-week extension phase, which confirmed initial results [32] (Table 3). Among patients with baseline Hb A1c of >7% on metformin monotherapy, the proportion achieving HbA1c <7% without hypoglycemia or weight gain was more than twice as high with added saxagliptin than with added glipizide (19.4% vs 8.7%) [33].

### 3.2. Saxagliptin versus another DPP-4 inhibitor

Sitagliptin was the first-in-class DPP-4 inhibitor and thereby may serve as reference. A 18-week double-blind, noninferiority trial compared the efficacy and safety of saxagliptin 5 mg and sitagliptin 100 mg in T2DM patients whose glycemia was inadequately controlled with metformin (stable doses of 1500-3000 mg/day) [34]. The adjusted mean changes in HbA1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were -0.52 and -0.62%, respectively (Table 3). The between-group difference was 0.09% (95% CI, -0.01 to 0.20%), demonstrating noninferiority of saxagliptin versus sitagliptin. Both DPP-4 inhibitors were generally well tolerated, with a modest weight reduction and a very low incidence of mild hypoglycemic events (Table 3).

### 3.3. Saxagliptin versus a thiazolidinedione

To our knowledge, there is no published trial comparing saxagliptin versus a TZD in T2DM patients with inadequate glycemic control on metformin therapy. In such a population, a randomized controlled trial demonstrated that the addition of sitagliptin 100 mg was slightly less effective than the addition of pioglitazone at a maximum daily dose of 45 mg [35]. However, other trials suggested comparable glucose-lowering effects with the addition of vildagliptin 100 mg and a TZD, either pioglitazone 30 mg or rosiglitazone 4-8 mg [36]. In all these studies, the DPP-4 inhibitor did not exert adverse effects, whereas the combination with a TZD induced some weight gain and fluid retention. Furthermore, some concerns have been raised regarding the safety of TZDs (fractures, congestive heart failure, bladder cancer) (Table 4).

### 3.4. Saxagliptin versus a GLP-1 receptor agonist

Scarce head-to-head trials comparing DPP-4 inhbitors and GLP-1 receptor agonists are available yet, but only sitagliptin has been evaluated in such studies. Two trials compared sitagliptin 100 mg versus exenatide injection either twice daily [37] or once weekly [35] and one trial compared sitagliptin 100 mg with liraglutide injection 1.2 or 1.8 mg once daily [38]. Although GLP-1 receptor agonists demonstrated superiority compared to sitagliptin regarding glucose and body weight control, the average differences in HbA1c and weight reduction were not impressive compared to several obvious disadvantages of GLP-1 receptor agonists (injectable versus oral, more nausea and vomiting) [39] (Table 4). Because saxagliptin 5 mg

has demonstrated its non-inferiority versus sitagliptin 100 mg in metformin-treatment patients [34], one may hypothesize that the results of saxagliptin versus a GLP-1 receptor agonist would be almost similar to those previously reported with sitagliptin.

### 3.5. Saxagliptin versus basal insulin

No study directly compared the effects of adding saxag iptin versus a basal insulin therapy on top of metformin monotherapy, an optional therapy proposed as tier 1 in the ADA-EASD consensus statement [1]. One trial demonstrated the efficacy and safety of the combination saxagliptin plus metformin added to insulin in T2DM patients. After 24 weeks, patients treated with saxagliptin achieved a statistically significant HbA1c reduction from baseline of -0.73% compared to -0.32% ($p < 0.0001$) in those receiving a placebo [40], a difference that was maintained over 52 weeks (-0.75% with saxagliptin versus -0.38% with placebo; $p < 0.0001$) [41]. Thus, this study demonstrated that metformin plus saxagliptin may be added to insulin therapy in the management of patients with T2DM (an indication that should be officially recognized very soon), but did not compare saxagliptin with basal insulin on top of baseline metformin monotherapy. However, besides efficacy, the ease of use of saxagliptin (one pill a day with a good tolerance profile) compared to basal insulin (one injection a day, need for dose titration based on home blood glucose monitoring, risk of hypoglycemia and weight gain) is obvious.

