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Efficacy and safety of Jentadueto (linagliptin plus metformin).

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SUMMARY

Introduction : Metformin is the first-choice drug in the management of type 2 diabetes. However, most patients require a combined therapy to reach and/or maintain targets of glucose control. Dipeptidyl peptidase-4 (DPP-4) inhibitors offer new options for combined therapy with metformin. Linagliptin shares a similar pharmacodynamic (PD) profile with other gliptins, but has a unique pharmacokinetic (PK) profile characterized by negligible renal excretion.

Areas covered : An extensive literature search was performed to analyze the potential PK/PD interactions between linagliptin and metformin. They are not prone to PK drug-drug interactions. The two compounds may be administered together, either separately or using a fixed-dose combination (FDC) as shown by bioequivalence studies. The addition of linagliptin in patients not well controlled with metformin alone has proven its efficacy in improving glucose levels with a good safety profile. Initial co-administration of linagliptin plus metformin improves glucose control more potently than either compound separately, without hypoglycaemia, weight gain or increased metformin-related gastrointestinal side effects.

Expert opinion : The linagliptin plus metformin combination may may offer some advantages over the classical sulfonylurea-metformin combination. Even if linagliptin is safe in patients with renal impairment, the use of metformin (and thus of the linagliptin plus metformin FDC) is still controversial in this population.

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

1. Introduction

Even if metformin is unanimously considered as the first-line drug therapy in type 2 diabetes (T2DM), which treatment to be added after metformin failure remains a quite challenging issue[1, 2]. Indeed, what ever the mode of action, almost all second-drug therapies offer quite similar efficacy regarding glycated hemoglobin (HbA1c) lowering effect[1, 3].However, T2DM is often accompanied by other conditions and risk factors, on which the various glucose-lowering agents may exert different effects that may have an impact on long-term clinical outcomes and, thereby, may influence physician's drug choice[4, 5]. Classical insulin secretagogues include sulfonylureas (still recommended because of their low cost),[2] but these glucose-lowering agents expose to a risk of potentially severe hypoglycemia, weight gain and drug-drug interactions (DDIs), which may worsen outcomes[5]. In this regard, dipeptidyl peptidase-4 (DPP-4) inhibitors, which inhibit the inactivation of glucagon-like peptide- 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), two gastrointestinal incretin hormones, may offer new opportunities in the management of T2DM[6-8]. Indeed, GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner, which explains the minimal risk of hypoglycemia associated with such incretin-based therapies[8]. Furthermore, GLP-1 contributes to appetite regulation and thereby may avoid or at least limit weight gain despite improvement of glucose control in T2DM patients, in contrast to what is generally observed with other glucose-lowering therapies[6, 9]. However, the positioning of DPP-4 inhibitors in the management of T2DM, especially their place compared with sulfonylureas after metformin failure[10-12], is still a matter of debate.

Several DPP-4 inhibitors are currently available (sitagliptin, saxagliptin, vildagliptin except in United States, alogliptin only in Japan, more recently linagliptin)[7, 8, 13]. They share a similar mode of action (pharmacodynamics or PD, i.e. selective inhibition of DPP-4), but they differ by some pharmacokinetics (PK) properties[14, 15]. Because they have been mostly studied as add-on therapy to metformin[10, 16, 17], most DPP-4 inhibitors are already available as fixed dose combination (FDC) with metformin, especially vildagliptin[18], sitagliptin[19, 20] and saxagliptin[21]. FDC can offer convenience, reduce the pill burden and simplify administration regimens for the patient, all conditions that may improve adherence to therapy[22, 23].

Linagliptin is the newest DPP-4 inhibitor and is characterized by specific PK properties[24-27]. The most clinically relevant specificity, relative to other already available DPP-4 inhibitors, is that linagliptin has a minimal renal excretion and a predominant biliary excretion (without previous hepatic metabolism)[14, 28]. Thus, it may be used in patients with

chronic kidney disease (CKD) without dose adjustment[28]. This contrasts with other DPP-4 inhibitors, for which an appropriate dose reduction is recommended according to the decrease of the estimated glomerular filtration rate (eGFR)[29]. Therefore, linagliptin may be considered as a valuable alternative in T2DM patients with impaired renal function in whom metformin may be contraindicated[30, 31]. Furthermore, in T2DM patients who may receive metformin (because of acceptable renal function and good gastrointestinal tolerance), linagliptin may also be added to the biguanide to reach HbA1c targets in case of failure of monotherapy. Linagliptin has also proven its efficacy and safety as a triple therapy in addition to a metformin plus sulfonylurea combination[32]. Consequently, numerous patients with T2DM are in a position to receive both metformin and linagliptin[27]. Thereby, a linagliptin plus metformin hydrochloride FDC (Jentadueto®) appears attractive for clinical use (see drug summary box).

The present paper provides a PK/PD evaluation of linagliptin plus metformin and an updated review of the randomized clinical trials and of the bioequivalence studies that have assessed both the efficacy and tolerability/safety of this linagliptin-metformin combination. We will particularly focus our analysis on the safety profile of the combination and what might be its potential use in patients with mild to moderate CKD and in elderly subjects despite the classical limitations of use of metformin in such clinical conditions. To identify relevant studies, an extensive literature search of MEDLINE was performed from January 2008 to December 2012, with the two key-words “metformin” and “linagliptin”. No language restrictions were imposed. Reference lists of original studies, narrative reviews, previous systematic reviews, the European Public Assessment Report (EPAR) of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) of the linagliptin plus metformin FDC[33] and the approval document of this FDC by the Food and Drug Administration (FDA)[34] have been also carefully examined.

2. Mechanism of action of linagliptin plus metformin

2.1. Pharmacokinetic evaluation

The individual PK characteristics of metformin[35, 36] and linagliptin[24, 37] have been reviewed elsewhere. Metformin is mainly excreted by the kidneys whereas linagliptin has a negligible renal excretion. This part of the present review will focus on the PK interactions

between linagliptin and metformin[38]. Only limited DDIs have been described with metformin and with linagliptin both in healthy volunteers and in T2DM patients[35, 39, 40]. Metformin is a substrate for organic cation transporter 1 (OCT1) and OCT2[36] and linagliptin showed inhibitory potency to OCT1 and OCT2[41]. However, considering the low therapeutic plasma concentration of linagliptin, available *in vitro* data clearly suggest a very low risk for transporter-mediated DDIs on comedications, including metformin, in clinical practice[41].

