New Drug Review

Review of Linagliptin for the Treatment of Type 2 Diabetes Mellitus

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ABSTRACT

Background: Linagliptin is a dipeptidyl peptidase-4 inhibitor that was approved in 2011 by the US Food and Drug Administration as a treatment adjunctive to diet and exercise for the improvement of glycemic control in adults with type 2 diabetes mellitus (T2DM).

Objective: The purpose of this article is to review the pharmacology, pharmacokinetic properties, efficacy, tolerability including drug–drug interactions, contraindications/precautions, and dosage and administration of linagliptin, and the potential role of linagliptin in the management of glycemia in adults with T2DM.

Methods: MEDLINE (1966–January 12, 2012), PubMed (1950–January 12, 2012), Science Direct (1994–January 12, 2012), Web of Science (1980–January 12, 2012), and the American Diabetes Association Scientific Abstracts (2008–2011) were searched using the term *linagliptin*. Articles and abstracts published in English, both original research and review articles, were identified for review. Reference lists from identified articles were also searched for additional references of interest. Manufacturers' prescribing information was additionally examined.

Results: Data from clinical trials of linagliptin suggest clinical efficacy in terms of reductions in hemoglobin A_{1c} (A_{1c}), fasting plasma glucose, and postprandial glucose when linagliptin was administered as monotherapy or in combination with other oral antidiabetic agents, with placebo-subtracted A_{1c} changes ranging from −0.47% to −0.69% in placebo-controlled trials. Adverse events that occurred in ≥2% of patients treated with linagliptin and at a prevalence of ≥2-fold greater compared with placebo were nasopharyngitis, hyperlipidemia, cough, hypertriglyceridemia, and weight increase (when used in combination with a thiazolidinedione [TZD]). Although linagliptin administered as monotherapy or in combination with metformin or a TZD may convey a low risk for hypoglycemia (0%–1.2%), caution is warranted when linagliptin is administered in combination with insulin secretagogues due to an increased risk for hypoglycemic events. Dosage adjustments based on renal or hepatic function are not required. Additionally, according to the currently approved prescribing information, the efficacy of linagliptin may be limited in patients receiving concurrent inducers of the cytochrome P450 3A4 isozyme or P-glycoprotein (eg, rifampin).

Conclusions: Based on the findings from the present review, patients and clinicians should be aware of the risk for hypoglycemia when linagliptin is prescribed as a treatment adjunctive to a regimen of an insulin secretagogue. An initial dose decrease in the secretagogue should be considered to prevent hypoglycemic events. Dosage adjustment of linagliptin is not required in patients with renal impairment. (*Clin Ther.* 2012;34: 993–1005) © 2012 Elsevier HS Journals, Inc. All rights reserved.

Key words: diabetes mellitus, dipeptidyl-peptidase 4 inhibitor, linagliptin, type 2 diabetes mellitus.

INTRODUCTION

The progressive nature of type 2 diabetes mellitus (T2DM) and its complex pathophysiology make combination pharmacotherapy almost inevitable for blood glucose optimization,[1,2] and clinical guidelines for the treatment of T2DM recognize the need to intensify treatment when therapeutic goals are not, or are no longer, being met. Intensification of therapy may involve the addition of a pharmacologic agent with a

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complimentary mechanism of action to achieve therapeutic synergy.[3] Advancement in the knowledge surrounding the physiology of endogenous glucoregulatory peptide hormones, or "incretin hormones," such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), has led to a new appreciation for the role of these hormones in the pathophysiology of T2DM and their use as potential therapeutic targets. Both GIP and GLP-1 are degraded by the serine protease dipeptidyl peptidase-4 (DPP-4).[4] DPP-4 is a cell surface serine protease found in highest concentration in the bone marrow, intestines, and kidney, but it is also found in the liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, and lymphoid and myeloid cells.[5,6] By blocking the enzymatic inactivation of incretin hormones, DPP-4 inhibitors enable higher levels of active incretins to circulate and carry out their physiologic glucoregulatory functions.

The present review focuses on the pharmacology, pharmacokinetic properties, efficacy, tolerability including drug–drug interactions, contraindications/precautions, and dosage and administration of linagliptin, and the potential role of linagliptin in the management of glycemia in adults with T2DM.

METHODS

MEDLINE (1966–January 12, 2012), PubMed (1950–January 12, 2012), Science Direct (1994–January 12, 2012), Web of Science (1980–January 12, 2012), and the American Diabetes Association Scientific Abstracts (2008–2011) were searched using the term *linagliptin*. Articles and abstracts published in English, both original research and review articles, were identified for review. Reference lists from identified articles were also searched for additional references of interest. Manufacturers' prescribing information was additionally examined.

Studies involving comparative agents not approved for use in the United States or Europe were excluded.

