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REVIEW

Linagliptin: a Novel Dipeptidyl Peptidase 4 Inhibitor with a Unique Place in Therapy

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ABSTRACT

The dipeptidyl peptidase 4 (DPP-4) inhibitors comprise a promising new class of agent for the management of type 2 diabetes. They possess a range of physiological effects associated with improved glycemic control including stimulation of glucose-dependent insulin secretion and suppression of glucagon secretion, and lower blood glucose levels through different, but potentially complementary, mechanisms to standard oral therapies. Linagliptin is the latest DPP-4 inhibitor to complete pivotal phase 3 trials. The data show that linagliptin provides significant, clinically meaningful and sustained improvements in glycemic control, with an incidence of adverse events similar to placebo and an excellent tolerability profile. In addition, linagliptin has been shown to be weight neutral and, importantly, there was no increased risk of hypoglycemia attributed to linagliptin use in monotherapy or combination therapy with metformin or pioglitazone. A unique characteristic of linagliptin that differentiates it from other members of the class is its primarily nonrenal route of excretion. The linagliptin phase 3 program included several hundred patients with type 2 diabetes and different stages of renal disease and the data suggest that the drug would not need dose adjustment, regardless of the degree of renal impairment. There is a particular need for safe and effective therapeutic agents that can be used when renal function declines. Linagliptin has recently been approved by the US Food and Drug Administration and may find a place in therapy as a treatment option for the significant number of patients in whom metformin and the other DPP-4 inhibitors are either contraindicated or require dose adjustment because of moderate to severe renal impairment.

Keywords: DPP-4 inhibitor; glycemic control; linagliptin; renal impairment; type 2 diabetes

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INTRODUCTION

With the global trend toward more sedentary lifestyles and a higher incidence of obesity, it is estimated that the number of people with diabetes

will reach 438 million internationally by 2030.[1] In the UK, the total diabetes prevalence in 2010 (both diagnosed and undiagnosed and adjusted for age, sex, ethnic group and social deprivation) for people aged 16 years and over was estimated to be 3.6 million and is predicted to increase to 5.3 million by 2030.[2] This prevalence is not estimated to increase uniformly across the UK, and some primary care trusts may see prevalence rates almost double between 2010 and 2030.[2]

The complications of diabetes cause considerable suffering and are associated with enormous economic costs. Diabetes is a leading cause of blindness, amputation, renal disease and cardiovascular disease, and high on the main causes of deaths in most high-income countries. For those who have diabetes, many of these complications can be prevented or delayed with access to the right support and healthcare. While the cornerstone for preventing and treating type 2 diabetes is lifestyle modifications, the majority of patients will unfortunately not reach glycemic targets with lifestyle change alone and will require the addition of pharmacological interventions. Treatment should return blood glucose to as near normal levels as possible to alleviate symptoms and minimize the risk of long-term complications, with the overall goal of enabling people with diabetes to achieve a quality of life and life expectancy similar to that of the general population. With time, secondary failure to oral antidiabetes agents may occur as a result of the ongoing decline in beta-cell function. An ideal treatment for type 2 diabetes would also preserve islet function, thereby maintaining the durability of a treatment's effect.

Although physicians now have at least five categories of oral antidiabetes agents at their disposal, the unmet need for drugs that are well tolerated and can effectively control disease in the long term coupled with the rapidly expanding type 2 diabetes population means that the need for continued development of new pharmacological therapies is considerable. Side effects and contraindications figure importantly in selection of individualized treatment. Common side effects of medications used to treat type 2 diabetes include hypoglycemia, gastrointestinal discomfort, weight gain, and fluid retention. Other medications are contraindicated in patients with renal or liver impairment or congestive heart failure. In this review we will focus on linagliptin, the fifth dipeptidyl peptidase 4 (DPP-4) inhibitor to complete clinical phase 3 approval studies and look at its likely place in therapy in relation to established agents in the oral type 2 diabetes field as well as the four currently marketed DPP-4 inhibitors.