The potential PK/PD interactions between linagliptin and metformin were investigated in a randomised, two-way crossover design study in 16 healthy male subjects[42]. Linagliptin (10 mg/day) and metformin (850 mg three times daily) were each administered alone and concomitantly (3-9 days to steady-state). Co-administration of linagliptin had no apparent effect on metformin exposure (area under the plasma concentration-time curve or AUC), with no significant changes in metformin $AUC_{\tau,ss}$ or $C_{max,ss}$. While co-administration of metformin did not significantly affect $C_{max,ss}$ of linagliptin, it slightly increased linagliptin $AUC_{\tau,ss}$ by 20% (Table 1). Metformin alone had no effect on DPP-4 activity, and the inhibition of DPP-4 caused by linagliptin was not affected by concomitant administration of metformin. Thus, in this study, co-administration of linagliptin with metformin did not have a clinically relevant effect on the PK or PD of either agent[42].

Three bioequivalence studies with a similar design (open-label, randomized, single dose, two-way crossover, trials, in 94-96 healthy volunteers each) were performed with three different linagliptin/metformin FDC tablet strengths (2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg). The results regarding AUC and C_{max} demonstrated that linagliptin/metformin hydrochloride FDC tablets are bioequivalent to coadministration of corresponding doses of linagliptin and metformin as individual tablets (Table 2)[33].

Food may influence the bioavailability of metformin, linagliptin or linagliptin/metformin FDC (Table 3). Even if the bioavailability of metformin is slightly reduced by food[43, 44], it is generally recommended to take metformin with a meal in order to improve gastrointestinal tolerance. Intake of a high-fat meal reduced the rate of linagliptin absorption (increase of T_{max} by about 2 hours), but had no influence on the extent of absorption[45]. These findings suggest that linagliptin can be given together with metformin during a meal. The effect of food on bioavailability of linagliptin/metformin FDC was evaluated with the higher strength of metformin. Administration of linagliptin 2.5 mg/metformin hydrochloride 1000 mg FDC with a fat meal resulted in no change in overall exposure of linagliptin. There was no change in metformin AUC; however, mean peak serum

concentration of metformin was decreased by 18% when administered with food, confirming previous observations when metformin was tested alone[43, 44]. Furthermore, a delayed time-to-peak serum concentrations by 2 hours was observed for metformin under fed conditions. These changes are not likely to be clinically significant[33].

2.2. Pharmacodynamic evaluation

The two antidiabetic agents exert their glucose-lowering effects via different mechanisms, metformin essentially independently of insulin secretion whereas linagliptin primarily (although not exclusively) via its incretin action on insulin secretion[38, 46]. The antihyperglycemic effect of metformin is already marked in the fasting state, by inhibiting overnight gluconeogenesis[47] whereas the DPP-4 inhibitor generally exerts a greater glucose-lowering effect in the postprandial state than after an overnight fast[48].

The mechanism of action of metformin mainly involves suppression of hepatic glucose output and modestly reduction of insulin resistance[49, 50]. The inhibition of hepatic glucose production occurs mostly through a mild and transient inhibition of the mitochondrial respiratory chain complex I. The resulting decrease in hepatic energy status activates AMPK (AMP-activated protein kinase), a cellular metabolic sensor, providing a generally accepted mechanism for the action of metformin on hepatic gluconeogenesis[51].

Linagliptin effectively inhibited plasma DPP-4 activity in patients with T2DM, producing immediate improvements in incretin levels (both GLP-1 and GIP), glucagon suppression, and better glycemic control[52, 53]. The improvement in glycemic control was associated with enhancement of markers of B-cell function, such as proinsulin/insulin ratio, Homeostasis Model Assessment (HOMA)-%B, and disposition index, mostly attributed to a GLP-1 effect[48].

Interestingly, almost 10 years ago already, metformin was shown to increase GLP-1 release in obese patients without or with T2DM[54, 55]. A more recent study confirmed that metformin monotherapy in obese patients with T2DM was associated with increased postprandial GLP-1 levels, including its active form, over a 6-h period following a standard mixed meal, without changes in DPP-4 activity[56]. These data confirmed that metformin-induced increase in GLP-1 levels is independent of DPP-4 inhibition after a meal[44, 57]. The mechanisms of action explaining why metformin may promote GLP-1 secretion from L cells are rather complex[58, 59]. Recent experimental studies in rats suggested that metformin enhances circulating levels

of GLP-1 through a peripheral muscarinic (M3) and gastrin-releasing peptide (GRP) receptor-dependent mechanism[58]. It has also been shown that metformin protects against lipoapoptosis (possibly by blocking JNK2 activation), and enhances GLP-1 secretion from GLP-1-producing cells in vitro[59]. Finally, in a recent study in T2DM patients, whose results contrast with some previous observations[42, 56], the use of metformin was associated with a significantly lower DPP-4 activity, independently of age, sex, body mass index and HbA1c[60]. All together, the combination of a DPP-4 inhibitor and metformin led to greater increases in active GLP-1 than either treatment alone[57], which may represent a further argument in favor of this combination and the commercialization of a gliptin-metformin FDC[61].

3. Clinical applications

3.1. Addition of linagliptin to metformin monotherapy (Table 4)

All clinical trials having tested the addition of linagliptin to metformin were performed in T2DM patients not well controlled (HbA1c 6.5-7% to 10-11%) with a dose of metformin ≥1500 mg/day or maximally tolerated dose. The follow up was rather short (12-24 weeks in placebo-controlled studies), except in one trial comparing linagliptin with glimepiride (104 weeks).

3.1.1. Comparison versus placebo

The efficacy and safety of linagliptin, added to ongoing metformin therapy, were assessed in 333 patients with T2DM who had inadequate glycemic control with metformin alone[62]. Patients were randomized to receive double-blind linagliptin (1, 5 or 10 mg once daily) or placebo or open-label glimepiride (1-3 mg once daily). Twelve weeks of treatment resulted in a mean placebo-corrected lowering in HbA1c levels of -0.73% for 5 mg and -0.67% for 10 mg, compared with -0.90% for glimepiride. There were no hypoglycemic events for linagliptin or placebo, whereas three patients (5%) receiving glimepiride experienced hypoglycemia.

