

Pharmacokinetic and pharmacodynamic evaluation of linagliptin for the treatment of type 2 diabetes mellitus, with consideration of Asian patient populations

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ABSTRACT

Our aims were to summarize the clinical pharmacokinetics and pharmacodynamics of the dipeptidyl-peptidase-4 inhibitor, linagliptin, and to consider how these characteristics influence its clinical utility. Differences between linagliptin and other dipeptidyl-peptidase-4 inhibitors were also considered, in addition to the influence of Asian race on the pharmacology of linagliptin. Linagliptin has a xanthine-based structure, a difference that might account for some of the pharmacological differences observed with linagliptin versus other dipeptidyl-peptidase-4 inhibitors. The long terminal half-life of linagliptin results from its strong binding to dipeptidyl-peptidase-4. Despite this, linagliptin shows a short accumulation half-life, as a result of saturable, high-affinity binding to dipeptidyl-peptidase-4. The pharmacokinetic characteristics of linagliptin make it suitable for once-daily dosing in a broad range of patients with type 2 diabetes mellitus. Unlike most other dipeptidyl-peptidase-4 inhibitors, linagliptin has a largely non-renal excretion route, and dose adjustment is not required in patients with renal impairment. Furthermore, linagliptin exposure is not substantially altered in patients with hepatic impairment, and dose adjustment is not necessary for these patients. The 5-mg dose is also suitable for patients of Asian ethnicity. Linagliptin shows unique pharmacological features within the dipeptidyl-peptidase-4 inhibitor class. Although most clinical trials of linagliptin have involved largely Caucasian populations, data on the pharmacokinetic/pharmacodynamic properties of linagliptin show that these features are not substantially altered in Asian populations. The 5-mg dose of linagliptin is suitable for patients with type 2 diabetes mellitus irrespective of their ethnicity or the presence of renal or hepatic impairment.

INTRODUCTION

The global burden of type 2 diabetes mellitus continues to grow¹, and is becoming an increasingly urgent health issue across the world, particularly in low- and middle-income countries; almost one-fifth of people with diabetes live in Southeast Asia¹. As a result of the growing burden of type 2 diabetes mellitus, there remains a need for effective, well-tolerated therapies, and a range of treatment options is available for the

management of hyperglycemia². However, some of the commonly used therapies for type 2 diabetes mellitus have limitations as a result of troublesome side-effects, such as risk of hypoglycemia and weight gain (e.g., sulfonylureas, thiazolidinediones, insulin), the possibility of gastrointestinal side-effects (e.g., metformin, α -glucosidase inhibitors), or are contraindicated in patients with moderate or severe renal impairment (e.g., metformin, sulfonylureas)².

An important advance in the management of type 2 diabetes mellitus has been the development of incretin-based therapies, including the dipeptidyl-peptidase (DPP)-4 inhibitors. These

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agents are being increasingly incorporated into clinical practice, and are listed as treatment options in the latest joint guidelines from the American Diabetes Association and the European Association for the Study of Diabetes², and guidelines from the American Association of Clinical Endocrinologists³ for diabetes management. The mechanism of action of DPP-4 inhibitors is distinct from that of other antidiabetes agents: their glucose-lowering efficacy is based on an effect on the incretin hormones, active glucagon-like peptide (GLP)-1 and gastric inhibitory peptide (also known as glucose-dependent insulinotropic polypeptide [GIP]), which are secreted from the intestine after a meal⁴. In the presence of hyperglycemia, these hormones are secreted in response to food intake, and exert a key role in the control of glucose levels by enhancing glucose-dependent insulin release and reducing glucagon secretion. Both active GLP-1 and GIP are rapidly inactivated through cleavage by DPP-4⁵, and thus, the antihyperglycemic activity of DPP-4 inhibitors results from enhancement of the incretin effect. Importantly, DPP-4 inhibitors have been shown to improve glycemic control with a low risk of hypoglycemia (when used without insulin secretagogues) or weight gain⁶.

Linagliptin is a selective and potent DPP-4 inhibitor with a xanthine-based molecular structure, and is indicated for the treatment of type 2 diabetes mellitus⁷. The efficacy of linagliptin has been shown in a range of clinical trials of patients with type 2 diabetes mellitus, both as monotherapy^{8–10} and in combination with other antidiabetes agents^{11–18}. The safety and tolerability of linagliptin has also been shown during its clinical development; a recent pooled analysis of 22 randomized, double-blind trials of linagliptin showed that the frequency of adverse events was similar for linagliptin- and placebo-treated patients across a wide range of patients, including elderly subjects and individuals with declining renal function¹⁹.