## 4. Expert opinion

There is a rationale for combining metformin and a DPP-4 inhibitor like saxagliptin. There is no deleterious pharmacokinetic interferences [12] and a FDC is available with proven bioequivalence compared with the two tablets taken separately [13]. Furthermore, a complementary pharmacodynamic action has been reported. A DPP-4 inhibitor (by inhibiting GLP-1 degradation into inactive products) and metformin (by enhancing intestinal preproglucagon gene expression in the large intestine, which results in increased total GLP-1 concentrations) may have additive effects with respect to increasing the concentrations of active GLP-1 in plasma [42]. The complementary effects of the two glucose-lowering agents lead to a reduction in HbA1c averaging 0.6-0.8% when saxagliptin 5 mg is added to metformin as basal therapy and a reduction of about 2% when the combination metformin plus saxagliptin is initiated immediately in T2DM patients not well controlled with diet and exercise [12]. Interestingly, this improvement in glucose control is associated with no weight

gain, and the risk of hypoglycemia is negligible, especially when compared to that associated with sulfonylureas. This may represent a major advantage, more particularly in the elderly population where hypoglycemic episodes may be more prevalent and more dangerous [23,24].

The main objective of combining two drugs is to improve efficacy and/or safety. Concerning efficacy, and besides the already proven improvement in glucose control, two major advances may be expected from the addition of a DPP-4 inhibitor like saxagliptin to metformin : first, a reduced escape of glucose control generally observed with metformin monotherapy or even more impressive with the classical metformin plus sulfonylurea combination, thus better durability of the glucose-lowering effect, although this remains to be better established; second, a positive synergistic effect of metformin and saxaglitpin on cardiovascular outcomes because both compounds have shown promising results in the reduction of major cardiovascular events, but again this should be proven in ongoing clinical trials [6].

Concerning the safety profile, a recent concern has been raised regarding a possible risk of pancreatitits and even pancreatic cancer witht the use of compounds increasing the levels of GLP-1, including DPP-4 inhibitors [43]. Of interest, some preliminary data suggested that the addition of metformin could counter these deleterious effects of GLP-1. Although this hypothesis should be confirmed by further studies, a saxagliptin plus metformin combination fits well with the recommendation that" it would be prudent to use GLP-1 mimetic therapy only in addition to metformin" [44].

DPP-4 inhibitors have been included as alternative first- or second-line therapies in recent guidelines despite their higher cost, especially compared with sulfonylureas [4,7]. Because of the complexity of the pathophysiology of T2DM and because of the complementary actions of glucose-lowering agents such as biguanides and DPP-4 inhibitors, we can speculate that more emphasis will be put on earlier use of combined therapy (especially metformin-gliptin) for the management of T2DM in the coming years. In this regard, the use of FDC may improve convenience of drug therapy, patient's adherence and possibly clinical endpoints [11,12,14]. A FDC combining saxagliptin and metformin XR (Kombiglyze® available in the US) would provide the advantage of one single administration per day whereas the currently available sitaglipin plus metformin immediate release FDC requires two administrations per day (as it will be the case for Komboglyze® in Europe using metformin film-coated tablet rather than metformin extended release formulation).

## 5. Conclusion

Saxagliptin in combination with metformin is an efficient, safe and tolerable combination therapy for T2DM and the new saxagliptin-metformin XR FDC offer some adavantages for clinical use. However, long-term experience with this dual therapy in comparison with other drug combinations is still limited and requires further careful clinical evaluation.


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**Drug summary box**

| | |
|---|---|
| Drug name | Kombiglyze XR 5/500, 5/1000 and 2.5/1000 (saxagliptin plus metformin XR) Komboglyze 2.5/850 and 2.5/1000 (saxagliptin plus metformin film-coated tablet) |
| Phase | Kombiglyze XR available in the US. Komboglyze : approved in EU |
| Indication | Treatment of type 2 diabetes |
| Pharmacology description | Combination of a DPP-4 inhibitor (acting as an incretin-based therapy by increasing GLP-1 levels) and a biguanide (exerting multiple effects, especially an inhibition of hepatic glucose output) |
| Route of administration | Oral |
| Chemical structure | |
| Pivotal trial(s) | DeFronzo RA, Hissa MN, Garber AJ *et al.* The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 32(9), 1649-1655 (2009).<br>Jadzinsky M, Pfutzner A, Paz-Pacheco E, Xu Z, Allen E, Chen R. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type 2 diabetes compared with either monotherapy: a randomized controlled trial. *Diabetes Obes Metab* 11(6), 611-622 (2009).<br>Goke B, Gallwitz B, Eriksson J, Hellqvist A, Gause-Nilsson I. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. *Int J Clin Pract* 64(12), 1619-1631 (2010).<br>Boulton DW, Smith CH, Li L, Huang J, Tang A, Lacreta FP. Bioequivalence of saxagliptin/metformin extended-release (XR) fixed-dose combination tablets and single-component saxagliptin and metformin XR tablets in healthy adult subjects. *Clin Drug Investig* 31(9), 619-630 (2011). |