The addition of linagliptin 5 mg once daily (n=524) to metformin in T2DM patients with inadequate glycemic control (mean baseline HbA1c of 8.1 % and mean fasting plasma glucose (FPG) of 9.4 mmol/l) showed significant reductions vs. placebo (n=177) in adjusted mean changes (24 weeks versus baseline) of HbA1c (-0.49 vs. 0.15%), FPG (-0.59 vs. 0.58

mmol/l) and 2h postprandial glucose (-2.7 vs. 1.0 mmol/l)[63]. Rescue glycemic therapy was less used in patients treated with linagliptin 5 mg than in those receiving placebo (7.8% vs.18.9%) and no increased risk of hypoglycemia was observed.

As metformin is administered twice daily, a FDC of these compounds would require twice-daily administration of linagliptin. Therefore, a study evaluated whether 2.5 mg twice-daily dosing of linagliptin has comparable efficacy and safety to 5 mg once-daily dosing when given in addition to metformin twice daily in patients with inadequate glycemic control[64]. A total of 491 T2DM patients were randomized to double-blind treatment with linagliptin 2.5 mg twice daily, 5 mg once daily or placebo, respectively, in addition to continuing metformin twice daily. After 12 weeks, linagliptin 2.5 mg twice daily and 5 mg once daily both significantly reduced HbA1c [placebo-adjusted changes from baseline (mean level : 7.97%) -0.74% (95% CI -0.97, -0.52) and -0.80% (95% CI -1.02, -0.58), respectively, both $p < 0.0001$]. The treatment difference (twice daily - once daily) between the linagliptin regimens was 0.06 (95% CI -0.07, 0.19), the upper bound of which was less than the predefined noninferiority margin (0.35%). Hypoglycemia was rare and similar to placebo, with no severe episodes.

3.1.2. Comparison versus a sulfonylurea

In a 2-year double-blind trial, T2DM patients on stable metformin alone or with one additional oral antidiabetic drug (washed out during screening) were randomly assigned to linagliptin (5 mg; n=777) or glimepiride (1-4 mg; n=775) orally once daily in addition to metformin (daily dose ≥ 1500 mg in 93% of patients)[65]. Reductions in adjusted mean HbA1c from baseline (7.69% in both groups) to week 104 were similar in the linagliptin (-0.16%) and glimepiride groups (-0.36%; difference 0.20%, 97.5% CI 0.09-0.30), meeting the predefined non-inferiority criterion of 0.35%. Fewer participants had hypoglycemia or severe hypoglycemia with linagliptin compared with glimepiride (see below : 4.3).

3.2. Initial linagliptin-metformin combined therapy

A potential benefit of early combined therapy in the management of T2DM may be explained by the complex pathophysiology of the disease and the numerous organ defects that may be targeted by various pharmacological interventions[66]. Because of the complementary mode of action between metformin and a DPP-4 inhibitor, it may sound clinically appealing to initiate a gliptin-metformin combination[38, 61].

The efficacy and safety of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in patients with T2DM were evaluated in a large (n=791) 24-week, double-blind, placebo-controlled, Phase III trial[67]. Two free combination therapy arms received linagliptin 2.5 mg twice daily + either low (500 mg) or high (1000 mg) dose metformin twice daily. Four monotherapy arms received linagliptin 5 mg once daily, metformin 500 mg or 1000 mg twice daily or placebo. Patients with HbA1c ≥11.0% were not eligible for randomization and received open-label linagliptin + high-dose metformin. The placebo-corrected mean change in HbA1c was superior with the two initial combined therapies compared to either monotherapy or placebo (Table 5). In the open-label arm, the mean change in HbA1c from baseline (11.8%) was -3.7%[68]. Hypoglycemia occurred at a similar low rate with linagliptin+metformin as with metformin alone.

4. Safety evaluation

The safety profiles of each separate glucose-lowering agent, the biguanide compound metformin[4, 49, 50] or the DPP-4 inhibitor linagliptin[24, 69, 70], are well documented. The most commonly reported adverse effects associated with metformin therapy are gastrointestinal, and include abdominal pain, diarrhea, nausea, and anorexia. Generally these digestive adverse events may be minimized by initiating a low dose of metformin, gradually uptitrating the metformin dose, and administering the medication with meals. Using this approach, digestive symptoms occurred in around 10 % of the patients receiving metformin as monotherapy in the US multicenter metformin study, and diarrhea and nausea were characterized as severe in only 8% and 4% of patients, respectively[71]. The most critical adverse event related to metformin therapy is lactic acidosis, but it is a rare complication provided that contra-indications of metformin use are respected, including CKD (see below)[72].

The safety profile of linagliptin has been analyzed in detail in previous dedicated reviews[24, 69, 70] and is generally good and quite similar to that previously reported with other DPP-4 inhibitors (i.e. almost comparable to that of placebo)[8, 73, 74]. The long-term (52 weeks) safety and tolerability of oral linagliptin at either 5 or 10 mg were recently confirmed in an extension study of a phase III trial with T2DM Japanese patients with T2DM[75]. Overall the safety/tolerance profile of linagliptin-metformin coadministration is similar to that of metformin alone (Table 5).

4.1. General tolerance profile

The safety of concomitantly administered linagliptin (daily dose 5 mg) and metformin (mean daily dose of approximately 1800 mg) has been evaluated in 2816 patients with T2DM treated for ≥12 weeks in clinical trials. Three placebo-controlled studies with linagliptin + metformin were conducted : 2 studies were 24 weeks in duration, 1 study was 12 weeks in duration. In the 3 placebo-controlled clinical studies, adverse events which occurred in ≥5% of patients receiving linagliptin + metformin (n=875) and were more common than in patients given placebo + metformin (n=539) included nasopharyngitis (5.7% vs 4.3%)[33]. In a 24-week factorial design study, adverse events reported in ≥5% of patients receiving linagliptin + metformin were more common than in patients given placebo (nasopharyngitis : 6.3 vs. 1.4%; diarrhea : 6.3 vs. 2.8%) and only slightly higher than with either monotherapy[67]. Of note, because of the physiological (instead of supraphysiological or pharmacological) levels of GLP-1 reached with the DPP-4 inhibitor, the addition of linagliptin to metformin therapy does not appear to cause a greater incidence of gastrointestinal side effects than does metformin alone.

4.2. Effects on body weight

Overall, no clinically relevant changes in body weight were observed with linagliptin added to metformin, contrasting with the weight gain commonly observed with other glucose-lowering agents[6]. In a pooled analysis of 24-week phase III trials followed by a 78-week open-label extension, treatment with linagliptin was not associated with a clinically relevant change in body weight (-0.03 kg change in subjects previously treated with linagliptin during the initial 24-week period, 0.47 kg in those switched from placebo)[76]. In a recent two-year head-to-head comparative trial in T2DM patients treated with metformin, body weight decreased with linagliptin (−1.4 kg) but increased with glimepiride (+1.3 kg) from similar mean baseline values; the treatment difference was −2.7 kg (97.5% CI −3.2 to −2.2, $p<0.0001$).

