Linagliptin: dpp-4 inhibition in the treatment of type 2 diabetes mellitus

Abstract

The complex pathophysiologic mechanisms of type 2 diabetes are one of the barriers that make its treatment so difficult and it is also one of the responsibilities for the high prevalence of the disease around the world. Patients with T2DM have dysfunction in incretin hormones (such as glucagon-like peptide-1 or GLP-1 and glucose-dependent insulinotropic polypeptide or GIP). By inhibiting the dipeptidyl peptidase-4 (DPP-4) enzyme, it is possible to slow the inactivation of GLP-1 and GIP, promoting blood glucose level decrease in a glucose-dependent manner. Linagliptin is a dipeptidyl peptidase-4 inhibitor. This article reviews the pharmacology, mechanism of action, chemical structure, enzymatic binding, pharmacokinetics, pharmacodynamics, clinical trials, indications, contraindications and drug interactions of linagliptin and the role of DPP-4 inhibitors in the management of hyperglycemia in adults with T2DM. Linagliptin clinical trials showed clinical efficacy in decreasing glycated hemoglobin (HbA1c), fasting plasma glucose and postprandial glucose when administered as monotherapy or in combination with other oral antihyperglycemic agents (such as sulphonylureas, pioglitazone or metformin) and also insulin, including non-inferior efficacy versus sulphonylurea without weight gain. Adverse events are uncommon and may include upper respiratory tract infection, nasopharyngitis and headache. The risk of hypoglycemia with linagliptin is very low and is increased when the drug is combined with insulin or an insulin secretagogue drug, such as a sulphonylurea. Dose adjustments based on liver or renal function are not necessary with linagliptin use. Given its safety and efficacy profile, linagliptin is a valid treatment for patients with T2DM and is a particularly interesting option in patients with renal failure.

Keywords: DPP-4 inhibitor, linagliptin, efficacy, safety, renal impairment, type 2 diabetes mellitus, therapy

Introduction

Type 2 diabetes mellitus (T2DM) has become a global epidemic. In recent years, the prevalence of T2DM has been gradually increasing, following the socio-demographic, cultural and behavioral changes of the population. In general, people are becoming increasingly sedentary, consuming more processed foods with high glucose and lipid content, which increases the rate overweight, obesity and metabolic syndrome.1 A recent analysis showed that there were 347 million people with diabetes in 2008 (more than 9% of adults worldwide) and another estimative suggests that the prevalence will increase to 439 million by 2030.2,3 T2DM, which accounts for approximately 90% of all diabetes cases in developed countries, is a chronic metabolic disorder caused by a pancreatic beta cell dysfunction (impaired insulin secretion), which worsens over time in a setting of resistance to insulin in muscles and liver.4 In addition to the change in lifestyle (diet and exercise), pharmacotherapy is required to maintain glycemic control and minimize chronic complications.5 Inhibitors of the dipeptidyl peptidase-4 (DPP-4) enzyme activity are one of the types of oral antihyperglycemic drugs. The antihyperglycemic effects of DPP-4 inhibitors (also known as gliptins) are mediated through the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1 and GIP are secreted into the bloodstream by gastrointestinal L and K cells, respectively. This secretion only occurs after food ingestion, causing the so-called incretin effect, characterized by increased insulin secretion and decreased glucagon secretion by the pancreas, stimulated by oral glucose intake.6

The incretin effect describes the observation that oral glucose administration induces a higher insulin response compared with an intravenous equivalent amount of glucose. Both GLP-1 and GIP are insulinotropic, however, incretins also modulate the release of postprandial glucose by inhibiting glucagon secretion (GLP-1), delaying gastric emptying (GLP-1) and possibly also by increasing peripheral insulin sensitivity (GLP-1 and GIP). The incretin response represents approximately 70% of total insulin secreted after the oral administration of glucose.6