RESULTS

Clinical Pharmacology

Linagliptin, 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione, is a xanthine-derived DPP-4 inhibitor.[7] Linagliptin has 40,000- and >10,000-fold greater selectivity for DPP-4 compared with DPP-8 and DPP-9, respectively.[8] Linagliptin is a competitive and reversible inhibitor of DPP-4 and has a slow rate of dissociation from its substrate.[9] Compared with other DPP-4 inhibitors, linagliptin has been reported to have an IC_{50} of ~ 1 nmol/L versus values of 19, 50, and 62 nmol/L for sitagliptin, saxagliptin, and vildagliptin, respectively.[9] DPP-4 inhibition with linagliptin is sustained, with enzyme activity inhibition >90% with once-daily oral doses of 5 and 10 mg in 1 clinical study that enrolled male patients with T2DM, thus allowing once-daily dosing.[10] **Figure 1** shows the chemical structure of linagliptin.[11]

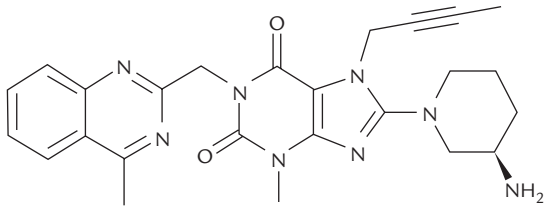

Figure 1. Chemical structure of linagliptin.[11]

Mechanism of Action

Per the manufacturer, linagliptin is a competitive, reversible DPP-4 inhibitor specifically designed for extended inhibition of the DPP-4 enzyme, with pharmacokinetic and pharmacodynamic properties suitable for once-daily dosing.[12] DPP-4 inhibitors such as linagliptin inhibit the enzymatic degradation of endogenous GLP-1 and GIP by the enzyme DPP-4.[5] This enzymatic inhibition in turn potentiates the effects of endogenous incretin hormones, resulting in enhanced glucose-dependent insulin secretion and suppression of postprandial glucagon secretion from α cells of the pancreas.[5] By prolonging the activity of endogenous incretin hormones, DPP-4 inhibitors regulate glucose levels in a glucose-dependent manner.

Pharmacokinetic Properties

Linagliptin has a $t_{½}$ of 131 hours[8] and achieves steady-state concentrations after 3 doses of 5 mg/d, as indicated in the package insert.[12] The long $t_{½}$ of linagliptin is largely due to its extensive binding to plasma proteins and its high-affinity binding to the DPP-4 enzyme, which produces a nonlinear pharmacokinetic profile for linagliptin.[10,13] The oral bioavailability of linagliptin is ~30%.[14] The long $t_{½}$ of linagliptin leads to sustained inhibition of the DPP-4 enzyme, allowing

for the currently approved once-daily oral dosing.[10] Pharmacokinetic studies in healthy volunteers reported a mean C_{max} of 8.32 nmol/L; T_{max}, 1.75 hours, and AUC_{0-24}, 118 nmol · h/L following the administration of single-dose linagliptin.[8] The accumulation $t_{½}$ for linagliptin is ~12 hours with multiple doses of linagliptin 5 mg.[15,16] Linagliptin undergoes primarily hepatic elimination (~85%), with an estimated 5% of a given dose eliminated renally.[8,15] Despite the predominantly hepatic elimination of linagliptin, the main metabolite (CD1790) is pharmacologically inactive,[15] and no adjustments are currently recommended per the prescribing information in patients with hepatic impairment.[12] Likewise, a study of linagliptin use in patients with various degrees of renal impairment concluded that dose adjustment was not required.[17] No meaningful impact of age, sex, or race on the pharmacokinetic properties of linagliptin has been observed to date, according to the manufacturer.[12]

Clinical Efficacy

Linagliptin has been studied for use as monotherapy[18,19]; as combination therapy[20–24]; and, in a comparative study versus glimepiride, as add-on treatment in patients whose glycemia was inadequately controlled with metformin monotherapy.[25]

Linagliptin Monotherapy

A multicenter, randomized, parallel-group, placebo-controlled clinical trial that assessed the efficacy and tolerability of linagliptin 5 mg/d over 24 weeks of therapy was conducted by Del Prato et al.[18] The primary efficacy end point was change in A_{1c} from baseline to 24 weeks. Participants enrolled in the trial were either treatment naive or receiving 1 oral antidiabetic drug (OAD) other than a thiazolidinedione (TZD). Enrolled participants were 18 to 80 years of age (mean [SD], 55.7 [10.2] years) with T2DM, defined as a baseline A_{1c} value of 6.5% to 9.0% in pretreated patients and 7.0% to 10.0% in treatment-naive patients. Eligible patients also had a baseline body mass index (BMI) of ≤40 kg/m^2 (mean, 29.05 [4.81] kg/m^2). In participants receiving an OAD, a washout period of 6 weeks was required. Following washout, participants underwent a 2-week placebo run-in phase, after which eligible patients had A_{1c} levels in the range of 7.0% to 10.0%. Participants were randomly assigned to receive linagliptin 5 mg/d (n = 336) or placebo (n = 167). For the primary efficacy end point, the mean changes from baseline in A_{1c} were −0.5% and +0.8% in the linagliptin and placebo groups, respectively (treatment difference, −0.69%; $P < 0.0001$). In addition to a decrease in A_{1c}, linagliptin treatment was associated with significantly greater reductions from baseline in fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG), with adjusted mean differences of −23.4 and −57.7 mg/dL (both, $P < 0.001$) compared with placebo. Improvements in glycemic end points with linagliptin therapy versus placebo also included improved markers of β-cell function, including proinsulin/insulin ratio, homeostatic model assessment B, and disposition index. The percentages of study participants who achieved an A_{1c} <7.0% at 24 weeks were 25.5% (77/306) and 11.6% (17/147) in the linagliptin and placebo groups (odds ratio [OR] = 2.9; $P = 0.0006$). Table I provides a summary of clinical efficacy data from this and other clinical trials, including a 12-week monotherapy study of linagliptin not discussed in detail here.[18–25]