4.3. Effects on hypoglycemia

As already mentioned, the likelihood of treatment-related hypoglycemia is very low with the dual metformin plus linagliptin comnibation. This is explained by the absence of insulin-secreting effect of metformin (in contrast metformin is commonly associated with an insulin-sparing effect)[49, 50] and by the glucose-dependent potentiation of insulin secretion of linagliptin (a property shared by all DPP-4 inhibitors leading to increased GLP-1 levels)[77]. The risk of hypoglycemia only increased when linagliptin or linaglipin-metformin are

coprescribed with a sulfonylurea[76]. In a large (n=1058 T2DM patients) multi-centre, 24-week, randomized, double-blind, parallel-group study comparing linagliptin (5 mg once daily) and placebo when added to metformin plus sulfonylurea, symptomatic hypoglycemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively[78]. Hypoglycemia was generally mild or moderate and no more severe hypoglycemia was reported with linagliptin than with placebo. In a 2-year head-to-head trial comparing linagliptin 5 mg or glimepiride 1-4 mg orally once daily in patients with T2DM insufficiently controlled with metformin, fewer participants had hypoglycaemia (7% vs 36%, $p<0{\cdot}0001$) or severe hypoglycaemia (1 episode vs. 12 episodes) with linagliptin compared with glimepiride[65].

4.4. Effects on pancreatitis and pancreatic cancer

Because patients with T2DM exhibit significantly increased rates of acute pancreatitis, large case control studies are required to ascertain whether a specific antidiabetic therapy independently modifies the risk of developing pancreatitis[79]. DPP-4 inhibitors, by increasing GLP-1 levels, were suspected to be associated with an increased risk of pancreatitis and even pancreatic cancer[80]. In a controversial paper that examined the US FDA database of reported adverse events, the use of sitagliptin was shown to increase the odds ratio for reported pancreatitis 6-fold (an increase almost similar to that noticed for the GLP-1 receptor agonist exenatide) as compared with other glucose-lowering therapies[81]. However, reporting bias may be suspected to explain these observations. In a general review on the tolerability of DPP-4 inhibitors, pancreatitis was reported at lower rates with gliptins compared with other oral antihyperglycemic agents[73]. In the large database on linagliptin, no case of acute pancreatitis (1 chronic pancreatitis among 2523 patients) and no case of pancreatic cancer have been described[69]. The conclusion of a recent review was that the available data set from multiple independent sources does not currently support a mechanistic or epidemiological link between incretin therapies and the development of acute pancreatitis; however, longer studies with greater numbers of patients are needed for more robust conclusions to be drawn[79].

Indeed, various experimental data in animal models suggested that there are grounds for concern that the GLP-1 class of drugs may induce asymptomatic pancreatitis and, perhaps over time in some individuals, induce pancreatic cancer[80]. Of potential interest, pancreatic ductal proliferation induced by GLP-1 could be prevented by coadministration of metformin in a rat model[82]. Whether such protection may also be expected in humans remains to be demonstrated, even if some experimental and clinical data have already suggested that metformin may reduce the risk of pancreatic cancer[83].

4.5. Effects on cardiovascular events

T2DM is associated with a higher risk of CV events and some glucose-lowering agents may be associated with an increased rather a decreased risk of CV events. Therefore, especially since the rosiglitazone story, the FDA now requests that new glucose-lowering agents demonstrate CV safety[84]. Metformin may be associated with a lower incidence of CV events when the drug is used as monotherapy[85]. However, the level of evidence of the CV protection of metformin has been challenged recently, perhaps partially because of the pollution by the coprescription with sulfonylureas[86].

Post-hoc analyses of phase II-III trials with DPP-4 inhibitors showed that this incretin-based class of pharmacological compounds may be associated with a reduced incidence of CV events[87]. In a a pre-specified, prospective and adjudicated meta-analysis of CV events in linagliptin or comparator-treated patients with T2DM from eight Phase 3 studies, primary CV events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving comparators; the hazard ratio (HR) for the primary endpoint showed significantly lower risk with linagliptin than comparators (HR 0.34; 95% CI 0.16-0.70). These preliminary results support the hypothesis that linagliptin may have CV benefits in patients with T2DM[88]. Whether the combination of linagliptin (or another DPP-4 inhibitor) and metformin would result in a significant reduction of the incidence of CV events in T2DM patients at high CV risk remains to be demonstrated. Of potential interest, recent data from a 104-week trial showed a lower incidence of CV events with linagliptin added to metformin compared with the addition of a sulfonylurea (glimepiride) to metformin (12 vs. 26 patients; relative risk 0.46, 95% CI 0.23-0.91, p=0.0213)[65]. This finding was mainly attributable to a significantly lower number of non-fatal strokes in patients on linagliptin compared with glimepiride (RR 0.27, 95% CI 0.08–0.97; p=0.0315) rather than to a reduction in mortality or acute coronary infarctions. Further information on the CV safety and efficacy of linagliptin versus glimepiride will be provided by the ongoing prospective CAROLINA ("CARdiovascular Outcome study of LINAagliptin versus glimepiride in patients with T2DM") study in which most probably numerous patients will receive metformin as baseline therapy[89]. The results of this trial are waited with interest because of the controversy concerning the CV safety of the metformin-sulfonylurea combination[86].

4.6. Safety concern in patients with CKD

Because patients with T2DM are better protected against CV disease and thereby live longer, more and more patients are exposed to the development of CKD[90]. Thus, the efficacy and more especially the safety of a gliptin plus metformin combination in patients with CKD deserve much attention[91].

4.6.1. Linagliptin in patients with CKD

The influence of various degrees of renal impairment on the exposure of linagliptin was assessed in subjects with and without T2DM[28]. Linagliptin PK (5 mg once daily) was studied under single-dose and steady-state conditions (administration for 7-10 days) in subjects with mild (creatinine clearance > 50 to $\leq$ 80 ml/min), moderate (> 30 to $\leq$ 50 ml/min), and severe (< 30 ml/min) CKD and end-stage renal disease (< 30 ml/min on hemodialysis), and compared with the PK in subjects with normal renal function. Renal excretion of unchanged linagliptin was <7% in all groups. Although there was a tendency towards slightly higher (20-60%) exposure in subjects with CKD compared with subjects with normal renal function, the steady-state AUC and C_{max} values showed a large overlap and were not affected by the degree of renal impairment (in contrast to what was observed with other DPP-4 inhibitors). Thus, CKD has a minor effect on linagliptin PK, a finding that has been confirmed in post-hoc analyses of the trough plasma levels of linagliptin in the global Phase III program investigating linagliptin 5 mg once daily for 24-52 weeks in patients with T2DM and various degress of renal impairment[24].