The hormones GLP-1 and GIP are rapidly degraded by dipeptidyl peptidase-4 (DPP-4); however, the GLP-1 metabolites can also have specific effects of clinical relevance. The discovery of defective incretin response in type 2 diabetes (T2DM) has led to the development of incretin-based therapies, being the first one approved in 2005. These therapeutic strategies are based on the GLP-1 because there is a resistance to the insulinotropic effects of GIP in T2DM patients. The two classes of incretin-based drugs available include GLP-1 agonists and DPP-4 inhibitors (DPP-4i), which inhibit DPP-4, the enzyme responsible for the short life of endogenous GLP-1 (less than two minutes). The incretin-based therapies led to a great interest in part because of the weight loss associated with GLP-1 agonists and the weight neutrality of DPP-4i. Furthermore, when GLP-1 agonists or DPP-4i are used in the absence of an insulin secretagogue or insulin itself, the risk of hypoglycemia is low. There are a number of possible nonglycemic (or extraglycemic) effects of the incretin therapy such as pancreatic cell tropism, cardioprotection, neuroprotection and effects on the bone. However, although some of these effects can reveal a
significant clinical benefit, their clinical significance has not yet been proved in large scale clinical trials. There are still many aspects of the incretin system that need to be explored. GLP-1 and GIP share many effects, in particular their effects on pancreatic cell are similar. GLP-1 and GIP promote insulin secretion and biosynthesis in a glucose-dependent manner, acting to regulate postprandial glycaemia. In contrast with GIP, GLP-1 inhibits the glucagon and somatostatin release. The somatostatin inhibition is mediated through direct effects on pancreatic cell. The GLP-1 antagonist, exendin 9-39, inhibits glucagon secretion; however the pathway by which the glucagon releases is inhibited is less clear. The currently available DPP-4i include sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin. DPP-4i is selective for DPP-4/CD26, however the DPP-4 is a widely expressed protease and with many substrates, including both GIP and GLP-1. Therefore, in contrast with GLP-1 receptor agonists (GLP-1R), DPP-4i increases the circulating levels of both GIP and GLP-1. The DPP-4 inhibition with these agents generally result in almost complete inhibition of DPP-4 for 24 hours, increasing circulating GLP-1 and GIP levels in two to three times higher than normal. Another difference between DPP-4i and GLP-1-R is that while the latter leads to supraphysiologic concentrations of GLP-1, the DPP-4 inhibition induces physiological concentrations of incretins. The DPP-4i recover the enteroinsular gradient of GLP-1, potentially explaining why DPP-4i are effective, although induce only modest increases in systemic concentrations of incretins. Linagliptin, sitagliptin, saxagliptin and alogliptin are given once daily, while vildagliptin is given twice daily. DPP-4i is all oral agents, in contrast with the GLP-1R agonists, which require parenteral administration. Linagliptin, a DPP-4 inhibitor, has a favorable pharmacokinetic profile in terms of its predominantly non-renal elimination. This therapeutic agent is characterized by a low rate of liver metabolism and is predominantly eliminated via the fecal route. It shows a potent and selective dose-dependent inhibition of DPP-4 activity, with more than 80% enzyme inhibition throughout a 24-hour interval.

Pharmacology

Mechanism of action

By design, DPP-4 inhibitors are readily absorbed orally. Measurable effects on circulating GLP-1 may start within few minutes after oral ingestion of most of these agents. Following oral administration, systemic absorption occurs mainly in the small intestine. Peak plasma concentrations are usually achieved within a few hours. Linagliptin is a reversible competitive inhibitor of DPP-4, designed specifically for the prolonged inhibition of this enzyme, with pharmacokinetic and pharmacodynamic properties which are suitable for a daily dose. DPP-4 inhibitors, such as linagliptin, inhibit the enzymatic degradation of endogenous GLP-1 and GIP by DPP-4 enzyme. This enzyme inhibition potentiates the effects of endogenous incretins, which results in increased glucose-dependent insulin secretion by pancreatic beta cells and suppression of postprandial glucagon secretion by pancreatic alpha cells. By prolonging the activity of endogenous incretins, the linagliptin regulates blood glucose in a glucose-dependent manner.

Chemical structure

Linagliptin is a small molecule derived from xanthine (Figure 1), with a molecular weight of 472.6g/mol. Since there are no other xanthine-based DPP-4 inhibitors currently approved for the treatment of T2DM, linagliptin represents a new class of chemicals for this therapeutic principle (Table 1). The water solubility of linagliptin is 0.9mg/mL. According to the Biopharmaceutics Classification System, linagliptin is considered as Class 3: high solubility, low permeability.

Enzymatic binding

Linagliptin shows a similar maximal efficacy for inhibition of DPP-4 in vitro when compared with other DPP-4 inhibitors, but with a higher potency. It shows an excellent selectivity for DPP-4 versus DPP-8(40,000-fold) and DPP-9(>10,000-fold) and few interactions with other proteases (prolyloligopeptidase, aminopeptidase N, aminopeptidase P, trypsin, plasmin, thrombin: >10,000-fold selectivity). Besides that, it has no clinical significant inhibitory effect on the CYP 450 enzymes.
Linagliptin: dpp-4 inhibition in the treatment of type 2 diabetes mellitus

moderate (creatinine clearance=31-50mL/min), or severe (creatinine clearance <30mL/min) renal dysfunction, without dose adjustment. No dose adjustment is required when initiating treatment of T2DM patients with linagliptin, saxagliptin, sitagliptin and alogliptin in patients with liver failure (Table 2). Vildagliptin is not recommended in diabetic patients with liver disease.