Combination Therapy

Linagliptin as Treatment Adjunctive to Metformin Versus Open-Label Glimepiride

Forst et al[20] conducted a 12-week, multicenter, randomized, double-blind, placebo-controlled study enrolled 333 participants with inadequately controlled type 2 diabetes despite background treatment with metformin with or without an additional OAD (excluding TZDs). In participants receiving metformin monotherapy at baseline, inadequate glycemic control was defined as an A_{1c} of 7.0% to 9.0%. In those receiving metformin plus an OAD, inadequate glycemic control was defined as an A_{1c} of 7.5% to 10.0%. Eligible participants on metformin monotherapy at screening entered a 2 week, open-label run-in period, whereas participants receiving metformin plus an OAD underwent a 6-week period in which the additional OAD was discontinued, followed by a 2 week run-in. Qualifying participants were randomly assigned to receive linagliptin (1, 5, or 10 mg/d), open-label glimepiride 1 to 3 mg/d (titrated from 1 mg/d at the discretion of the investigator), or placebo. The primary efficacy outcome was change from baseline in A_{1c}. Mean baseline A_{1c} values in the 5 treatment groups were 8.2%, 8.5%, 8.4%, 8.2%, and 8.4%, respectively. Following the 12-week treatment period, treatment differences with linagliptin versus placebo were −0.40%, −0.73%, and −0.67% in the 1-, 5-,

Table I. Select efficacy data from clinical trials of linagliptin. Data are adjusted mean changes from baseline unless otherwise specified.

Study/Treatment Groups	A_{1c}, %	FPG, mg/dL	PPG, mg/dL	Weight,[a] kg	Achievement of Target A_{1c} (<7%), % of Patients
Del Prato et al[18] (24-Wk study in patients with T2DM who were treatment-naive or receiving 1 OAD)					
Linagliptin 5 mg/d (n = 336)	−0.44[b]	−9.0[b]	−34.2[b]	NR	25.2[c]
Placebo (n = 167)	+0.25	+14.4	+25.2	NR	11.6
Kawamori et al[19,d] (12-Wk study in patients with T2DM who were treatment-naive or receiving an OAD)					
Linagliptin 5 mg/d (n = 159)	NR (−0.87)[b,e]	NR (−19.7)[b,e]	—	—	26.4
Linagliptin 10 mg/d (n = 160)	NR (−0.88)[b,e]	NR (−20.4)[b,e]	—	—	35.7
Placebo (n = 80)	NR	NR	—	—	10.0
Forst et al[20] (12-Wk study in patients with T2DM who were receiving metformin with or without an additional OAD[f])					
Linagliptin 1 mg/d (n = 65)	−0.15[g]	−6.5[e]	NR	−0.15	15
Linagliptin 5 mg/d (n = 66)	−0.48[b]	−22.0[b]	NR	−0.57	15
Linagliptin 10 mg/d (n = 66)	−0.42[b]	−16.2[b]	NR	−1.27	21
Glimepiride (n = 65)	−0.90	NR	NR	+0.73	NR
Placebo (n = 71)	+0.25	+12.6	NR	−0.84	1.4
Taskinen et al[21] (24-Wk study in patients with T2DM who were receiving metformin with or without an additional OAD[f])					
Linagliptin 5 mg/d (n = 524)	−0.49[b]	−10.8[b]	−48.6[b]	NR	26
Placebo (n = 177)	+0.15	+10.8	+18.0	NR	9
Lewin et al[22] (18-Wk study in patients with T2DM who were receiving a sulfonylurea + an OAD)					
Linagliptin 5 mg/d (n = 161)	NR (−0.47)[b,e]	NR (−6.4)[g]	NR	NR	15.2
Placebo (n = 84)	NR	NR	NR	NR	3.7
Owens et al[23] (24-Wk study in patients with T2DM who were receiving metformin + a sulfonylurea)					
Linagliptin 5 mg/d (n = 792)	−0.72[b]	−5.4[b]	NR	+0.27	29.2
Placebo (n = 263)	−0.10	+7.2	NR	−0.06	8.1
Gomis et al[24] (24-Wk study in patients with T2DM who were treatment-naive or receiving an OAD)					
Linagliptin 5 mg/d (n = 259)	−1.06[b]	−32.4[b]	NR	+2.3[h]	42.9
Placebo (n = 130)	−0.56	−18.0	NR	+1.2	30.5

(continued)

Table I (continued).

Study/Treatment Groups	A_{1c}, %	FPG, mg/dL	PPG, mg/dL	Weight,[a] kg	Achievement of Target A_{1c} (<7%), % of Patients
Gallwitz et al[25] (104-Wk study in patients with T2DM who were receiving metformin)					
Linagliptin 5 mg/d (n = 764)	−0.4[i]	NR	NR	−1.4[b]	NR
Glimepiride 1–4 mg/d (n = 755)	−0.5	NR	NR	+1.3	NR

A_{1c} = hemoglobin A_{1c}; FPG = fasting plasma glucose; NR = not reported; OAD = oral antidiabetic drug; PPG = postprandial glucose; T2DM = type 2 diabetes mellitus.
[a]No adjustment.
[b]$P < 0.001$ versus placebo.
[c]$P = 0.0006$.
[d]Baseline A_{1c} reported for entire cohort as "similar between groups."
[e]Mean placebo-subtracted value reported.
[f]Excluding a thiazolidinedione.
[g]$P < 0.01$.
[h]$P = 0.014$.
[i]$P < 0.001$ for noninferiority.