THE DPP-4 INHIBITOR CLASS

Research on new treatments for type 2 diabetes is focused on agents that can treat the condition effectively, avoid the complications inherent to the condition, and delay disease progression. In addition, therapies should be easy to take with good tolerability, low risk of drug-drug interactions, and a low risk of side effects, including weight gain and hypoglycemia. Furthermore, it is essential that treatments not only help prevent the long-term complications often found in advanced stages of the disease, but also prove to be a therapeutic option in those patients who have already developed complications, such as renal impairment.

The DPP-4 inhibitors are a new class of pharmacological agent with a mechanism of action distinct from that of any currently available glucose-lowering agent. Multiple stimuli in addition to glucose cause beta cells to secrete insulin, including neural signals and incretin hormones. The DPP-4 inhibitors enhance the body's own ability to control blood

glucose levels by increasing the active levels of incretin hormones in the body. The role of gut hormones is particularly important because they affect many aspects related to glycemic control, including glucose-dependent insulin secretion, glucagon inhibition, gastric emptying, and satiety. The two most well-characterized incretin hormones are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Currently, therapeutic agents in this class act either as incretin mimetics, such as the GLP-1 analogs exenatide and liraglutide, or as inhibitors of the enzyme responsible for the breakdown of GLP-1 (the DPP-4 inhibitors). The DPP-4 inhibitors improve glycemic control by preventing the rapid degradation of incretin hormones, with a resulting increase in stimulation of insulin secretion and inhibition of glucagon secretion.

Structure and Pharmacokinetics

Although members of the same class, the DPP-4 inhibitors are structurally distinct with important structure-activity relationships. Linagliptin is a xanthine derivative, saxagliptin a hydroxyadamantyl compound, sitagliptin a triazolepyrazine compound, vildagliptin and saxagliptin are pyrrolidine-carbonitrile compounds, and alogliptin is a quinazolinone-based compound. Linagliptin selectively and reversibly inhibits DPP-4 compared to inhibition of other members of the DPP family. Due to the functional homology of DPP-4 with other human dipeptidyl peptidases including DPP-8, DPP-9, and fibroblast activation protein (FAP), and the toxicity reported for one compound with strong DPP-8/DPP-9 inhibitory potency in animal studies,[3] selectivity of the current DPP-4 inhibitors has been extensively investigated.[4] In vitro studies have shown that at 1 nmol/L, linagliptin inhibits DPP-4 by 50%, whereas 50% inhibition of DPP-8 and DPP-9 requires linagliptin concentrations of more than 10,000 nmol/L.[5] Comparable IC_{50} values for inhibition of DPP-4 by currently available agents are 19 nmol/L (sitagliptin), 24 nmol/L (alogliptin), 50 nmol/L (saxagliptin) and 62 nmol/L (vildagliptin).[5] While linagliptin possesses at least 10,000-fold selectivity for DPP-4 relative to DPP-8 and DPP-9, selectivity is less for FAP versus DPP-4 (IC_{50}=89 nmol/L), in contrast to vildagliptin, sitagliptin, alogliptin (IC_{50} values for FAP inhibition >10 µmol/L), and saxagliptin (IC_{50} >1 µmol/L).[5] FAP is expressed by the activated stromal fibroblasts in many epithelial cancers, but not by most normal adult human tissues and the significance of this is not known. However, therapeutically relevant doses of linagliptin are approximately 10-fold lower than the IC_{50} value for FAP.