Table 2 Use of DPP-4 inhibitors in clinical practice

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Renal failure</th>
<th>Hepatic failure</th>
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<tbody>
<tr>
<td></td>
<td>Mild (CC=51-80mL/min)</td>
<td>Moderate (CC=31-50mL/min)</td>
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<tr>
<td>Linagliptin</td>
<td>√</td>
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<tr>
<td>Saxagliptin**</td>
<td>√</td>
<td>½ dose</td>
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<tr>
<td>Sitagliptin</td>
<td>√</td>
<td>½ dose</td>
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<tr>
<td>Vildagliptin</td>
<td>√</td>
<td>½ dose</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>√</td>
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*Guidance may be different depending on local regulatory approvals;

CC, creatinine clearance; √, approved; X, use not recommended; **, dose reduction (2.5mg) is recommended when saxagliptin is coadministered with another potent inhibitor of cytochrome P450 3A4/5 (e.g. ketoconazole).19,19,20

Clinical studies

Linagliptin is approved by FDA and EMA for the T2DM treatment as an antihyperglycemic agent that can be used as monotherapy or in combination with other medications (metformin, sulphonylurea, pioglitazone, metformin plus sulphonylurea or insulin).19

Monotherapy

Although metformin is the first-line drug in the early pharmacological treatment of T2DM, some patients do not tolerate the drug, or exhibit contraindications. In these cases, the DPP-4 inhibitors such as linagliptin can be an effective option for use as monotherapy.20,21 Studies with linagliptin in monotherapy during 6, 12 and 24 weeks have shown improvement in glycaemic control when compared to placebo, based on mean changes in corrected HbA1c levels at the end of the studies.22 In a Phase III, randomized, double-blind, placebo-controlled trial, 503 patients with T2DM were evaluated and a significant (placebo-corrected) decrease (linagliptin monotherapy versus placebo) in HbA1c levels of -0.69%±0.08% (p<0.0001) was shown, as well as a reduction in fasting plasma glucose and 2hour postprandial glucose of ±23.4mg/dL (±3.6, p<0.0001) and ±57.6mg/dL (±12.6, p<0.0001), respectively. In the linagliptin group, 25% of patients achieved HbA1c <7.0% compared with 11.6% in the placebo group. The reduction in HbA1c was proportional to the baseline values of each patient.22 Regardless of baseline HbA1c, the results were favorable for linagliptin; for baseline HbA1c ≥9.0%, 8.0% to <9.0%, 7.5% to <8.0% and <7.5%, the respective placebo-adjusted mean changes were -1.1% (p<0.0001), -0.71% (p<0.0001), -0.55% (p<0.0005) and -0.57 (p<0.0001).22 Kawamori et al.21 also compared linagliptin monotherapy with voglibose, an α-glucosidase inhibitor, in a 26week study.17 More patients receiving linagliptin achieved HbA1c ≤7%(30.3%) when compared to voglibose (22.2%). The percentage of patients achieving a reduction ≥0.5% in HbA1c with linagliptin (57.2%) was also greater than those with voglibose (37.7%) (p<0.0001).23