and 10-mg groups, respectively (all, $P < 0.0001$) compared with a difference of −0.90% in the glimepiride group. Mean FPG was also decreased among patients taking linagliptin treatment, with treatment differences versus placebo of −19.8, −34.2, and −28.8 mg/dL in the 3 linagliptin groups. Mean weight reductions in the linagliptin groups ranged from 0.15 to 1.27 kg compared with a mean weight reduction of 0.84 kg in the placebo group. In contrast, participants in the glimepiride group experienced a mean weight gain of 0.73 kg. Although these apparent differences suggest a weight advantage for linagliptin over glimepiride, no statistical data were presented. The response to linagliptin therapy in this trial was not found to differ significantly when stratified by age ($P = 0.58$), sex ($P = 0.49$), or BMI ($P = 0.30$).

Linagliptin as Treatment Adjunctive to Metformin

A multicenter, randomized, placebo-controlled, double-blind, parallel-group study examined the efficacy and tolerability of linagliptin as treatment adjunctive to metformin in patients T2DM.[21] Eligible participants were aged 18 to 80 years (mean, 56.5 years) with a BMI of ≤40 kg/m^2 (mean baseline BMI, 29.9 kg/m^2) and were receiving metformin at a dosage of ≥1500 mg/d (or maximum tolerated dose) with or without an additional OAD other than a TZD. Eligible participants receiving metformin monotherapy had a baseline A_{1c} of 7.0% to 10.0%; in those taking metformin plus an OAD, the A_{1c} range for eligibility was 6.5% to 9.0%. In participants receiving an OAD in addition to metformin at screening, the additional OAD was discontinued, and metformin ≥1500 mg/d was continued throughout a 6-week washout period prior to randomization. All participants completed a 2-week placebo run-in phase before random assignment to either linagliptin 5 mg/d (n = 524) or placebo (n = 177). All participants were required to have an A_{1c} of 7.0% to 10.0% at randomization. The primary end point was change in A_{1c} from baseline to 24 weeks of treatment. The mean adjusted change from baseline in A_{1c} in the linagliptin group was −0.49% compared with an increase of 0.15% in the placebo group (treatment difference, −0.64%; 95% CI, −0.78 to −0.50; $P < 0.0001$), with 26% and 9% of participants in the linagliptin and placebo groups, respectively, achieving an A_{1c} <7.0% at 24 weeks. Linagliptin treatment was associated with significant decreases from baseline in FPG (−10.6 mg/dL vs + 10.5 mg/dL; $P < 0.0001$) and 2-hour PPG (−48.6 mg/dL vs +18 mg/dL; $P < 0.0001$) compared with placebo. Neither treatment group realized a statistically significant decrease in mean weight (changes from baseline, −0.4 kg and −0.5 kg with linagliptin and placebo).

Linagliptin as Treatment Adjunctive to a Sulfonylurea

Data related to the use of linagliptin as treatment adjunctive to a sulfonylurea have been published in abstract format.[22] The 18-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study enrolled participants with insufficient glycemic control (mean [SD] baseline A_{1c}, 8.6% [0.8%]) despite receiving treatment with a sulfonylurea. The mean age of study participants was 56.9 (9.9) years; baseline BMI, 28.3 kg/m^2. Prior to randomization, all participants participated in a 2-week placebo run-in phase (following a 4-week washout phase for those receiving an OAD other than a sulfonylurea at screening) and were subsequently randomly assigned to receive either linagliptin 5 mg/d (n = 161) or placebo (n = 84). After 18 weeks of treatment, the placebo-adjusted mean change from baseline in A_{1c} in the linagliptin group was −0.47% ($P < 0.0001$). Participants in the linagliptin group were more likely to have achieved an A_{1c} <7%, with the percentages of participants achieving this goal being 15.2% and 3.7% in the 2 cohorts (OR = 6.47; $P = 0.006$). The treatment difference in change from baseline in mean FPG was −6.4 mg/dL ($P = 0.24$).

Linagliptin as Treatment Adjunctive to Metformin Plus a Sulfonylurea

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessed the efficacy and tolerability of linagliptin as adjunctive treatment in participants with T2DM receiving both metformin and a sulfonylurea at baseline.[23] Participants enrolled were between the ages of 18 and 80 years of age (mean age, 58.1 years), with a baseline A_{1c} of 7.0% to 10.0% (mean in both groups, 8.1%). All participants underwent a 2-week placebo run-in period followed by random assignment to 24 weeks of treatment with linagliptin 5 mg/d (n = 793) or placebo (n = 265) in addition to ongoing background therapy of ≥1500 mg/d of metformin (or maximum tolerated dose) plus the maximum tolerated dose of a sulfonylurea. Following 24 weeks of treatment, the linagliptin group had an adjusted mean change from baseline in A_{1c} of −0.72% compared with a mean change of −0.10 in the placebo group (difference, −0.62%; $P < 0.0001$), with 29.2% of linagliptin-treated participants achieving an A_{1c} level <7% compared with 8.1% in the placebo group ($P < 0.0001$). With regard to the mean change from baseline in FPG, an adjusted mean between-group difference of −12.7 mg/dL was observed (−5.4 vs +7.2 mg/dL; $P < 0.0001$). Although the addition of linagliptin to background treatment with metformin and a sulfonylurea had reported efficacy in terms of the glycemic end points noted previously, a higher rate of hypoglycemia was seen in the linagliptin group (22.7%) compared with placebo (14.8%).[18–24]