Linagliptin inhibits the DPP-4 enzyme by competition for the substrate binding site with a ligand/receptor association (K_i) of 1 nmol/L, indicating tight binding.[5] Tight-binding inhibitors are important from a pharmacological point of view, because once bound to their target they inhibit the enzyme function even after the free drug has been cleared from the circulation, a profile that is important for 24-hour inhibition and once-daily dosing. A dose-ranging study in 47 patients with type 2 diabetes has confirmed that the long terminal half-life of linagliptin (113-131 hours) results in sustained inhibition of DPP-4 activity.[6]

Studies in healthy volunteers and patients with type 2 diabetes show that linagliptin has modest oral availability, but is rapidly absorbed (median t_{max} [time after drug administration to reach maximum plasma concentration] 1.5 hours) and inhibits plasma DPP-4 activity by more than 80% over 24 hours.[6-8] In contrast to other DPP-4 inhibitors, the mode of excretion of linagliptin is predominantly nonrenal,

instead it is mainly excreted unchanged via the enterohepatic system,[6,7] a potentially important attribute for an antidiabetes therapy as renal impairment is a common complication in patients with type 2 diabetes. Linagliptin is not a substrate for cytochrome P450 and does not act as an inducer or inhibitor of this system and is therefore associated with a low risk of drug interactions.[9]

Pharmacokinetics in Patients with Renal Impairment

One of the unique characteristics of linagliptin among the DPP-4 inhibitors is its primarily nonrenal route of excretion, which suggests that decreases in renal function would have little or no effect on the elimination of linagliptin and therefore no clinically relevant increase in linagliptin exposure when administered to patients with any degree of renal impairment. To test this assumption a pharmacokinetic study evaluated the pharmacokinetics of linagliptin in patients with various degrees of renal impairment including: mild (creatinine clearance [CrCl] 51-80 mL/min; *n*=6), moderate (CrCl 31-50 mL/min; *n*=6), severe (CrCl ≤30 mL/min; *n*=6), end-stage renal disease (ESRD; *n*=6) as well as in healthy volunteers (CrCl >80 mL/min, *n*=6).[10] In addition, linagliptin pharmacokinetics were compared in 10 patients with type 2 diabetes and severe renal impairment and in 11 patients with type 2 diabetes with normal renal function. Subjects received linagliptin 5 mg once daily as a single dose (severe renal impairment and ESRD groups) or for 7 days (healthy volunteers, mild or moderate renal impairment) or for 10 days (patients with type 2 diabetes). The results from this study confirm that decreases in renal function have little effect on the elimination of linagliptin and only minor changes in linagliptin exposure were observed in patients with renal impairment (1.4-fold increase in exposure in patients with type 2

Table 1. Steady state total linagliptin exposure ($AUC_{\tau,ss}$) and maximum concentrations ($C_{max,ss}$) were comparable between subjects with mild renal impairment (RI) and the control group, and showed a modest increase of 71% and 42% in patients with moderate or severe RI, respectively.[10]

RI groups	Steady state		C_{max} (nM)	AUC_{0-24} (nM per hour)
	$C_{max,ss}$ (nM)	$AUC_{\tau,ss}$ (nM per hour)		
Mild RI*, mean	0.98 (0.70, 1.39)	1.08 (0.91, 1.28)	1.26 (0.80, 1.96)	1.29 (1.01, 1.66)
Moderate RI*, mean	1.46 (0.98, 2.19)	1.71 (1.34, 2.18)	1.57 (0.77, 3.19)	1.56 (1.06, 2.32)
Type 2 diabetes with severe RI†, mean	1.36 (0.97, 1.90)	1.42 (1.10, 1.82)	1.23 (0.82, 1.84)	1.22 (0.92, 1.62)
Severe RI*, mean	-	-	1.47 (0.83, 2.61)	1.41 (1.04, 1.91)
ESRD*, mean	-	-	1.50 (0.94, 2.41)	1.54 (1.18, 2.00)

Data are geometric mean ratios (90% CI).
*Compared with healthy volunteers.
†Compared with patients with type 2 diabetes and normal renal function (RF).
AUC=area under the curve; C_{max}=time to maximum concentration; ESRD=end-stage renal disease.

diabetes and severe renal impairment compared with type 2 diabetes patients with normal renal function) (Table 1).