Combination therapy

Combination with metformin: The glycemic control in patients with T2DM is not achieved or sustained for a long period using only metformin monotherapy sometimes, thus requiring the addition of other antihyperglycemic agents. The DPP-4 inhibitors have been shown to be an excellent combination option. The combination of linagliptin plus metformin results in a significant improvement in glycaemic control. A single daily dose of 5mg/day was associated with greater effectiveness in glycaemic control.24 The decrease in HbA1c levels after drug administration occurs regardless of its baseline levels.24 A study conducted for a 12week period in 451 patients with T2DM uncontrolled on metformin alone, suggested that the addition of linagliptin 2.5mg administered twice daily showed non-inferior HbA1c-lowering effects (0.74% and 0.80%) compared to a fixed dose of 5mg once daily, with comparable safety and tolerability.25 At the end of the 24week follow-up period in a study with linagliptin in addition to metformin therapy, patients were four-times more likely to achieve the target HbA1c level ≤7% and/or obtain a 0.5% reduction in HbA1c level from baseline compared to placebo plus metformin and HbA1c reduction from baseline was 0.64% within the linagliptin group compared to placebo group.26 Patients treated with linagliptin also achieved greater adjusted mean reductions in fasting plasma glucose, with placebo-corrected mean of -21.6mg/dL.22 The treatment effect in terms of corrected mean reductions in fasting plasma glucose was significant at all points from the week 6, compared with its baseline levels (p <0.0001). There was also improvement in 2hour postprandial glucose levels compared to the placebo group, with an adjusted mean reduced by 48.6mg/dL in the linagliptin group, while there was an increase of 18.0mg/dL in the placebo group, resulting in a treatment effect of -66.7mg/dL(P <0.0001).22 Haak et al.26 reported the findings of early combination of linagliptin and metformin in treatment-naive diabetic patients, in a 24week double-blind study.26 Compared to metformin monotherapy (1000mg), the early combination of metformin (1000mg) and linagliptin (5mg) was more effective in reducing HbA1c (-1.7% versus -0.8%, p<0.0001). Substantial reduction in FPG from baseline to Week 24 was found with the combination therapy.26 In a one year evaluation, the reductions in glycosylated hemoglobin was maintained.27 Graefe-Mody et al.18 evaluated in a randomized, open-label, crossover, single-center study, the potential pharmacokinetic and pharmacodynamic interaction between metformin and linagliptin. The coadministration of metformin 850mg, three times daily and linagliptin 10mg once daily

did not modify the pharmacological profile of each drug alone. This study suggested that the combination of metformin and linagliptin can be done safely in patients with T2DM, without requiring dose adjustment.18

Combination with glitazone: The use of linagliptin associated with pioglitazone also showed improvement in glycemic control (placebo-corrected mean reduction in HbA1c of -0.51% at 24weeks). The effects occurred regardless of baseline HbA1c levels and were numerically greater in patients with higher baseline levels. Linagliptin group patients were twice more likely than the placebo group to achieve the target HbA1c<7% and four-times more likely to achieve a 0.5% reduction in its baseline levels. Improvements were also described in fasting plasma glucose (−14.4mg/dL) with linagliptin associated with pioglitazone.28 The HbA1c reduction was greater in patients with baseline HbA1c≥9% and treated with linagliptin in combination with pioglitazone (−1.49%). Body weight remained stable for up to 24weeks in the two groups. This combination can be interesting, even for early therapy in patients with an intolerance or contraindication to metformin.29

Combination with sulphonylurea: The linagliptin plus sulphonylurea combination significantly improved glycemic control of patients in comparison to sulphonylurea plus placebo therapy. The placebo-corrected mean changes in HbA1c were -0.47% following 18weeks of treatment. Patients receiving linagliptin and sulphonylurea were about six-times more likely to achieve HbA1c levels ≤7% compared with sulphonylurea and placebo treatment and about five-times more likely to reduce HbA1c levels by 0.5%. There was no statistically significant difference between the groups regarding the adjusted mean change in fasting plasma glucose, with a treatment effect of -6.4mg/dL for the group treated with combination with linagliptin.29

Triple combination: The progressive failure of the pancreatic beta cell function contributes to the progressive characteristic of the disease and the need for adjustment of treatment strategies. Some studies have shown advantages of adding a third non-insulin agent to a two-drug combination that is not yet or no longer achieving the glycemic target.1 In another 24week, placebo-controlled study conducted with 1,058 patients, randomized in a 3:1 ratio (793 linagliptin and 265 placebo), in which linagliptin was added to patients on stable doses of metformin and sulphonylurea. The study enrolled men and women with Type 2 diabetes aged ≥18 and ≤80years, with a BMI >40kg/m² and HbA1c ≥7.0% and ≤10.0% despite receiving a total daily dose of ≥1500mg metformin (or the maximum tolerated dose, if lower) and HbA1c ≥7.0% and ≤10.0% despite receiving a total daily dose of metformin and basal insulin with or without oral agents was tested. A total of 1,261 patients (HbA1c ≥7.0%[53mmol/mol] to ≤10.0%[86mmol/mol]) on basal insulin alone or combined with metformin and/or pioglitazone were randomized (1:1:1) to double-blind treatment with linagliptin 5mg once daily or placebo for ≥52weeks. At week 24, HbA1c changed from a baseline of 8.3% (67mmol/mol) to −0.6% (−6.6mmol/mol) and by 0.1% (1.1mmol/mol) with linagliptin and placebo, respectively (treatment difference -0.65% [95% CI -0.74 to -0.55] [-7.1mmol/ mol]; P<0.0001). Despite the option to up titrate basal insulin, it was adjusted only slightly upward (week 52, linagliptin 2.6 IU/day, placebo 4.2 IU/day; P<0.003), resulting in no further HbA1c improvements. Frequencies of hypoglycemia (week 24, linagliptin 22.0%, placebo 23.2%; treatment end, linagliptin 31.4%, placebo 32.9%) and adverse events (linagliptin 78.4%, placebo 81.4%) were similar between groups. Mean body weight remained unchanged (week 52, linagliptin -0.30kg, placebo -0.04kg).33