Readers are referred to Informa-Pipeline (http://informa-pipeline.citeline.com) and Citeline (http://informa.citeline.com).

Table 1 : Randomized controlled trials assessing the efficacy of adding saxagliptin 5 mg versus placebo in patients with T2DM inadequately controlled with metformin monotherapy. ? = change at end of follow up versus baseline. FPG : fasting plasma glucose. PPG : postprandial glucose. Reported hypos : hypoglycemias reported by patients but not necessarily confirmed by a glucose measurement.

| | Number of patients | Study Duration (weeks) | $HbA_{1c}$ Baseline (%) | ? $HbA_{1c}$ (%) | Patients with HbA1c < 7% (%) | ? FPG (mmol/l) | ? 120 min PPG (mmol/l) | ? Body weight (kg) | Reported hypos (% patients) |
|---|---|---|---|---|---|---|---|---|---|
| DeFronzo et al 2009 [15] | | | | | | | | | |
| Saxagliptin 5 mg | 191 | 24 | 8.10 | -0.69 | 44 | -1.22 | -3.23 | -0.87 | 5.2 |
| Placebo | 179 | 24 | 8.10 | +0.13 | 17 | +0.07 | -1.00 | -0.92 | 5.0 |
| DeFronzo et al 2009 [17] | | | | | | | | | |
| Saxagliptin 5 mg | 191 | 102 | 8.10 | -0.40 | 30.4 | -0.63 | -1.94 | -0.40 | 8.9 |
| Placebo | 179 | 102 | 8.10 | +0.32 | 11.6 | +0.38 | -0.22 | -0.80 | 10.1 |
| Yang et al 2011 [16] | | | | | | | | | |
| Saxagliptin 5 mg | 283 | 24 | 7.90 | -0.78 | 46.5 | -1.14 | -2.00 | -1.05 | 1.4 |
| Placebo | 287 | 24 | 7.90 | -0.37 | 30.5 | -0.58 | -1.00 | -0.97 | 1.4 |

Table 2 : Randomized controlled trials assessing the efficacy of the initial combination saxagliptin-metformin in T2DM patients treated with diet alone compared with either monotherapy with metformin or saxagliptin. ? = change at end of follow up versus baseline (not versus comparator). FPG : fasting plasma glucose. PPG : postprandial glucose.

| | Number of patients | Study Duration (weeks) | $HbA_{1c}$ Baseline (%) | ? $HbA_{1c}$ (%) | Patients with HbA1c < 7% (%) | ? FPG (mmol/) | ? 120 min PPG (mmol/l) | ? Body weight (kg) | Reported hypos (% patients) |
|---|---|---|---|---|---|---|---|---|---|
| Jadzinsky et al [20] | | | | | | | | | |
| Saxa 5 mg + Met 500-2000 mg | 320 | 24 | 9.41 | -2.50 | 60.3 | -3.33 | -7.67 | -1.8 | 3.4 |
| Saxa 10 mg + Met 500-2000 mg(*) | 323 | 24 | 9.53 | -2.50 | 59.7 | -3.44 | -7.61 | -1.4 | 5.0 |
| Met 500-2000 mg alone | 328 | 24 | 9.43 | -2.00 | 41.1 | -2.61 | -5.39 | -1.6 | 4.0 |
| Saxa 10 mg alone | 335 | 24 | 9.61 | -1.70 | 32.2 | -1.72 | -5.89 | -1.1 | 1.5 |
| Pfützner et al [21] | | | | | | | | | |
| Saxa 5 mg + Met 500-2000 mg | 320 | 76 | 9.41 | -2.31 | 51.1 | -3.00 | -7.61 | -1.2 | 4.7 |
| Saxa 10 mg + Met 500-2000 mg(*) | 323 | 76 | 9.53 | -2.33 | 50.8 | -3.10 | -7.17 | -0.7 | 6.8 |
| Met 500-2000 mg alone | 328 | 76 | 9.43 | -1.79 | 34.7 | -2.22 | -4.78 | -1.0 | 6.1 |
| Saxa 10 mg alone | 335 | 76 | 9.61 | -1.55 | 25.0 | -1.33 | -5.22 | -0.3 | 2.1 |