The aim of the present review is to provide a summary of the clinical pharmacokinetics (PK) and pharmacodynamics (PD) of linagliptin, and to show how the PK/PD profile of linagliptin influences its clinical utility. The features of linagliptin will be compared with other drugs in its class. In view of the high prevalence of type 2 diabetes mellitus in Asian populations, consideration will be given to how the PK/PD of linagliptin compare between Caucasian and Asian populations.

METHODS

The Medline database was searched through PubMed to retrieve relevant references from the past 10 years. Search terms included: linagliptin, DPP-4 inhibitors, PK, PD, Japanese, Chinese, Asian, renal, hepatic and interactions. Other relevant literature was obtained based on personal knowledge and experience. A narrative overview of the literature was then synthesized based on manual assessment of the retrieved literature.

Pharmacology of linagliptin

In contrast with other DPP-4 inhibitors, linagliptin has a xanthine-based chemical structure^{20,21}. This structural difference

might account for some of the pharmacological differences observed with linagliptin compared with other drugs in its class²². Linagliptin is a potent and selective inhibitor of DPP-4, with >10,000-fold selectivity for DPP-4 compared with the enzymes DPP-8 and DPP-9²². In clinical studies, linagliptin administration has been shown to produce dose-dependent DPP-4 inhibition in healthy volunteers^{23,24} and in patients with type 2 diabetes mellitus^{25–27}. In healthy subjects, linagliptin doses of up to 600 mg (120 times higher than the 5-mg dose) have been shown to be well tolerated²⁴, and this wide therapeutic window might, at least in part, be related to the high selectivity of linagliptin for DPP-4²². For clinical use, linagliptin has an oral route of administration^{21,22} and is indicated, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus, either alone or in combination with other oral antidiabetes agents^{7,28}.

CLINICAL PK

Absorption

After oral administration of linagliptin 5 mg, the drug is rapidly absorbed, and geometric mean values for the maximum plasma concentration are approximately 6–10 nmol/L after a single dose^{24,27}, and 11–12 nmol/L at steady state^{25,27}. The time taken to achieve maximum plasma concentration is approximately 1.5–2.0 h^{24,25,27}. After multiple oral doses of linagliptin 1–10 mg, two studies have shown the mean area under the plasma concentration–time curve at steady state ($AUC_{\tau,ss}$) to be approximately 81.7–207 nmol h/L in patients with type 2 diabetes mellitus^{25,27}. The absolute bioavailability of linagliptin has been estimated to be approximately 30%²⁹. Administration of linagliptin with food has been shown to have no clinically relevant effect on its absorption³⁰.

Distribution

In a study of healthy men, the apparent volume of distribution at steady state after intravenous infusion of linagliptin 0.5–10 mg was shown to be 380–1,540 L²⁹. After a single intravenous dose of 5 mg, the volume of distribution at steady state was 1,110 L²⁹. This large apparent volume of distribution indicates extensive distribution of linagliptin in the tissues. In addition, linagliptin has been shown to bind extensively to plasma proteins (70–80%) in a concentration-dependent manner³¹. This high-affinity binding of linagliptin to DPP-4 in the plasma and tissues contributes to its long terminal half-life (>100 h)^{25,27}, short accumulation half-life (approximately 10 h)^{25,27} and non-linear PK profile, as shown in both animal^{31–33} and human²⁰ studies. Furthermore, the saturable binding of linagliptin to DPP-4 results in less than dose-proportional increases in exposure to linagliptin within the therapeutic dose range, and thus, a non-linear relationship between linagliptin dose and drug exposure^{24,25}.

Metabolism

Metabolism is a minor contributor to the overall disposition and elimination of linagliptin, which is mainly eliminated