Clinical safety
Numerous studies have been conducted to evaluate the clinical safety of linagliptin. Studies conducted in T2DM patients with insufficient glycemic control, with administration of linagliptin 5mg in a single daily dose, showed efficacy, safety and tolerability: in initial combination therapy with pioglitazone 30mg compared to placebo for

24weeks; in adjunctive therapy to metformin plus a sulphonylurea compared to placebo for 24weeks; as adjunctive therapy to metformin with a dose higher than 1.5g/day compared to glimepiride for 104weeks; in combination with sulphonylurea compared to placebo for 18weeks; in monotherapy for patients with contraindications to the use of metformin compared to placebo for 18weeks, and compared to glimepiride for 34weeks and in addition to insulin.25,35

Patients with renal impairment

Linagliptin administration to patients with renal impairment does not require dosage adjustment.7 When administered in a 5mg dose, less than 1% of linagliptin is excreted unchanged in the urine. Thus, in therapeutic dose, renal excretion is a minor route of elimination for linagliptin, unlike other DPP-4 inhibitors.36 In an analysis of three randomized, Phase III, placebo-controlled clinical trials the efficacy and safety of linagliptin were evidenced in patients with T2DM with mild (creatinine clearance >50 to >80mL/min), moderate (creatinine clearance >30 to ≤50mL/min) and severe (creatinine clearance <30mL/min) renal impairment, in addition to the end-stage renal disease (creatinine clearance <30mL/min on hemodialysis), renal excretion of linagliptin remained unchanged and represents less than 7% in all groups.6,19,28 In patients with type-2 diabetes, RI had a minor effect on linagliptin exposure. Therefore, neither dose-adjustment nor drug-related monitoring of estimated glomerular filtration rate is necessary for patients with renal impairment.17

Patients with liver failure

Linagliptin administration to patients with impaired liver function does not require dose adjustment. Although reductions occur in the linagliptin pharmacokinetic parameters as the liver failure degree increases, this has no impact on DPP-4 inhibition.7

Elderly patients

No changes were observed in safety and tolerability of linagliptin in patients aged 70years or older. In elderly patients with T2DM linagliptin was efficacious in lowering glucose with a safety profile similar to placebo. These findings could inform treatment decisions for achieving individualized glycemic goals with minimal risk in this important population of patients.18

Adverse events

The most frequent adverse events described in linagliptin trials compared to placebo were: headache (2.9 vs 3.1%), hypertension (2.3 vs 1.9%) and back pain (2.0 vs 2.6%).35 In contrast to sulphonylureas, the DPP-4 inhibitors do not have inherent risk of causing hypoglycemia.25,35,39 The effects on body weight have also been attractive to the use of DPP-4 inhibitors, since they exhibit a neutral profile on it.25,29 In the 24week follow-up with linagliptin use, no significant difference was shown in body weight or waist circumference when compared to placebo.22,23 In an analysis of 2,523 patients receiving linagliptin 5mg once daily and 1,049 patients who received placebo, both overall incidence of adverse events (55.8% vs 55.0%) and severe adverse effects was similar between groups (2.8% vs 2.7%). Similar or reduced incidence of adverse events was seen in patients who used linagliptin when compared to placebo: upper respiratory tract infection (3.3% vs 4.9%), headache (2.9% vs 3.1%), urinary tract infection (2.2% vs 2.7%), hypersensitivity (0.1% vs 0.1%), increased liver enzymes (0.1% and 0.1%) and increased serum creatinine (0.0% vs 0.1%). There was a slight increase in frequency of nasopharyngitis (5.9% vs 5.1%) and cough (1.7% vs 1.0%) with linagliptin. Hypoglycemia incidence was 8.2% for linagliptin and 5.1% for placebo. The incidence was higher in patients who were taking a sulphonylurea (20.7% vs 13.3%). In patients not receiving concomitant sulphonylurea, the hypoglycemia incidence with linagliptin was very low (<1%) also in elderly or renal impaired patients (<1%).29 Cardiovascular disorders occurred in 2.1% of patients treated with linagliptin, compared to 1% of those receiving placebo. Although the incidence of some cardiac disorders was slightly higher in the treatment group, further studies are needed to assess the impact of these findings. The results from a metaanalysis involving trials from the large linagliptin Phase III programme support the hypothesis that linagliptin may have CV benefits in patients with T2DM.19 Two large long-term studies are ongoing in order to evaluate the cardiovascular safety with the use of linagliptin (CAROLINA16 Study and CARMELINA19) and its results should reveal important clinical data on the effect of linagliptin on cardiovascular and renal micro vascular outcomes.30 There is a debate in recent times if the incretin-based therapies, including DPP-4 inhibitors, would be associated with a high risk of pancreatitis. Combined safety analyses or retrospective analyses of large health databases do not seem to confirm this risk. However, continuous monitoring and further long-term studies are needed to confirm these observations.20