Another pooled analysis of 3 randomized, placebo-controlled, Phase 3 clinical trials evaluated the effect of renal function on the efficacy and safety of linagliptin. Data were available for 2141 patients with T2DM who were grouped by renal function as normal (GFR ≥80 mL/min, n=1684), mild CKD (GFR, 50 to <80 mL/min, n=418), or moderate CKD (GFR, 30 to <50 mL/min, n=39). Linagliptin showed consistent placebo-corrected adjusted mean HbA_{1c} changes after 24 weeks across all 3 groups: normal renal function (-0.63%), mild CKD (-0.69%), and moderate CKD (-0.69%), with no significant inter-group difference. Linagliptin was generally well tolerated, with an incidence rate of serious adverse events with linagliptin similar to placebo[92].

Finally, a recent randomized, double-blind, placebo-controlled Phase 3 trial evaluated the efficacy and safety of linagliptin in patients with T2DM and severe CKD (GFR <30 mL/min/1.73 m^2; average level at inclusion : 23.5±6.7 mL/min/1.73 m^2)[93]. Patients were treated with either linagliptin 5 mg once daily (n=68) or placebo (n=65); antidiabetic background therapy remained unchanged. Linagliptin induced significantly greater HbA_{1c} reductions at week 12 compared to baseline in the full analysis set (-0.8% versus -0.2% with placebo) and in the subgroup of poorly controlled patients (baseline HbA_{1c} ≥9%) (-1.5% vs. -0.3%). Hypoglycemia occurred more frequently in linagliptin-treated patients than in placebo-treated patients, an observation that may be explained by unchanged doses of insulin and/or sulfonylurea background therapy. Other adverse event rates were similar for linagliptin and placebo.

Because metformin is classically contraindicated in patients with renal impairment, GFR < 60/min was considered an exclusion criterion in all these trials and thereby the linagliptin plus metformin combination has not been evaluated in patients with moderate to severe CKD.

4.6.2. Metformin in patients with CKD

The use of metformin is classically contraindicated in patients with CKD, as stated in the labeling of the drug. However, the biological criteria used to define CKD may vary between countries. Today's U.S. Food and Drug Administration prescribing guidelines for metformin contraindicate its use in men and women with serum creatinine concentrations ≥ 1.5 and ≥ 1.4 mg/dL (≥ 132 and ≥ 123 mmol/L), respectively. According to the EU label, metformin is contraindicated in patients with a creatinine clearance < 60 ml/min and this parameter should be determined before initiating treatment and regularly thereafter. There is an ongoing debate, however, as to whether these thresholds are too restrictive and that those T2DM patients with mild–moderate renal impairment would gain more benefit than harm from using metformin.[30] As an example, in patients having T2DM with established atherothrombosis participating in the Reduction of Atherothrombosis for Continued Health (REACH) Registry, the 2-year mortality rate associated with metformin vs. other glucose-lowering agents was significantly lower in patients with an estimated creatinine clearance of 30 to 60 mL/min/1.73 m² (adjusted hazard ratio 0.64; 95% CI, 0.48-0.86; P=0.003)[94]. In the UK, the National Institute for Health and Clinical Excellence (NICE) guidelines are less proscriptive and more evidence-based than those in the USA, generally allowing use of

metformin down to a GFR of 30 ml/min, with dose reduction advised at 45 ml/min.[95] Given the current widespread reporting of estimated GFR and the available evidence of the safety profile of metformin in patients with mild-moderate CKD[30], these guidelines appear very reasonable as stated in the recent ADA-EASD position statement[2]. If this extension of use of metformin is accepted in the future, this will result in an extension of the opportunities of prescribing a linagliptin plus metformin combination in patients with T2DM.

4.7. Safety concern in the elderly T2DM patients

Because of their overall safety profile, especially the negligible risk of hypoglycemia, DDP-4 inhibitors are attractive for the management of elderly patients with T2DM[96, 97]. A large cohort study of elderly (> 65 years) patients with T2DM uncontrolled on metformin alone showed that the incidence of hypoglycemia was three times higher in patients prescribed a conventional oral antidiabetic drug (a sulfonylurea in most instances) versus a DPP4 inhibitor after 6 months (incidence of hypoglycemia/severe hypoglycemia : 20.1%/2.4% versus 6.4%/0.1%; P<0.001) while both treatments induced satisfactory glycemic control[98]. No study was published regarding the use of linagliptin in the elderly population[97], but a specific trial in this population is ongoing[99]. In the large database from eight randomized, double-blind, placebo-controlled Phase III clinical trials lasting ≥ 24 weeks, 21.2% among 2523 patients were aged between 65 and 75 years and only 3.1% were ≥ 75 years[69].

During many years, metformin has been contraindicated in elderly patients because a higher risk of lactic acidosis[72]. However, in T2DM patients of the REACH Registry, the 2-year mortality rate associated with metformin vs. other glucose-lowering agents was significantly lower in patients older than 65 years (adjusted HR : 0.77; 0.62-0.95; P = 0.02), as it was in younger individuals. Mortality was also decreased among metformin users older than 80 years but not significantly (HR, 0.92; 95% CI, 0.66-1.28)[94]. A recent study in Poland indicated a relatively good tolerability of metformin by elderly patients (mean age 67 years) with the traditional contraindications to this drug[100]. These findings support the suggestion that indications and contraindications to metformin should be re-evaluated[2].

5. Linagliptin plus metformin FDC

The linagliptin plus metformin FDC has been developed as tablets with three different dosage forms and strengths to be administered twice daily : linagliptin 2.5 mg plus metformin hydrochloride 500 mg, linagliptin 2.5 mg plus metformin hydrochloride 850 mg and linagliptin 2.5 mg plus metformin hydrochloride 1000 mg. This FDC may be prescribed when treatment with both linagliptin and metformin are appropriate. The dosage should be individualized on the basis of both effectiveness and tolerability, while not exceeding the maximum recommended dose of 2.5 mg linagliptin/1000 mg metformin hydrochloride twice daily. Dose escalation should be gradual to reduce the gastrointestinal side effects associated with metformin use. Because of the presence of metformin, the FDC is not recommended in hepatic impairment or hypoxic states and is contraindicated in renal impairment, although such later restriction might be dampened in a near future provided that patient's careful supervision of renal function is warranted.