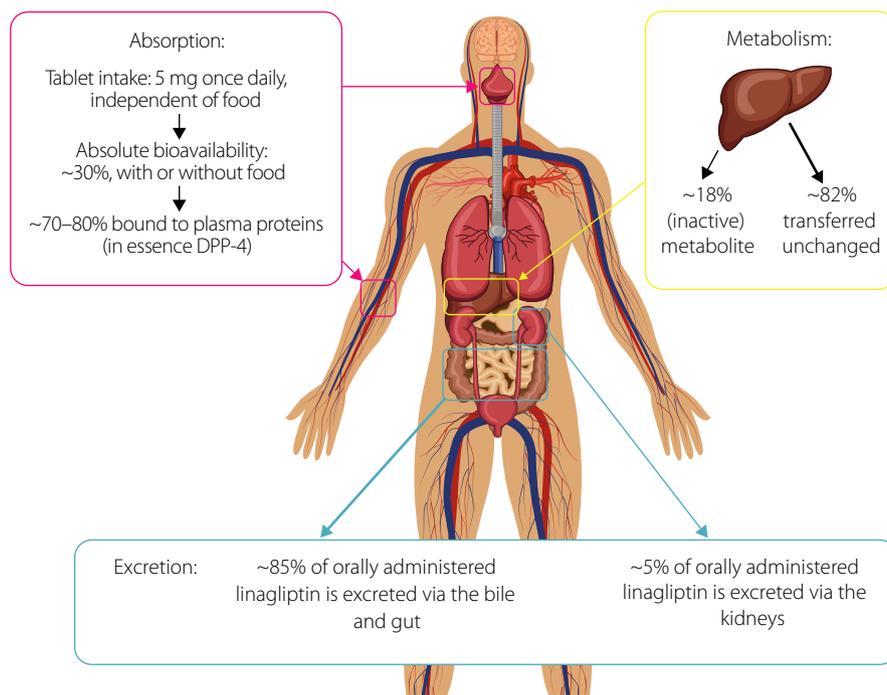


Figure 1 | The absorption, metabolism and excretion of linagliptin after oral administration. The percentages shown for the excretion of linagliptin are based on data obtained up to 120 h after the oral administration of a 10-mg dose of linagliptin³⁴. DPP-4, dipeptidyl-peptidase-4.

unchanged through feces. Its main metabolite (CD 1790) accounts for approximately 18% of the molar linagliptin plasma exposure (AUC_{24}) after a single oral 10-mg dose of linagliptin, and is pharmacologically inactive³⁴.

Elimination

Linagliptin has a mainly non-renal route of excretion, with 84.7% of an orally administered 10-mg dose being eliminated through bile and the gut, and 5.4% excreted in urine (Figure 1)³⁴. Experiments in rats have shown that the bioavailability of orally administered linagliptin is enhanced by inhibition of intestinal P-glycoprotein, indicating that this transport system can decrease the intestinal absorption of linagliptin. Although the potent, reversible binding of linagliptin to DPP-4 in the plasma and tissues means that a proportion of the administered dose is not directly available for elimination, these studies showed that the systemically available linagliptin is mainly excreted with bile, with a minor proportion (12% of an intravenous dose) being secreted directly into the gut³⁵. It is therefore possible that, in the presence of hepatic or renal impairment, the direct excretion of linagliptin into the gut could provide an alternative route of excretion of the drug.

CLINICAL PD

DPP-4 inhibition

The inhibition of DPP-4 is an attractive strategy for the management of type 2 diabetes mellitus, in particular because the

associated stimulation of insulin release is glucose-dependent and, therefore, DPP-4 inhibitors have a low risk of hypoglycemia³⁶. Linagliptin provides sustained inhibition of DPP-4 activity in a dose-dependent manner. A once-daily 5-mg dose of linagliptin has been shown to achieve >80% inhibition of DPP-4 in healthy volunteers²³ and patients with type 2 diabetes mellitus²⁵. This level of DPP-4 inhibition is considered to be the threshold for glycemic control for DPP-4 inhibitors, with maximum glucose-lowering efficacy being achieved with DPP-4 inhibitors that achieve at least 80% inhibition of DPP-4³⁷. In a study of linagliptin doses of 2.5, 5 and 10 mg, inhibition of DPP-4 was shown to be rapidly achieved; the mean maximum DPP-4 inhibition ranged from 86% for the 2.5-mg dose to 93% for linagliptin 10 mg, after a single dose²⁷. At steady state, the mean maximum inhibition of DPP-4 was 91–93% across all linagliptin doses. Therefore, it would be expected that maximum glucose-lowering efficacy can be achieved with the evaluated linagliptin doses.