The implication of the above is that linagliptin may not require dose adjustment in patients with type 2 diabetes and any degree of renal impairment. This is in contrast to the other DPP-4 inhibitors, which are eliminated primarily by renal excretion. With these drugs the area under the curve (AUC) and time to maximum concentration (C_{max}) values increase with the level of insufficiency. As a result, patients with moderate or severe renal insufficiency, or ESRD require dose reductions to achieve an exposure of DPP-4 inhibitor similar to patients without renal insufficiency.[11-13]

Linagliptin Clinical Trial Program

In line with the phase 3 clinical trial programs conducted for the other DPP-4 inhibitors, the efficacy and tolerability of linagliptin has been evaluated as monotherapy and in combination with several commonly used diabetes treatments including metformin, sulfonylureas and thiazolidinediones. The pivotal studies were multicenter, 24-week trials with a primary outcome measure of change in glycated hemoglobin (HbA_{1c}) from baseline to endpoint.[14-17] Data from these trials have recently been complemented by two smaller 18-week studies.[14,18] The program overall includes more than 5000 patients, several hundred with different stages of renal impairment, as well as two independent longer term studies.

Clinical Efficacy in Monotherapy Studies

In a phase 3 monotherapy study, drug-naïve or previously-treated patients with type 2 diabetes (baseline HbA_{1c} 4.9% to 10.6%) were randomized to linagliptin 5 mg once daily (n=336) or placebo (n=167).[14] Mean baseline HbA_{1c} was 8% in both groups. Linagliptin monotherapy significantly improved glycemic control with a mean reduction from baseline HbA_{1c} of –0.69% compared with placebo (P<0001). The decrease in HbA_{1c} was continuous from –0.46% at 6 weeks to –0.69% at 24 weeks (both P<0.0001). Patients with baseline HbA_{1c} levels of ≥9.0% showed the greatest reduction (–0.86%) from baseline. Fasting and postprandial plasma glucose levels were also significantly improved compared with placebo.

Using a similar design, two Japanese studies have also investigated the effects of linagliptin monotherapy versus placebo. In the first study, patients were randomized to linagliptin 5 mg (n=159), linagliptin 10 mg (n=160), or placebo (n=80) for 12 weeks.[19] Compared with placebo, the differences in mean changes from baseline HbA_{1c} were –0.87% for linagliptin 5 mg (P<0.0001) and –0.88% for linagliptin 10 mg (P<0.0001). Fasting plasma glucose was significantly improved with both linagliptin 5 mg and 10 mg compared with placebo. In a second Japanese study, the efficacy of linagliptin monotherapy was compared to that of voglibose monotherapy in patients with type 2 diabetes.[20] Patients were randomized to linagliptin 5 mg (n=159), linagliptin 10 mg once daily (n=160), or voglibose (0.2 mg three times daily; n=162) for 26 weeks. Compared with voglibose, the differences in mean changes from baseline HbA_{1c} at 26 weeks were –0.32% for linagliptin 5 mg (P=0.0003) and –0.39% for linagliptin 10 mg (P<0.0001). Fasting plasma glucose was significantly improved in both linagliptin groups compared with voglibose.

Metformin is currently the standard first-line treatment for patients with type 2 diabetes, but is not tolerated at high doses in all patients and is contraindicated in others.

The efficacy of linagliptin as initial therapy has been evaluated in 227 patients with type 2 diabetes who were either treatment-naive or pretreated with one oral antidiabetes agent after a 6-week washout period.[17] The majority were considered unsuitable for metformin therapy because of gastrointestinal adverse events (93%); the remainder had raised creatinine levels indicative of renal impairment. The 18-week trial randomized patients to linagliptin 5 mg once daily (n=151) or placebo (n=76); patients on placebo were then switched to glimepiride for an ongoing 34-week double-blind extension. The interim analysis conducted after all patients had completed 18 weeks of their assigned treatment showed that the difference in mean change from baseline HbA_{1c} was –0.57% compared with placebo (P<0.0001). Among patients with a baseline HbA_{1c} ≥7.0%, 11.8% of patients in the placebo group and 23.5% of patients in the linagliptin group achieved an HbA_{1c}<7.0% at Week 18. Linagliptin was also superior to placebo in reducing mean fasting plasma glucose from baseline (P=0.0002).