Linagliptin plus metformin combination, given separately, has proven its superiority as compared to either monotherapy, with a good safety profile[67]. However, there is no study having evaluated the long-term effect of the FDC linagliptin plus metformin so far.

6. Conclusion

The combination of metformin, the first choice glucose-lowering drug, and a DPP-4 inhibitor such as linagliptin sounds as a valuable option in the management of patients with T2DM. Indeed, the two compounds act via different, albeit complementary, mechanisms leading to an additive glucose-lowering activity. Together, the two compounds tackle various main defects in the pathophysiology of T2DM, i.e. impaired insulin secretion, increased glucagon levels, increased hepatic glucose production and decreased insulin sensitivity, resulting in significant reductions in both fasting and posprandial glucose plasma concentrations. Statistically significant and clinically relevant reductions in HbA1c levels have been described when linagliptin 5 mg was added in patients not reaching individually selected HbA1c targets with metformin alone or even with metformin plus sulfonylurea therapy. There are no clinically relevant PK DDIs between linagliptin and metformin reported so far and no major influence of food on PK of either compound has been described. Linagliptin 2.5 mg twice daily had non-inferior HbA1c-lowering effects compared to 5 mg once daily, with comparable safety and tolerability, in T2DM patients inadequately controlled

with metformin. These observations open the door to the launch of a linagliptin plus metformin FDC to be given twice daily with a meal.

Overall, the safety profile of linagliptin is comparable to that of placebo, even when the DPP-4 inhibitor is combined with metformin; in particular, there is no worsening of the well known gastrointestinal side effects of the biguanide present in some patients. No special adverse effects have been reported, especially no weight gain and no severe hypoglycemia, so that this combination may be used safely in a large proportion of patients with T2DM, including elderly people, even if some concern remains in presence of CKD.

Linagliptin may be used in T2DM patients with any degree of renal impairment, because of its negligible renal excretion, a characteristic that differentates this compound from other DPP-4 inhibitors. In contrast, caution is recommended with metformin use in patients with CKD because of the risk of drug accumulation and lactic acidosis, a rare but potentially fatal complication. Thus, linagliptin plus metformin, either separately or as FDC, can only be prescribed when treatment with both pharmacological agents is appropriate. Recent observations suggest that metformin may be used in patients with mild to moderate CKD under strict medical supervision. Further studies are expected to prove the long-term benefit of the linagliptin plus metformin combination, especially with the demonstration of a reduced incidence of vascular complications as currently investigated in the prospective trial CAROLINA.

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Table 1 : Pharmacokinetics interactions between linagliptin (10 mg/day) and metformin (850 mg three times daily) in healthy volunteers. Results are expressed as geometric mean ratio [GMR] co-administration:individual administration (90% confidence interval)[42]. AUC(tau,ss) : area under the concentration-time curve at steady state. C(max,ss) : maximum observed concentration during a dosing interval.

Effect of linagliptin on metformin exposure	Metformin plasma levels	
	AUC(tau,ss)	C(max,ss)
	101 (89-114)	89 (78-100)
Effect of metformin on linagliptin exposure	Linagliptin plasma levels	
	AUC(tau,ss)	C(max,ss)
	120 (107-134)	103 (86-124)

Table 2 : Results from open-label, randomised, single dose, two-way crossover, trials studying the bioequivalence between fixed-dose combinations (FDC) and separate tablets (reference) of linagliptin (2.5 mg) and three different strengths of metformin hydrochloride (1000 mg 500 mg and 850 mg) in 94-96 healthy volunteers. Results are expressed as geometric mean ratio [GMR] FDC : reference with separate tablets (90% confidence interval). Adapted from reference[33].

Treatment	LINA/MET 2.5 mg/1000 mg FDC vs. LINA 2.5 mg + MET 1000 mg		LINA/MET 2.5 mg/500 mg FDC vs. LINA 2.5 mg + MET 500 mg		LINA/MET 2.5 mg/850 mg FDC vs. LINA 2.5 mg + MET 850 mg	
	AUC_{0-72} nmol.h/L	C_{max} nmol/L	AUC_{0-72} nmol.h/L	C_{max} nmol/L	AUC_{0-72} nmol.h/L	C_{max} nmol/L
Linagliptin plasma levels						
Ratio FDC/reference (90% CI)	106.4 (102.7-110.2)	103.4 (100.3-106.7)	100.0 (96.7-103.4)	98.2 (94.5-102.1)	104.5 (100.6-108.5)	106.2 (102.9-109.7)
	AUC_{0-Z} ng.h/ml	C_{max} ng/ml	AUC_{0-Z} ng.h/ml	C_{max} ng/ml	AUC_{0-Z} ng.h/ml	C_{max} ng/ml
Metformin plasma levels						
Ratio FDC/reference (90% CI)	103.6 (100.0-107.4)	104.3 (99.8-108.9)	99.4 (96.5-102.3)	97.9 (94.4-101.5)	101.0 (98.1-103.9)	100.1 (96.5-104.0)

LINA = linagliptin. MET = metformin. FDC : fixed-dose combination. AUC_{0-72} : area under the plasma concentration-time curve from time zero to 72 hours. AUC_{0-Z} : area under the plasma concentration-time curve from time zero to last timepoint with a plasma concentration above the quantification limit. C_{max} : maximum plasma concentration.

Table 3 : Effects of food (high-fat meal) on the bioavailability of metformin and linagliptin. Results are expressed as geometric mean ratio [GMR] fed:fasted state (90% confidence interval). AUC ; Area under the concentration-time curve. Cmax : maximum measured plasma concentration. NA : not available.