Linagliptin as Treatment Adjunctive to Pioglitazone

A 24-week, randomized, placebo-controlled, double-blind, parallel-group study assessed the efficacy and tolerability of linagliptin in combination with pioglitazone in participants with T2DM.[24] Participants were between the ages of 18 and 80 years (mean, 57.5 years), had a mean baseline BMI of 29.0 kg/m^2, and had uncontrolled glycemia (baseline A_{1c}, 7.5%–11%). Participants were either treatment naive or previously treated with OADs. Prior to randomization, participants previously receiving OAD treatment underwent a 4-week washout period followed by a 2-week placebo run-in phase; treatment-naive patients underwent the 2-week placebo run-in only. Following run-in, participants were randomly assigned to receive either pioglitazone 30 mg/d plus linagliptin 5 mg/d (n = 259) or pioglitazone 30 mg/d plus placebo (n = 130). At baseline, the linagliptin group had a mean baseline A_{1c} of 8.60% and a mean (SD) weight of 78.3 (15.6) kg, whereas the placebo group had mean baseline values of 8.58% and 82.7 (15.8) kg, respectively. At 24 weeks, mean adjusted changes in A_{1c} in the linagliptin and placebo groups were −1.25% and −0.75% (difference, −0.51%; $P < 0.0001$). In addition, 42% and 30.5% of participants in the linagliptin and placebo groups achieved an A_{1c} of <7% ($P = 0.0051$). Mean FPG reductions were additionally seen in both treatment groups. The linagliptin group had a mean FPG change of −32.4 mg/dL compared with −18 mg/dL in the placebo group ($P < 0.0001$). As noted in **Table I**, the linagliptin group had a statistically significant mean weight gain from baseline compared with the placebo group (+2.3 kg vs +1.2 kg; $P = 0.014$). This finding of an increase in weight with the combination of a DPP-4 inhibitor plus a TZD is consistent with clinical trial findings from other trials of DPP-4 inhibitors.[26]

Comparative Efficacy Data

Linagliptin Versus Glimepiride

Limited results from a 104-week efficacy study that compared linagliptin and glimepiride as treatment adjunctive to metformin in patients whose glycemia was inadequately controlled have been published in abstract format.[25] That double-blind trial enrolled participants receiving stable dosages (≥10 weeks) of metformin ≥1500 mg/d. Participants were randomly assigned to receive either linagliptin 5 mg/d (n = 764) or glimepiride 1 to 4 mg/d (mean dose, 3 mg/d) (n = 755). The mean baseline A_{1c} in both treatment groups was reported as 7.7%. Changes from baseline in A_{1c} were −0.4% and −0.5% in the linagliptin and glimepiride groups, respectively ($P < 0.0001$ for noninferiority). Mean weight was decreased with linagliptin at 104 weeks (−1.4 kg) and was increased in the glimepiride group (+1.3 kg; $P < 0.0001$).

Tolerability

Adverse events reported in ≥2% of study participants treated with linagliptin in placebo-controlled clinical trials included nasopharyngitis, hyperlipidemia, cough, hypertriglyceridemia, and weight increase (when linagliptin was administered in combination with pioglitazone), as indicated in the package insert.[12] Table II provides a summary of the prevalences of select adverse events, based on frequency of report and rates of discontinuation from clinical trials of linagliptin.[18–25] Data from the clinical trial program additionally indicate that linagliptin, similar to other agents in the DPP-4 inhibitor class, is generally weight-neutral when used as monotherapy or in combination with metformin or a sulfonylurea.[18,23] When linagliptin was used in combination with the TZD pioglitazone, however, an increase in weight was observed (2.3 versus 1.2 kg; 95% CI, 0.2–2.0; $P = 0.014$).[24] When used as treatment adjunctive to a regimen of metformin and a sulfonylurea agent, the risk for hypoglycemia was significantly increased compared with placebo (OR = 1.64; 95% CI, 1.14–2.38; $P = 0.0083$),[23] and fewer patients were reported to have had hypoglycemia in the comparison of linagliptin versus glimepiride as add-on therapy to metformin over a period of 104 weeks (7.5% vs 36.1%; $P < 0.001$).[25] Overall, the percentages of enrolled participants in whom a serious adverse event (SAE) was reported and/or who were discontinued from participation due to an adverse event were similar to those with placebo.[18–24]

Because postmarketing reports of the development of pancreatitis in patients on DPP-4 have been reported, the FDA announced revisions to the prescribing information for sitagliptin and sitagliptin/metformin fixed-dose combination to include information on those reports.[27] In the linagliptin clinical trial program, according to the prescribing information, 8 of 4687 participants (4311 patient-years of exposure) who received linagliptin were reported to have experienced pancreatitis while receiving treatment, compared with zero cases in the 1183 participants (433 patient-years of exposure) who received placebo.[12] In addition, 3 cases of pancreatitis were reported following the last administered dose of linagliptin. The mechanism in which DPP-4 inhibitors may contribute to pancreatitis, and the timeframe in which this rare adverse event may develop, are unknown. Similar to findings from reports on other DPP-4 inhibitors, this adverse event appears to be infrequent, but patients and clinicians should be aware of the potential risk for acute pancreatitis, and patients should be counseled regarding the signs and symptoms (eg, persistent nausea and vomiting, abdominal pain).