Clinical Efficacy in Combination Therapy Studies

Metformin Monotherapy

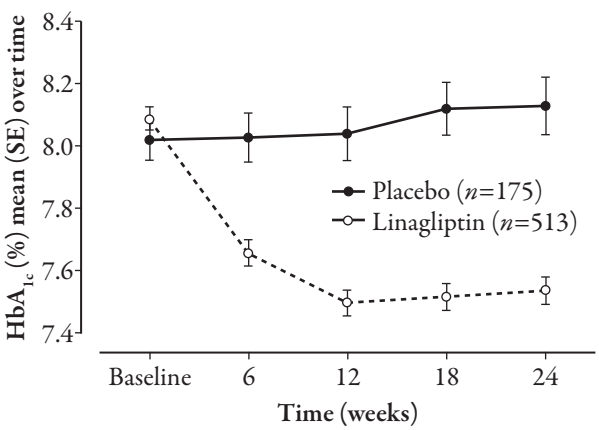
Many patients with type 2 diabetes require a combination of antidiabetes drugs with complementary mechanisms of action to lower their HbA_{1c} levels to achieve therapeutic targets and reduce the risk of long-term complications. The efficacy and safety of linagliptin has been investigated in combination with currently approved first-line and second-line therapies. A preliminary study in patients not adequately controlled on a maximum tolerated dose of metformin randomized patients to double-blind linagliptin (1, 5, or 10 mg once daily), placebo or open-label glimepiride (1-3 mg once daily) for 12 weeks.[21] Linagliptin-treated patients demonstrated significant and clinically relevant improvements in glycemic control compared with placebo, with linagliptin 5 mg being the most effective dose.

In one of the pivotal phase 3 trials, 700 patients inadequately controlled (HbA_{1c} levels from ≥7% to ≤10.0%) on a maximum tolerated dose of metformin monotherapy were randomized to linagliptin 5 mg (n=523) or placebo (n=177).[15] After 24 weeks of treatment, the difference in mean change from baseline HbA_{1c} was –0.64% compared with placebo (P<0.0001) (Figure 1). Linagliptin was also associated with significantly greater reductions in both fasting and postprandial plasma glucose, P<0.0001 and P<0.001, respectively.

Sulfonylurea Monotherapy

In an 18-week study the efficacy of linagliptin was evaluated in patients not achieving adequate glycemic control on sulfonylurea monotherapy.[18] The study randomized 245 patients to linagliptin

Figure 1. Change over time (mean±SE) in glycated hemoglobin (HbA_{1c}) following treatment with linagliptin 5 mg or placebo for 24 weeks.[15] *Reproduced from Taskinen M-R, Rosenstock J, Tamminen I, et al. Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomised, double-blind, placebo controlled study. Diabetes Obes Metab. 2011;13:65-74.*



5 mg once daily (*n*=161) or placebo (*n*=84). Any oral antidiabetes agent other than a sulfonylurea was withdrawn at the beginning of a 4-week washout period prior to the 2-week run-in. The sulfonylurea was administered at an unchanged dose for the duration of the trial. At Week 18, the difference in mean change from baseline HbA_{1c} was –0.47% compared with placebo (*P*<0.0001). Statistically significant differences in HbA_{1c} reductions between linagliptin and placebo were sustained at all visits (weeks 6, 12, and 18, all *P*<0.0001).

Metformin and Sulfonylurea Combination

The efficacy of linagliptin 5 mg once daily has also been investigated in patients with inadequate glycemic control (HbA_{1c} 7.0% to 10.0%) on a combination of metformin plus a sulfonylurea.[16] Patients were randomized to adjunctive linagliptin (*n*=793) or placebo (*n*=265); the majority (73.3%) had had type 2 diabetes for at least 5 years before enrollment. After 24 weeks of treatment, the difference in mean change from baseline HbA_{1c} was –0.62% compared with placebo (*P*<0.0001). The maximum mean HbA_{1c} reduction with linagliptin was seen at Week 12 (–0.84%). In this study, patients with a baseline HbA_{1c} ≥7.0% were more likely to achieve a target HbA_{1c} of <7.0% at 24 weeks when treated with linagliptin (29.2%) compared with placebo (8.1%, *P*<0.0001). Fasting plasma glucose was also significantly reduced in the linagliptin group compared with placebo (*P*<0.0001).