Effects on GLP-1 and blood glucose

The antihyperglycemic effect of linagliptin arises from its effect on the incretin hormones, active GLP-1 and GIP. In response to hyperglycemia, these hormones stimulate glucose-dependent insulin secretion, and inhibit the secretion of glucagon^{38–40}. DPP-4 is the main enzyme involved in the breakdown of both GLP-1 and GIP⁴¹, and DPP-4 inhibition, therefore, prolongs the activity of GLP-1 and potentiates its antihyperglycemic

effects. For example, in a study of linagliptin administration to patients with type 2 diabetes mellitus, marked increases in plasma levels of GLP-1 were observed after 28 days of linagliptin dosing²⁷. After a meal tolerance test, carried out 24 h after the last linagliptin intake, there were statistically significant reductions in the AUC of the plasma glucose concentration–time graph²⁷. Because both GIP and GLP-1 promote glucose-dependent insulin secretion^{42,43}, linagliptin therapy is associated with a low risk of hypoglycemia. This is supported by the findings of clinical trials of linagliptin, both alone⁹ and in combination with other non-sulfonylurea oral antidiabetes agents^{11,14,18}, and by an exploratory analysis of data from a 2-year randomized, double-blind study of linagliptin versus glimepiride in patients with type 2 diabetes mellitus and inadequate glycemic control despite metformin therapy⁴⁴.

SPECIAL POPULATIONS

Renal impairment

The development of moderate-to-severe renal impairment (defined as an estimated glomerular filtration rate [eGFR] below 60 mL/min/1.73 m²) is a frequent complication of type 2 diabetes mellitus, and some degree of renal disease is estimated to be present in up to 40% of patients^{45–47}. As a result, the impact of renal disease on antidiabetes therapies is an important consideration. The effect of various degrees of renal impairment on exposure to linagliptin has been evaluated under single-dose and steady-state conditions in subjects with or without type 2 diabetes mellitus, and mild, moderate or severe renal impairment, or end-stage renal disease⁴⁸. The findings showed that the renal excretion of unchanged linagliptin did not exceed 7%, regardless of renal function status. Although exposure to linagliptin was slightly increased (20–60%) among patients with renal impairment versus subjects with normal renal function, renal impairment was shown to have only a minor effect on the PK of linagliptin. These results were further confirmed in a pooled analysis of three randomized studies from the global phase III program for linagliptin; mean trough levels of linagliptin over time were similar for patients with normal renal function (eGFR \geq 90 mL/min) and those with mild (eGFR 60 to <90 mL/min), moderate (eGFR 30 to <60 mL/min) or severe (eGFR <30 mL/min) renal impairment⁴⁹. Therefore, no dose adjustment of linagliptin or drug-related monitoring of eGFR is deemed necessary on the basis of renal function^{7,28,48}.

Hepatic impairment

In addition to renal dysfunction, patients with type 2 diabetes mellitus frequently show evidence of hepatic disease, including non-alcoholic fatty liver disease⁵⁰ and cirrhosis⁵¹. Despite the largely hepatic route of elimination of linagliptin, the presence of hepatic impairment has been shown to have no clinically important effect on the PK, PD or tolerability of linagliptin⁵². In a study of subjects with mild, moderate or severe hepatic impairment, exposure to single or multiple doses of linagliptin

5 mg was not shown to be affected to a clinically relevant extent by the presence of hepatic impairment⁵². The degree of DPP-4 inhibition was similar for all patient groups, with median DPP-4 inhibition values of >80% for all patients regardless of the degree of hepatic impairment. These results show that dose adjustment is not required for patients with hepatic impairment^{7,28}.

DRUG INTERACTIONS

Linagliptin is a weak-to-moderate inhibitor of cytochrome P450 enzymes^{7,21}. Because of the small proportion of linagliptin that is metabolized by these enzymes, changes in exposure to linagliptin by inhibition or induction of P450-dependent pathways by concomitantly administered drugs are considered to be unlikely. Importantly, linagliptin has shown no clinically relevant PK interaction with commonly prescribed antidiabetes drugs, such as metformin⁵³, pioglitazone⁵⁴ and glyburide⁵⁵.

Linagliptin is a P-glycoprotein substrate, and full efficacy of linagliptin might not be achieved when administered in combination with strong inducers of P-glycoprotein (such as rifampicin), particularly if these drugs are administered long term^{7,28,34,56}. As a consequence, alternative treatment is recommended in these circumstances.