Data from Phase III clinical trials of linagliptin have also been assessed to determine the cardiovascular (CV) risk of therapy in patients with T2DM (N = 5239).[28] A cardiovascular safety analysis was conducted as a prespecified meta-analysis of all CV events from 8 Phase III, randomized, double-blind, controlled trials of ≥12 weeks of duration. The primary end point of the analysis was a composite of CV death, nonfatal stroke, nonfatal myocardial infarction, and hospitalization for unstable angina pectoris. Overall, the cumulative exposure to linagliptin was 2060 person-years, and 1372 person-years for comparators. Primary CV events occurred in 11 (0.3%) and 23 (1.2%) of patients receiving linagliptin and comparator agents, respectively, with linagliptin treatment having a lower hazard ratio for the composite CV end point compared with comparators. Although the findings from that meta-analysis suggest a level of CV tolerability with linagliptin treatment, a head-to-head, events-driven, randomized, double-blind, active-comparator study designed to compare the impact of linagliptin 5 mg/d to that of glimepiride 4 mg/d on CV events in 6000 patients with T2DM at elevated CV risk, named the CAROLINA study (An Active Comparator Cardiovascular Outcome Study of the DPP-4 Inhibitor

Table II. Tolerability reported in clinical trials of linagliptin.* Data are number (%) of patients.

Study/Treatment Groups	Infections and Infestations†	Dyslipidemia	Headache	MS Pain‡	Hypoglycemia	Discontinuation Due to ADE	Serious Adverse Events
Del Prato et al[18] (24-Wk study in patients with T2DM who were treatment-naive or receiving 1 OAD)							
Linagliptin 5 mg/d (n = 336)	55 (16.4)	4 (1.2)	9 (2.7)	9 (2.7)	1 (0.3)	4 (1.2)	10 (3.0)
Placebo (n = 167)	38 (22.8)	4 (2.4)	2 (1.2)	3 (1.8)	1 (0.6)	4 (2.4)	7 (4.2)
Forst et al[20] (12-Wk study in patients with T2DM who were receiving metformin with or without an additional OAD§)							
Linagliptin 1 mg/d (n = 65)	5 (8)	2 (3)	NR	2 (3)	0	6 (9)	3 (5)
Linagliptin 5 mg/d (n = 66)	7 (11)	0	NR	3 (5)	0	3 (5)	1 (2)
Linagliptin 10 mg/d (n = 66)	7 (11)	1 (2)	NR	1 (2)	0	2 (3)	4 (6)
Glimepiride (n = 65)	5 (8)	0	NR	0 (0)	3 (5)	3 (5)	1 (2)
Placebo (n = 71)	12 (16)	0	NR	3 (7)	0	2 (3)	1 (1)
Taskinen et al[21] (24-Wk study in patients with T2DM who were receiving metformin with or without an additional OAD§)							
Linagliptin 5 mg/d (n = 524)	76 (14.6)	NR	15 (2.9)	23 (4.4)	3 (0.6)	8 (1.5)	18 (3.4)
Placebo (n = 177)	25 (14.2)	NR	7 (4.0)	8 (4.5)	5 (2.8)	3 (1.7)	4 (2.3)
Lewin et al[22] (18-Wk study in patients with T2DM who were receiving a sulfonylurea + an OAD)							
Linagliptin 5 mg/d (n = 161)	NR	NR	NR	NR	NR	NR	4 (2.5)
Placebo (n = 84)	NR	NR	NR	NR	NR	NR	0
Owens et al[23] (24-Wk study in patients with T2DM who were receiving metformin + a sulfonylurea)							
Linagliptin 5 mg/d (n = 792)	170 (21.5)	NR	33 (4.2)	97 (12.2)	180 (22.7)	23 (2.9)	25 (3.2)
Placebo (n = 263)	76 (28.9)	NR	13 (4.9)	24 (9.1)	39 (14.8)	5 (1.9)	10 (3.8)
Gomis et al[24] (24-Wk study in patients with T2DM who were treatment-naive or receiving an OAD)							
Linagliptin 5 mg/d (n = 259)	NR	NR	1 (0.4)	NR	3 (1.2)	NR	NR
Placebo (n = 130)	NR	NR	0	NR	0	NR	NR

ADE = adverse drug event; MS = musculoskeletal; NR = not reported.
*Tolerability data from Kawamori et al[19] and Gallwitz et al[25] were not reported.
†Inclusive of cases of nasopharyngitis, upper respiratory tract infection, urinary tract infection, and viral infections.
‡Inclusive of cases of back pain, arthralgia, and musculoskeletal pain.
§Excluding a thiazolidinedione.

Linagliptin in Patients with Type 2 Diabetes at High Cardiovascular Risk), is currently underway.[29]