Pioglitazone

An additional pivotal phase 3 study has investigated the efficacy of initial combination therapy with linagliptin and pioglitazone.[17] Patients with type 2 diabetes and insufficient glycemic control (HbA_{1c} 7.5% to 11.0%) who were drug naïve or previously treated with any oral antidiabetes agent, were randomized to linagliptin 5 mg and pioglitazone 30 mg both once daily (*n*=259) or to pioglitazone 30 mg plus placebo once daily (*n*=130). Patients did not receive any oral agent for at least 6 weeks before randomization. After 24 weeks of treatment, linagliptin-pioglitazone as initial therapy reduced mean HbA_{1c} by –1.06% from baseline with a 0.51% difference compared with the placebo-pioglitazone combination (*P*<0.0001). Reductions in fasting plasma glucose were also significantly greater for the linagliptin-pioglitazone group (*P*<0.0001). Patients in the linagliptin-pioglitazone group were more likely to achieve a target HbA_{1c} of <7% compared with those on placebo-pioglitazone (42.9% vs. 30.5%, respectively, *P*=0.0051), as well as a reduction in HbA_{1c} of ≥0.5% (75% vs. 50.8%, respectively, *P*<0.001).

SAFETY AND TOLERABILITY

Hypoglycemia

As the glucose-lowering effects of GLP-1 are dependent on elevated blood glucose and subside as glucose levels return to normal, the probability of hypoglycemia during treatment with a DPP-4 inhibitor is low. As monotherapy[14,17,19,20] and in combination with metformin[15,21] and pioglitazone,[17] the overall incidence of hypoglycemia with linagliptin was comparable to placebo. Similar to observations with other DPP-4 inhibitors, there was an increased incidence of hypoglycemia when linagliptin was used in patients not achieving adequate glycemic control with a metformin-sulfonylurea combination (22.7% with addition of linagliptin to combination vs. 14.8% with addition of placebo).[16] However, in a smaller 18-week study in which linagliptin was added to sulfonylurea monotherapy, hypoglycemia

occurred in 5.6% and 4.8% of participants in the linagliptin and placebo groups, respectively.[18] No cases of severe hypoglycemia (ie, requiring third party help) were recorded in these trials.

Body Weight Gain

Most pharmacological approaches for the management of type 2 diabetes contribute to weight gain. While the DPP-4 inhibitors do not result in the weight losses that are observed with the GLP-1 analogs,[22] they are weight neutral, with no significant increases in body weight observed either as monotherapy or combination therapy. Linagliptin was not associated with weight gain in any of the phase 3 clinical trials even when administered in combination with pioglitazone[17] or a sulfonylurea.[16,18]

Other Adverse Events

The safety profiles of DPP-4 inhibitors are well documented, those most commonly reported being mild infections (ie, nasopharyngitis, urinary tract infection, and upper respiratory tract infection) and headache.[23] Data from the linagliptin clinical trial program indicate an overall incidence of side effects similar to placebo in the monotherapy trials,[14,17] with the most common side effects reflecting those observed with other DPP-4 inhibitors.[15,21] DPP-4 has effects beyond its proteolytic action, including T-cell activation and proliferation.[24] As a result there have been theoretical safety concerns associated with long-term DPP-4 inhibitor use in humans. Sitagliptin has the longest-term safety data to date demonstrating no clinically relevant changes in laboratory parameters in clinical trials of up to 2 years duration.[25] Although the safety of the other agents cannot be inferred from these data, the results are reassuring. Ongoing trials will continue to evaluate any potential effect of the DPP-4 inhibitors on immune function.