Effect of food on metformin exposure (metformin tablet 850 mg; 24 healthy volunteers)[43]	Changes in plasma levels	
	AUC	Cmax
	- 24 % (NA)	- 39 % (NA)
Effect of food on metformin exposure (metformin tablet 1000 mg; 6 healthy volunteers)[44]	- 23% (NA)	NA (NA)
Effect of food on linagliptin exposure (linagliptin tablet 5 mg; 32 healthy volunteers)[45]	GMR (fed/fasted state)	
	AUC (0-72h)	Cmax
	103.5 (98.1-109.2)	84.7 (75.9-94.6)
Effect of food on metformin exposure (linagliptin 2.5 mg + metformin hydrochloride 1000 mg FDC; 32 healthy volunteers)[33]	GMR (fed/fasted state)	
	AUC	Cmax
	95.2 (88.5-102.3)	81.9 (76.8-87.3)
Effect of food on linagliptin exposure (linagliptin 2.5 mg + metformin hydrochloride 1000 mg FDC; 32 healthy volunteers)[33]	GMR (fed/fasted state)	
	AUC	Cmax
	98.7 (94.5-103.0)	91.4 (86.2-96.9)

Table 4 : Main randomized controlled trials assessing the efficacy of adding linagliptin versus placebo or glimepiride in patients with T2DM not well controlled with metformin alone (≥ 1500 mg/day).

		Number of patients	Study Duration (weeks)	HbA_{1c} Baseline (%/ mmol/mol)	HbA_{1c} Change from baseline (%)	FPG Change from baseline (mmol/l)	Body weight Change from baseline (kg)	Hypoglycemia (% patients)
Forst et al 2010[62]	Linagliptin 5 mg od	66	12	8.50/69.4	-0.48	-1.22	-0.57	0
	Linagliptin 10 mg od	66	12	8.40/68.3	-0.42	-0.90	-1.27	0
	Placebo od	71	12	8.40/68.3	+0.25	+0.70	-0.84	0
Taskinen et al 2011[63]	Linagliptin 5 mg od	523	24	8.09/64.9	-0.49	-0.60	-0.50	0.6
	Placebo od	177	24	8.02/64.2	+0.15	+0.60	-0.40	2.8
Ross et al 2012[64]	Linagliptin 5 mg od	224	12	7.98/63.7	-0.52	-0.99*	-1.0	0.9
	Linagliptin 2.5 mg bid	223	12	7.96/63.5	-0.46	-0.76*	-0.4	3.1
	Placebo	44	12	7.92/63.1	+0.28	-	-1.1	2.3
Forst et al 2010[62]	Linagliptin 5 mg od	66	12	8.50/69.4	-0.48	-1.22	-0.57	0
	Glimepiride 1-3 mg od	65	12	8.20/66.1	-0.68	NA	+0.73	4.6
Gallwitz et al 2012[65]	Linagliptin 5 mg od	776	104	7.70/60.7	-0.16	-0.13	-1.4	7
	Glimepiride 1-4 mg od	775	104	7.70/60.7	-0.36	-0.48	+1.3	36 **

FPG : fasting plasma glucose. NA : not available. Od : once daily. Bid : twice daily. *Adjusted mean difference from placebo instead of change versus baseline. ** Severe hypoglycemia : 12 (2%) with glimepiride versus 1 (<1%) with linagliptin

Table 5 : Efficacy of the initial linagliptin-metformin combination therapy versus either monotherapy or placebo in patients with T2DM treated with diet alone (24-week randomized double-blind trial)[67].

Treatment	Number of patients	HbA_{1c} Baseline (%/ mmol/mol)	HbA_{1c} Change from baseline (%)	FPG Change from baseline	Body weight Change from baseline	Hypo-glycemia* (% patients)	GI adverse events ** (% patients
Linagliptin 5mg od	135	8.70/71.6	-0.50	-0.50	+0.2	0	12.0
Metformin 500mg bid	141	8.70/71.6	-0.60	-0.90	-0.7	1.4	9.7
Metformin 1000 mg bid	138	8.50/69.4	-1.10	-1.80	-0.5	3.4	15.6
Linagliptin 2.5 mg + Metformin 500 bid	137	8.70/71.6	-0.20	-1.80	-0.1	3.5	14.0
Linagliptin 2.5 mg + Metformin 1000 mg bid	140	8.70/71.6	-1.60	-2.70	-0.8	0	19.6
Placebo	65	8.70/71.6	+0.10	+0.60	-0.7	1.4	13.9
Linagliptin 2.5 mg + Metformin 1000 mg bid***	66	11.80	-3.70	-4.10	NA	1.5	19.7

FPG : fasting plasma glucose. od : once daily. bid : twice daily. NA : not available * Investigator-reported hypoglycemic events. ** GI adverse events : gastrointestinal adverse events (constipation, diarrhoea, gastritis, hyperchlorhydria, nausea, vomiting). *** Open-label arm in patients with HbA1c ≥11.0% not eligible for randomization.

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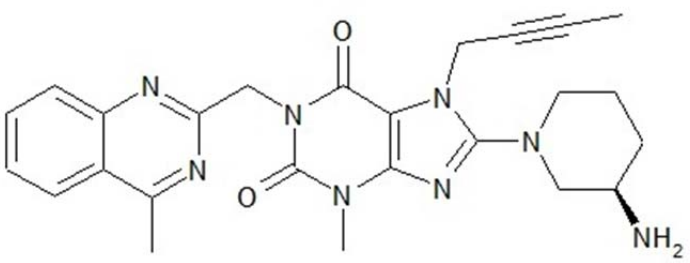
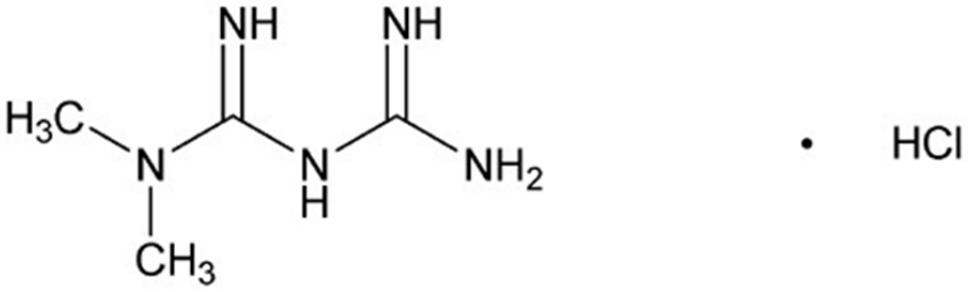
Drug summary box

Drug name (generic)	Linagliptin plus metformin (Jentadueto®)
Phase	Approval by FDA and EMA
Indication	1) as an adjunct to diet and exercise to improve glycemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone; 2) in those already being treated with the combination of linagliptin and metformin; and 3) in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.
Pharmacology	Linagliptin = Inhibitor of dipeptidyl peptidase-4 (DPP-4) = incretin-based therapy

description/mechanism of action	Metformin = AMPK activator = inhibition of hepatic glucose output
Route of administration	Oral
Chemical structure	Linagliptin 
	Metformin 
Pivota trial (s)	. Forst, T. et al. Linagliptin (BI 1356), a potent and selective DPP-4 inhibitor, is safe and efficacious in combination with metformin in patients with inadequately controlled Type 2 diabetes. *Diabet Med* **27**, 1409-19 (2010). . Taskinen, M.R. et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study. *Diabetes Obes Metab* **13**, 65-74 (2011). . Ross, S.A. et al. Efficacy and safety of linagliptin 2.5 mg twice daily versus 5 mg once daily in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, placebo-controlled trial. *Curr Med Res Opin* (2012). . Gallwitz, B. et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* **380**, 475-83 (2012). . Haak, T. et al. Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study. Diabetes Obes Metab 14, 565-74 (2012).