PK/PD IN ASIAN VS CAUCASIAN PATIENTS

The presentation of type 2 diabetes mellitus can differ between patients of Asian and Caucasian origin; in Asian patients, the condition generally starts at a younger age in individuals with a relatively low body mass index⁵⁷. Asian individuals tend to show greater adiposity and a higher percentage of body fat for a given body mass index compared with Western populations^{57,58}. This feature is probably linked to the higher frequency of insulin resistance observed in Asian versus Caucasian populations⁵⁸. Asian patients with type 2 diabetes mellitus are also at heightened risk of comorbidities, such as renal complications and cardiovascular disease⁵⁹. In addition to these clinical factors, there is evidence to show that ethnic differences in dietary habits result in variations in glucose regulation between different Asian populations. For example, one study showed that Japanese subjects, with or without type 2 diabetes mellitus, demonstrated higher fasting insulin levels compared with Korean or Chinese participants⁶⁰. These differences based on ethnicity could affect the PK and PD characteristics of antidiabetes therapies and, therefore, are an important consideration.

In a study of Japanese patients with type 2 diabetes mellitus, linagliptin showed a non-linear PK profile, low accumulation and low (<7%) urinary excretion rate, all of which were consistent with findings in healthy Japanese subjects and Caucasian populations²⁶. After 4-week administration of multiple doses of linagliptin (0.5, 2.5, 10 mg), a long terminal half-life (223–260 h) was reported, in contrast with a shorter accumulation half-life (10.0–38.5 h), resulting in a moderate accumulation ratio of <2.9 that decreased with rising doses. As with

other populations, this observation reflects the saturable high-affinity binding of linagliptin to DPP-4 at the evaluated doses, leading to slow dissociation of the drug from its target. Similar findings have been reported from another study of multiple doses of linagliptin (1, 2.5, 5, 10 mg) given to healthy Japanese men²³. Although exposure to linagliptin at steady state is increased by approximately 30% in Japanese versus Caucasian subjects, this is not considered to be clinically relevant because of the wide therapeutic window of linagliptin²⁴. Furthermore, data obtained from Japanese patients with type 2 diabetes mellitus have shown that the efficacy and safety of linagliptin is not substantially altered by the presence of renal impairment, indicating that, as in Western populations, dose adjustment in these patients is not required on the basis of renal function⁶¹. The 5-mg and 10-mg doses of linagliptin have been shown to inhibit DPP-4 by >80% at 24-h post-dose in Japanese subjects^{23,26}, which is comparable with the efficacy that has been observed in Caucasian populations. The PK profile of linagliptin in healthy Chinese volunteers^{62,63} has also been shown to be similar to that in other populations, including Japanese and Caucasian subjects (Table 1)^{23–27,29,34,62–64}.

Data from two studies on the bioequivalence of linagliptin fixed-dose combination treatments versus administration of the individual drugs can provide some insight into the comparative PK characteristics of linagliptin in Chinese and Caucasian populations. Although the total exposure to linagliptin (AUC_{0–72} and maximum plasma concentration) was approximately 40% higher among Chinese participants⁶³ than previously reported in a similar study of Caucasian subjects⁶⁵, this is in line with the findings reported above for Japanese subjects, and is not considered to be clinically relevant⁶³.

Mean bodyweight in some Asian populations can be lower than in Caucasians. However, bodyweight has been shown to have no clinically meaningful impact on the PK or PD of linagliptin⁶⁶, and so dose adjustment is not required on the basis of bodyweight⁷.

COMPARISON WITH OTHER DPP-4 INHIBITORS

Although the DPP-4 inhibitors share a common mode of action, they are structurally heterogeneous, and linagliptin has a unique chemical structure and pharmacological profile compared with the other agents in its class (Table 2)^{7,20,22,28,67–83}.

In vitro studies of the inhibition of DPP-4 activity have shown that the potency of linagliptin was higher than that of other DPP-4 inhibitors (vildagliptin, sitagliptin, saxagliptin and alogliptin; based on half maximal inhibitory concentration values)²². Furthermore, the non-linear PK profile of linagliptin is not shown by other DPP-4 inhibitors. In addition, linagliptin shows a much higher binding to plasma proteins than other DPP-4 inhibitors, with a very long terminal half-life^{22,68}. From a clinical perspective, an important difference between linagliptin and other DPP-4 inhibitors is its mainly non-renal route of elimination³⁵, which means that unlike several other DPP-4 inhibitors, linagliptin does not require dose adjustment in the presence of renal impairment⁴⁸.