Drug–Drug Interactions

According to the manufacturer, in vitro assessments suggested that linagliptin is a weak to moderate inhibitor of the cytochrome P450 (CYP) 3A4 isozyme and is a P-glycoprotein (P-gp) substrate.[12] Although linagliptin at high concentrations inhibited P-gp–mediated transport of digoxin, when used at the approved 5-mg/d dosage the drug is considered by the manufacturer as unlikely to be associated with interactions with other P-gp substrates. Because rifampin (a CYP3A4 and P-gp inducer) has been reported to be associated with decreased linagliptin exposure, when linagliptin is given concurrently with a strong inducer of P-gp or CYP3A4, the efficacy of linagliptin may be reduced; thus, alternative therapies are recommended by the manufacturer in patients receiving CYP3A4 or P-gp inducers.[12] According to the prescribing information for linagliptin, in vivo studies have suggested a low propensity for drug interactions between linagliptin and substrates of CYP3A4, CYP2C9, CYP2C8, P-gp, and the organic cationic transporter; however, based on these findings, no dose adjustments of linagliptin were recommended by the manufacturer at the time of this publication.[12] Targeted drug-interaction studies have reported linagliptin to have no clinically relevant pharmacokinetic interactions with drugs commonly used in patients with T2DM, including metformin, pioglitazone or glyburide,[30] warfarin,[31] digoxin,[32] or simvastatin.[33] Another study reported that linagliptin did not significantly alter the steady-state pharmacokinetic properties of the combined oral contraceptive ethinylestradiol/levonorgestrel.[34]

Contraindications/Precautions

Hypersensitivity

Linagliptin is contraindicated in individuals with a history of hypersensitivity to linagliptin, including such reactions as urticaria, angioedema or bronchial hyperreactivity, because such reactions were reported in the linagliptin clinical trial program.[12,18,20–21,23,24]

Use With Medications Known to Cause Hypoglycemia

As noted previously, the use of linagliptin in combination with an insulin secretagogue was associated with an increased risk for hypoglycemia.[20,22,25] Accordingly, the prescribing information for linagliptin indicates that a lower dose of insulin secretagogue may be necessary to avoid hypoglycemia when used in combination with linagliptin.[12]

Special Considerations

Pregnancy and Breastfeeding

According to the manufacturer, linagliptin is rated as a pregnancy category B medication.[12] Controlled studies of linagliptin in pregnant or breastfeeding women have not been conducted, although in studies in animals, linagliptin was reported to have crossed the placenta and to have been excreted in milk.[12] As a result, the manufacturer recommends that linagliptin be used during pregnancy only if clearly needed, and that caution be exercised when prescribing linagliptin in breastfeeding women.[12]

Pediatric Patients

Studies characterizing the pharmacokinetic properties, tolerability, and effectiveness of linagliptin in pediatric patients were not identified in the literature. The manufacturer does not recommended its use in this population.[12]

Geriatric Patients

According to the prescribing information, of the total number of participants in the linagliptin clinical program (N = 4040), 1085 were ≥65 years of age.[12] No differences in efficacy or tolerability were noted in clinical studies based on participants' age. In an analysis of pooled data from 2258 patients presented at the 93rd Annual Meeting and Expo of The Endocrine Society, efficacy outcomes did not differ significantly between age subgroups (≤50, 51–64, 65–74, and ≥75 years).[35] Although no dose adjustments based on age are currently recommended, a greater sensitivity of older individuals to the effects of linagliptin cannot be ruled out, and caution is warranted when initiating and maintaining treatment with a new drug in any elderly or frail patient.

Linagliptin Use in Renal Impairment

Studies have examined the use of linagliptin in participants with compromised renal function.[17,36] One such study examined linagliptin use specifically in patients with T2DM and severe renal impairment (glomerular filtration rate, <30 mL/min/1.73 m^2) and a baseline A_{1c} of 7.0% to 10.0%.[36] In that randomized, double-blind, placebo-controlled trial, participants

were treated with either linagliptin 5 mg/d (n = 68) or placebo (n = 65) and were allowed to continue taking their background antidiabetic medications. Following 12 weeks of treatment, mean adjusted A_{1c} changes were −0.8% and −0.2% in the linagliptin and placebo groups, respectively ($P = 0.0001$). During the study, renal function remained unchanged in both treatment arms.

In a second study, by Graefe-Mody et al,[17] participants (with and without T2DM) with various degrees of renal impairment (N = 51) were enrolled to assess the influence of renal impairment on linagliptin exposure. Participants enrolled in that open-label study ranged from 18 to 80 years of age and were stratified by extent of renal function (normal [creatinine clearance (CrCl), >80 mL/min], mild renal impairment [CrCl >50–≤80 mL/min], moderate renal impairment [>30–≤50 mL/min], severe renal impairment [≤30 mL/min], and end-stage renal disease [ESRD] [on hemodialysis]). Under single-dose conditions, the degree of renal impairment was not reported to have significantly affected the plasma linagliptin concentration–time profiles, and the renal excretion of unchanged linagliptin was reported to be <7% in all study groups. Although there was numerically (20%–60%) greater linagliptin exposure in participants with renal impairment, the CIs of the geometric mean ratios of the steady-state AUC and C_{max} values overlapped across groups, suggesting that linagliptin exposure was not affected by the extent of renal impairment. **Table III** provides a summary of AUC and C_{max} data under single- and multiple-dose conditions. During that study, no adverse events were reported to have led to participant discontinuation from the study.[17] Two patients (4%) were reported to have experienced adverse events while receiving treatment; these events included 1 case of headache and 1 case of diarrhea and fatigue. Although these adverse-events data suggest that linagliptin was well tolerated in that population, that study was relatively short in duration. Overall, the investigators deemed the differences in pharmacokinetic properties as not clinically significant and concluded that dose adjustments based on renal function are not required.

Table III. Effects of renal impairment on linagliptin exposure. Data are geometric mean ratios (2-sided 90% CI).