Beta-Cell Function

While DPP-4 inhibitor-mediated improvements in beta-cell mass and function have so far only been demonstrated in in vitro studies with human tissues[26] and in animal models,[27,28] several lines of evidence suggest that DPP-4 inhibitors act to improve beta-cell function and increase insulin sensitivity in humans. In the linagliptin phase 3 program significant improvements in surrogate markers of beta-cell function/insulin secretion were observed compared with placebo, including the homeostasis model assessment of beta-cell function (HOMA-B) index,[14-16,19] proinsulin/insulin ratio,[14,19] and the disposition index.[14]

LINAGLIPTIN'S PLACE IN THERAPY

First-generation incretins are now established antidiabetes therapies and with four DPP-4 inhibitors already approved, linagliptin will enter a crowded market. Despite this, the product differentiates itself as a potential future option for patients with type 2 diabetes. As a class, the DPP-4 inhibitors have a number of favorable characteristics that set them apart from older antidiabetes therapies including excellent tolerability, low risk of hypoglycemia, and weight neutrality.

The profile may go beyond the established benefits of the DPP-4 inhibitors as it is the first agent in this class to have a primarily nonrenal route of elimination. This is an important consideration given that renal impairment is a frequent comorbid condition in patients with type 2 diabetes[29] and can significantly limit treatment options (Table 2). In people with diagnosed diabetes the prevalence of

Table 2. Prescribing in renal impairment.[30]

Drug	Mild (eGFR 50-80 mL/min)	Moderate (eGFR 30-50 mL/min)	Severe (eGFR 19-30 mL/min)	End stage/ dialysis
Metformin	Y	Y (half maximal dose below eGFR 45 mL/min)	N	
Gliclazide	Y	Y	N (although only 5% of gliclazide is excreted in urine)	N
Pioglitazone	Y	Y	Y	Y (eGFR >4 mL/min)
Sitagliptin	Y	N		
Vildagliptin	Y	N		
Saxagliptin	Y	N		
Exenatide	Y	Y	N	
Liraglutide	Y (>60 mL/min)	N		

eGFR=estimated glomerular filtration rate. Y, yes; N, no.

chronic kidney disease, characterized by either albuminuria or reduced kidney function, is high and estimated at 40% or more.[31] Furthermore, several studies have shown that up to one-third of adults with undiagnosed diabetes also have evidence of kidney damage and/or kidney function decline as well as approximately 10% of individuals with prediabetes and no self-reported hypertension.[32-34] Not only are these findings concerning because of the substantial proportion of patients at increased risk of diabetes-related kidney disease and cardiovascular disease, but also because the presence of reduced kidney function can significantly limit the antidiabetes therapy options available to patients. For example, metformin is contraindicated in people with any condition that could increase the risk of lactic acidosis, including renal disorders (creatinine levels over 150 µmol/L). Thiazolidinediones may be used in the setting of renal impairment, but patients should be monitored for symptoms and signs of fluid overload. Sulfonylureas and insulin may also be used, although there may be an increased risk of provoking hypoglycemia with these agents in the setting of renal impairment. Currently available DPP-4 inhibitors are mainly eliminated via the kidney and therefore not recommended in patients with advanced renal impairment in many countries. Others either require dose adjustment or are contraindicated for such patients. The clinical data for linagliptin seen to date suggest an advantage in this respect due to its primarily nonrenal route of excretion with a recent pharmacokinetic study showing no clinically relevant increase in linagliptin exposure when administered in patients with any degree of renal impairment.[10] The convenience of a drug that can be used in patients with renal impairment, and not needing additional monitoring of kidney function and not requiring dose adjustment as kidney function declines could be a potentially significant advance when coupled with other benefits of the class.