(*) Please note that the official and approved dose of saxagliptin 5 mg + metformin 2000 mg

Table 3 : Main randomized controlled trials assessing the efficacy of the addition of saxagliptin 5 mg once a day versus another oral glucose-mowering agent in patients with T2DM inadequately controlled with metformin monotherapy. ? = changes at end of follow up versus baseline. FPG : fasting plasma glucose.

| | Number of patients | Study Duration (weeks) | $HbA_{1c}$ Baseline (%) | ? $HbA_{1c}$ (%) | Patients with HbA1c < 6.5% (%) | ? FPG (mmol/) | ? Body weight (kg) | Reported hypos (% patients) |
|---|---|---|---|---|---|---|---|---|
| **Comparison versus glipizide** | | | | | | | | |
| Göke et al 2010 [31] | | | | | | | | |
| Saxagliptin 5 mg | 428 | 52 | 7.46 | -0.74 | 35.9 | -0.50 | -1.1 | 3.0 |
| Glipizide 5-20 mg | 430 | 52 | 7.53 | -0.80 | 34.3 | -0.89 | +1.1 | 36.3 |
| Göke et al 2011 [32] | | | | | | | | |
| Saxagliptin 5 mg | 428 | 104 | 7.46 | -0.40 | 23.1 | -0.69 | -1.5 | 3.5 |
| Glipizide 5-20 mg | 430 | 104 | 7.53 | -0.40 | 22.7 | -0.54 | +1.3 | 38.4 |
| **Comparison versus sitagliptin** | | | | | | | | |
| Scheen et al 2010 [34] | | | | | | | | |
| Saxagliptin 5 mg | 403 | 18 | 7.68 | -0.52 | 26.3 | -0.60 | -0.4 | 3.2 |
| Sitagliptin 100 mg | 398 | 18 | 7.69 | -0.62 | 29.1 | -0.90 | -0.4 | 2.8 |

Table 4 : Saxagliptin plus metformin combination in a competitive environment : comparison of adding a DPP-4 inhibitor versus another glucose-lowering agent to metformin baseline therapy.

| | DPP-4 inhibitor (a) | Sulfonylurea | Pioglitazone | GLP-1 R agonist | Basal insulin |
|---|---|---|---|---|---|
| HbA1c reduction (b) | Yes | Yes | Yes | Yes | Yes |
| Weight change | Neutral | Increase | Increase | Reduction | Increase |
| Hypoglycemia | No risk | Increased risk | No risk | No risk | Increased risk |
| Need of titration | No | Yes | Yes | Yes | Yes |
| Dose adjustment if RI (c) | Yes | Yes | No | Probably not | Possibly yes |
| Administration | Oral | Oral | Oral | Injectable | Injectable |
| Glucose control escape (d) | Mild | High | Very mild | Mild | Mild if appropriate titration |
| Tolerance | Excellent | Good (except hypoglycemia) | Fluid retention, fractures | Nausea, vomiting | Good (except hypoglycemia) |
| Cardiovascular safety | Yes (e) | Doubtful | Yes (pioglitazone) | Yes (e) | Probably yes |
| Other possible safety issue | Pancreatitis Pancreatic cancer | Cancer (?) | Bladder cancer | Pancreatitis Pancreatic cancer | Breast cancer (glargine) |

(a) : Saxagliptin (sitagliptin, vildagliptin, linagliptin, alogliptin)
(b) : Clinically relevant 0.5-1.5 % HbA1c reduction with all compounds but precise quantitative comparison is difficult because HbA1c reduction may depend on daily dose, duration of the study and baseline HbA1c levels
(c) : RI : renal impairment (however, metformin itself should be used with caution in patients with mild to moderate RI and is contraindicated in patients with severe RI [28]
(d) : Secondary increase in plasma glucose and HbA1c levels following initial improvement
(e) Possible favourable effects currently tested in prospective clinical trials

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