Property	Mild Renal Impairment*	Moderate Renal Impairment*	Severe Renal Impairment With T2DM†	Severe Renal Impairment	ESRD
Single-dose conditions					
C_{max}, nmol/L	1.26 (0.80–1.96)	1.57 (0.77–3.19)	1.23 (0.82–1.84)	1.47 (0.83–2.61)*	1.50 (0.94–2.41)*
AUC_{0-24}, nmol · h/L	1.29 (1.01–1.66)	1.56 (1.06–2.32)	1.22 (0.92–1.62)	1.41 (1.04–1.91)*	1.54 (1.18–2.00)*
Multiple-dose conditions					
C_{max}, nmol/L	0.98 (0.70–1.39)	1.46 (0.98–2.19)	1.36 (0.97–1.90)	NR	NR
AUC_{0-24}, nmol · h/L	1.08 (0.91–1.28)	1.71 (1.34–2.18)	1.42 (1.10–1.82)	1.34†,‡; 1.65*,‡	1.54†,‡; 1.89*,‡

Adapted from reference 17.
ESRD = end-stage renal disease; NR = not reported; T2DM = type 2 diabetes mellitus.
*Compared with healthy volunteers with normal renal function.
†Compared with patients with T2DM and normal renal function.
‡Predicted value.

Dosing and Administration

Some clinical trials of linagliptin used a once-daily dose of 5 or 10 mg.[18–24] Linagliptin has been approved by the FDA for use as treatment adjunctive to diet and exercise for the improvement of glycemic control in

adults with T2DM at a once-daily dose of 5 mg.[12] In contrast to other DPP-4 inhibitors available in the United States, with linagliptin, dosage adjustments based on renal function are not required. In addition, linagliptin can be administered without regard to mealtimes.[12]

Pharmacoeconomics

On review of the literature, no specific studies of the pharmacoeconomics of linagliptin in the treatment of T2DM were identified. In an examination of the acquisition costs of linagliptin compared with those of other currently available DPP-4 inhibitors, the costs were comparable between agents, with 30-day supplies of sitagliptin 100 mg/d, saxagliptin 5 mg/d, and linagliptin 5 mg/d costing $229.99, $235.98, and $241.00, respectively, at the time of this publication.[37]

DISCUSSION

Potentially desirable characteristics of DPP-4 inhibitors include once-daily oral dosing, a minimal risk for hypoglycemia when used as monotherapy, and weight neutrality.[38] Data from clinical trials of linagliptin administered as monotherapy or in combination with other OADs have suggested clinical efficacy in terms reductions in the surrogate marker A_{1c}, FPG, and PPG.[18–24] Overall, currently available clinical evidence suggests that linagliptin is generally well tolerated, with an adverse-events profile comparable to those of other currently available DPP-4 inhibitors. Similar to findings from clinical trials of other DPP-4 inhibitors, the concurrent administration of linagliptin and an insulin secretagogue has been associated with an increased risk for hypoglycemia; thus, caution is warranted when adding linagliptin to a regimen of insulin secretagogue therapy, and a dose reduction in the insulin secretagogue may be warranted to avoid hypoglycemic events. Also similar to other DPP-4 agents, linagliptin appears to augment the weight gain induced by TZDs.

Although there are no published head-to-head trials comparing linagliptin to other currently available DPP-4 inhibitors, data from clinical trials suggest that there are no obvious advantages for 1 agent over another with regard to efficacy. The lack of a need for dosage adjustments based on renal or hepatic function confers a unique attribute of linagliptin within the expanding DPP-4 inhibitor class of medications, and linagliptin may have a niche in the context of managing glycemia patients with T2DM and some degree of renal compromise.

DPP-4 inhibitors as a class are generally well tolerated and have been reported to have similar adverse-events profiles in clinical trials. These agents are becoming an increasingly utilized therapy in the management of postprandial glycemic excursions in patients with T2DM, without a significant risk for hypoglycemia. Clinical guidance from the American Association of Clinical Endocrinologists/American College of Endocrinology recommends DPP-4 inhibitors as 1 of the preferred choices for initial therapy in patients with T2DM and A_{1c} of 6.5% to 7.5%, and in combination with other OADs in patients with A_{1c} $\geq$7.6%.[39] The National Institute for Health and Clinical Excellence recommends considering DPP-4 inhibitors as second-line therapy instead of sulfonylurea agents in patients at significant risk for hypoglycemia and its complications; specifically, older adults, individuals with hazardous jobs, or those who live alone may benefit from treatment with DPP-4 inhibitors.[40]

Of particular clinical concern is the association of DPP-4 therapy with potentially life-threatening pancreatitis. Vigilant postmarketing surveillance is imperative, with mechanisms in place to ensure that busy practitioners can report suspected cases.

CONCLUSIONS

Linagliptin is a DPP-4 inhibitor recently approved by the FDA as a once-daily oral tablet for the treatment of T2DM. Data suggest that linagliptin may be useful in achieving modest improvements in glycemic parameters, similar to those achievable with other currently available agents in the DPP-4 inhibitor class. Linagliptin appears to be well tolerated in most patients and is generally weight-neutral unless used in combination with a TZD. Patients and clinicians should be aware of the risk for hypoglycemia when linagliptin or another DPP-4 inhibitor is used as a treatment adjunctive to an insulin secretagogue, and an initial dose decrease in background secretagogue medication should be considered to prevent hypoglycemic events. According to the prescribing information on linagliptin, the efficacy of linagliptin may be limited in patients receiving concurrent inducers of CYP3A4 or P-gp (eg, rifampin).

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CONFLICT OF INTEREST

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