EXPERT OPINION

All diabetes guidelines recommend metformin, if not contraindicated and if well tolerated, as the preferred and most cost-effective first pharmacological agent for the management of type 2 diabetes (T2DM). If monotherapy does not achieve/maintain glycated hemoglobin (HbA1c) target, adjusted to patient's individual pattern, the next step would be to add a second glucose-lowering agent. Choice is based on patient characteristics and drug properties, with the overriding goal of improving glycemic control while minimising side effects. In this regard, the addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor may offer potential benefits over classical sulfonylureas in T2DM patients, despite a higher cost. A lower risk of hypoglycemia and weight gain is already well demonstrated with a gliptin as compared to a sulfonylurea, despite an almost comparable reduction in HbA1c level. This advantage was confirmed with linagliptin compared to glimepiride. The negligible risk of hypoglycemia associated with DPP-4 inhibition is of major interest, especially in subjects at higher risk such as elderly people and patients with renal insufficiency.

Another potential advantage of DPP-4 inhibitors may consist in a better B-cell protection, which should result in a longer durability of the glucose-lowering activity. Indeed, sulfonylureas are generally associated with a progressive, and sometimes quite rapid, deterioration of glucose control, even when added to metformin. This failure requires increased complexity of the glucose-lowering therapy with the progression to a strategy including a triple oral treatment or the use of injections (GLP-1 receptor agonists or insulin). However, clinical evidence remains scarce in humans and further studies should demonstrate whether gliptins really offer a better durability of glucose control compared to sulfonylureas. The recent 2-year data of a controlled trial comparing linagliptin with glimepiride in patients with T2DM not well controlled with metformin monotherapy are insufficient to draw any firm conclusion in this regard.

A further potential benefit of a DPP-4 inhibitor compared to a sulfonylurea might be a better cardiovascular (CV) protection. Indeed, since the University Group Diabetes Program (UGDP) in the seventies, the CV safety of sulfonylureas remains questionable. The results of the United Kingdom Prospective Diabetes Study (UKPDS) in the late nineties were not completely reassuring with the demonstration of an unexplained higher risk in T2DM patients receiving a metformin-sulfonylurea combination. In contrast, all available data with DPP-4 inhibitors support the CV safety of this incretin-based therapy and suggest a CV protection versus placebo or an active comparator. Considering the high CV risk commonly associated with T2DM, the fact that gliptins could offer a better CV protection than sulfonylureas in patients not well controlled with metformin would be of major interest in clinical practice. This hypothesis is currently evaluated in the CAROLINA ("CARdiovascular Outcome study of LINAagliptin versus glimepiride in patients with T2DM") prospective trial comparing linagliptin with glimepiride. This is the only prospective trial comparing a DPP-4 inhibitor with an active compound as all other ongoing trials are comparing alogliptin, saxagliptin or sitagliptin versus a placebo.

In the recent ADA-EASD position statement, initial combination drug therapy is limited to patients with a high baseline HbA1c (e.g. ≥9.0% [≥75 mmol/mol]) who have a low probability of achieving a near-normal target with monotherapy. Introducing initial combination therapy (instead of metformin alone) when pharmacological treatment is required makes sense considering the complexity of the pathophysiology of T2DM, in order to reach therapeutic goal at an earlier stage, have a better stabilisation of this evolving disease and avoid or delay subsequent more complex therapies. Because the complementary effects of linagliptin and metformin lead to robust and sustained improvements in glycemic control, initial combination of the two agents may be considered as a useful treatment option for patients with T2DM as it reulst in better glucose control than either monotherapy, with a similar good tolerance profile.

By increasing convenience and thereby patient's adherence, a fixed-dose combination (FDC) may offer some advantages in clinical practice. That is the reason why several gliptin plus metformin FDCs are now available, the most recently proposed one being Jentadueto® (linagliptin plus metformin). Adherence

to therapy is, indeed, a major concern in patients with T2DM who generally share several chronic comorbidities and thus should receive multiple medications. However, as the classical formulation of metformin hydrochloride should be given twice daily, the linagliptin plus metformin FDC has also to be given twice daily while once daily administration of linagliptin is enough to maintain sustained DPP-4 inhibition over 24 hours. Because metformin should be titrated to improve gastrointestinal tolerance, various FDC forms with different strengths of metformin have been developed. If the use of metformin would be extended to patients with mild to moderate renal impairment in the future, this may also allow the prudent use of such combination, with a reduced metformin dosage, in these circumstances.

Linagliptin has a unique pharmacokinetic profile compared to other DPP-4 inhibitors, with a very low renal excretion. This characteristic allows use linagliptin in T2DM patients with chronic kidney disease (from mild to severe) without contra-indication and any dose adjustment. Considering the large number of patients with some degree of renal impairment (especially in the elderly population), this may represent an advantage over other DPP-4 inhibitors whose daily dose should be adjusted according to the reduction of estimated glomerular filtration rate (eGFR). However, the situation of Juntadueto®) is less clear because of the presence of metformin. Indeed, renal impairment (eGFR < 60 ml/min) is considered as an official contraindication of metformin because of the potential risk of lactic acidosis in case of biguanide accumulation. Nevertheless, there is an ongoing debate as to whether these thresholds are too restrictive and thereby not allow patients with mild-moderate renal impairment gain more benefit than harm from using metformin. In the recent ADA-EASD position statement, it is considered that metformin may be used down to a GFR of 30 ml/min, with dose reduction advised below 45 ml/min. If so, the use of linagliptin plus metformin, either separately or as FDC, would be extended to a larger population of patients with T2DM and the specific advantage of linagliptin regarding its use independent of renal function would even be better appreciated in clinical practice.