Drug interactions

Most of linagliptin is excreted unchanged through enterhepatic elimination and with negligible use of CYP450 isoenzyme system, so the potential for drug-drug interactions by these mechanisms is limited. In vitro, linagliptin is a weak to moderate inhibitor of CYP3A4. However, in vivo evidence shows that the clinical significance of these interactions is low and does not require dose adjustment.31 Linagliptin has also been studied in combination with digoxin, simvastatin, metformin, oral contraceptives, warfarin, pioglitazone and glyburide, and its concomitant use demonstrated to be safe.11,18

Conclusion

DPP-4 inhibitors are a therapeutic class of oral antihyperglycemic drugs for the treatment of T2DM. These inhibitors were designed for the disease treatment based on prior knowledge about the physiology of incretin GLP-1 and an understanding of the target (DPP-4). In other cases, the discovery of antihyperglycemic agents was initially more by chance than by planning based on the pathophysiologically of T2DM (e.g., metformin, sulphonylureas and glitazones).

Nowadays, although there are some practical differences between different inhibitors of DPP-4 in respect to dose frequency and their ability to be used in different subpopulations of patients, it appears to be little difference among them in terms of efficacy and safety. Linagliptin effects on HbA1c appear to be moderate (compared with other oral agents, such as metformin: -1% to -2%, sulphonylurea: -1% to -2% and thiazolidinediones: -0.5% to -1.4%) and similar to sitagliptin, saxagliptin, alogliptin and vildagliptin (results from individual studies, these compounds have not been compared in head-to-head studies). Such as the other DPP-4 inhibitors, linagliptin has a relatively low rate of hypoglycemia and it is weight neutral. Thus, linagliptin can be used as a second-line therapy associated with metformin in the treatment of adult T2DM patients or even as a first-line therapy in those patients intolerant to metformin. It can be used as monotherapy with diet and exercise, or in combination with metformin, pioglitazone, or a sulphonylurea in a double or triple therapy regimen and also added to insulin regimen.
One characteristic that distinguishes linagliptin from the other three DPP-4 inhibitors currently available is that it does not require dose adjustment in patients with renal impairment, a common chronic complication in T2DM, or in patients with hepatic failure. It has a relatively favorable profile of adverse effects and a very low risk of hypoglycemia. Regarding drug interactions, linagliptin has no relevant drug-drug interactions. Due to its safety and efficacy profile, linagliptin is proven to be very useful in the treatment of T2DM, particularly in patients with renal failure.

Competing interests
Hohl A has received fees for lecturing and/or consultancy from the following pharmaceutical companies with interest in type 2 diabetes mellitus: Merck Sharp Dohme, Bristol-Meyers-Squibb, Novartis, Merck Serono, Boehringer-Ingelheim, Eli Lilly, Sanofi and Abbott Ronsoni MF has no conflicts of interest to declare Guedes EP has received lecture and/or consulting fees from the following pharmaceutical companies with interest in type 2 diabetes mellitus: Astra Zeneca, Bristol-Meyers-Squibb, Novo Nordisk, Boehringer-Ingelheim, Torrent and Abbott

Melo TG is medical manager of the Diabetes area at Boehringer-Ingelheim do Brazil Lauand F is medical manager of the Diabetes area at Eli Lilly do Brazil.

Authors’ contributions
All authors participated equally in the development of this paper. All authors also read and approved the final manuscript.

Acknowledgements
None.

Conflicts of interest
Authors declared that there are no conflicts of interest.

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