The key efficacy data for linagliptin are provided by four 24-week, placebo-controlled trials as monotherapy or add-on therapy in adults with type 2 diabetes.[14-17] In the studies, statistically significant placebo-adjusted changes in HbA_{1c} were observed with linagliptin 5 mg monotherapy versus placebo (–0.69%)[14] and when used in combination with other commonly used oral antidiabetes agents, including metformin (–0.64%),[15] metformin plus sulfonylurea (–0.62%)[16] and as initial combination therapy with pioglitazone (–0.51%).[17] Two additional 18-week studies have further confirmed the benefits of linagliptin demonstrating placebo-adjusted changes in HbA_{1c} of –0.57% as monotherapy in patients for whom metformin is not appropriate[18] and –0.47% in combination with a sulfonylurea.[18] In all the studies, linagliptin was also associated with significant reductions in fasting and postprandial plasma glucose. These properties compare favorably with those reported for other DPP-4 inhibitors with HbA_{1c} reductions ranging from 0.6 to 1%.[35] Linagliptin is also a tight-binding inhibitor and has the highest K_i of available DPP-4 inhibitors,[5] which suggests that it may have a longer-lasting effect and true 24-hour efficacy after once-daily dosing (whether this has any clinical relevance needs further study).

The potential of the DPP-4 inhibitors for use in the treatment of type 2 diabetes has been recognized by the UK National Institute for Health and Clinical Excellence (NICE) blood glucose-lowering algorithm, with approved DPP-4 inhibitors recommended as a possible second-line or third-line therapy.[36] Linagliptin and the other DPP-4 inhibitors offer clinically meaningful reductions in HbA_{1c} without significant risk of hypoglycemia and without causing weight gain. They also offer the theoretical potential of improving or maintaining beta-cell function and thus, favorably affecting the progressive loss of function that is characteristic of type 2 diabetes. As understanding of, and experience with, the growing number of DPP-4 inhibitors broadens, increasing evidence suggests that the class may offer advantages over other antidiabetes drugs in particular patient populations. They may be particularly suitable for use in patients with an excessive risk of hypoglycemia or where it needs to be avoided at all costs, in those in whom weight gain is undesirable, and in older people, and linagliptin is no exception. Linagliptin is associated with a low risk of hypoglycemia as monotherapy or when used in combination with metformin or a thiazolidinedione, and has demonstrated weight neutrality in all studies to date even when used in combination with a sulfonylurea or thiazolidinedione.

Older patients with type 2 diabetes can be a particularly challenging population to manage. They often have a high incidence of comorbidities for which they are taking numerous medications, a high prevalence of cardiovascular risk factors, and are more likely to be suffering from some form of renal impairment. In addition, hypoglycemia is a common clinical problem in older patients with diabetes as aging modifies the counter-regulatory and symptomatic responses to hypoglycemia. As a result there is a continued unmet need for safe and effective therapeutic agents in this population. The good efficacy and tolerability profile, lack of drug interactions, and once-daily oral route of administration of the DPP-4 inhibitors make them viable treatment alternatives for older patients with type 2 diabetes. Linagliptin has the added advantage of not requiring dose adjustment in patients with renal impairment, which may make it a particularly suitable option for this population.

CONCLUSION

In May 2011, linagliptin was approved by the US Food and Drug Administration for the treatment of type 2 diabetes as a monotherapy or together with different commonly prescribed oral antidiabetes drugs - metformin, sulfonylurea, pioglitazone. Linagliptin appears to possess characteristics that may set it apart from the current DPP-4 inhibitors. There is a real need for antidiabetes treatments that can be used when renal function declines and linagliptin's particular niche in therapy is likely to be the substantial number of patients in whom metformin and the other DPP-4 inhibitors are either contraindicated or require dose adjustment because of moderate to severe renal impairment. In the FDA approval no dosage adjustment is required in patients with renal impairment.

Further investigations are still needed to confirm that the unique pharmacological properties of linagliptin, together with the predominantly nonrenal route of elimination, will lead to clinical benefits beyond those already observed with other agents in the DPP-4 inhibitor class. However, current evidence suggests that certain differences between DPP-4 inhibitors may prove to be clinically significant. This range of therapeutic options should help physicians tailor treatment to the individual patient, thereby increasing the proportion that can safely attain target HbA_{1c} levels and reducing morbidity and mortality.

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