Table 1 | Comparison of the main pharmacokinetic parameters of linagliptin (5 mg, unless otherwise indicated) in mixed and Asian patient populations

Parameter	Estimate (mixed populations)	Estimate (Asian population)	
		Japanese	Chinese
C _{max} (nmol/L)	5.7 ²⁴	9.0 ²³	6.8 ^{63†}
	8.3 ²⁵		10.4 ⁶²
	9.6 ²⁷		
T _{max} (h)	1.5 ²⁴	1.5 ^{26‡}	4.0 ^{63†}
	1.8 ²⁵		
	2.0 ²⁷		
AUC _{0–24} (nmol h/L)	100 ²⁴	159 ²³	150 ⁶²
T _{1/2} (h)	118 ²⁵		
	69.7 ²⁴	105 ²³	58.0–75.6 ^{63†}
	127 ²⁹		82.4 ⁶²
CL/F (mL/min)		231 ²³	163–204 ^{63†}
C _{max,ss} (nmol/L)	11.1 ²⁵	5.0–44.0 ^{26‡}	14.1 ⁶²
	12.3 ²⁷	11.9 ²³	
T _{max,ss} (h)	1.0 ²⁷	1.3–1.5 ^{26‡}	–
	1.5 ²⁵		
AUC _{τ,ss} (nmol h/L)	148 ²⁷	89.4–373 ^{26‡}	204 ⁶²
T _{1/2,ss} (h)	131 ²⁵	143 ²³	103 ⁶²
	194 ²⁷	223–260 ^{26‡}	
Accumulation T _{1/2} (h)	9.5 ²⁷	10–15 ²³	11.5 ⁶²
	11.4 ²⁵	10.0–38.5 ^{26‡}	
CL/F _{ss} (mL/min)	1,190 ²⁷	197–945 ^{26‡}	–
Renal elimination (%)	1,330 ⁶⁴		
	<1 ^{24,25}	1.2–4.9 ²³ , <7 ^{26‡}	1.9–7.9 ⁶²
	3.2 ⁶⁴		
	5.4 ³⁴		
	6.2 ²⁵		

Values are geometric mean. Superscript numbers refer to source references. †In the pharmacokinetic study by Pichereau *et al.*⁶³, data are shown for subjects who received linagliptin 2.5 mg daily. ‡In the study of Japanese patients with type 2 diabetes mellitus by Horie *et al.*²⁶, data shown are for subjects receiving linagliptin 0.5–10 mg daily. AUC_{0–24}, area under the plasma concentration–time curve from zero to 24 h; AUC_{τ,ss}, area under the plasma concentration–time curve at steady state; CL/F, apparent total clearance; CL/F_{ss}, apparent clearance at steady state; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady state; PK, pharmacokinetic; T_{1/2}, half-life; T_{1/2,ss}, half-life at steady state; T2DM, type 2 diabetes mellitus; T_{max}, time to reach maximum plasma concentration; T_{max,ss}, time to reach maximum plasma concentration at steady state.

CONCLUSIONS

Linagliptin has unique pharmacological properties within the DPP-4 inhibitor class. The long terminal half-life of linagliptin is related to its non-linear PK profile that results from strong binding to its primary target, DPP-4. Despite having a long terminal half-life, linagliptin also exhibits a short accumulation half-life, which can be attributed to the saturable, high-affinity binding to DPP-4. When DPP-4 is saturated, unbound

Table 2 | Main pharmacological differences between currently available dipeptidyl-peptidase-4 inhibitors

Characteristic	Sitagliptin ^{69,82}	Vildagliptin ⁷⁰	Saxagliptin ^{71,81}	Alogliptin ^{72,80}	Linagliptin ^{7,28}
Therapeutic dose (mg)	100	50	5	25	5
Relative (fold) <i>in vitro</i> selectivity for DPP-4 vs DPP-8 or DPP-9	>2,600 ⁷³	<300 ⁷⁴	<450 ⁷⁵	>10,000 ⁷⁶	>10,000 ²²
Fraction bound to plasma protein	Intermediate	Low	Low	Low	High
Renal excretion route	Major	Intermediate	Major	Major	Minor
Need for dose adjustment for renal impairment	Yes (moderate or severe)	May be required (limited experience)	Yes (moderate or severe)	Yes (moderate or severe)	No
Need for dose reduction with hepatic impairment (mild/moderate)	No (No experience in patients with severe hepatic impairment)	Not recommended for patients with hepatic impairment	No (Not recommended for patients with severe hepatic impairment)	No (No experience in patients with severe hepatic impairment)	No
Drug interaction potential	Low	Low	Intermediate	Low	Low
Efficacy – HbA1c lowering	Similar efficacy	Similar efficacy	Similar efficacy	Similar efficacy	Similar efficacy
Overall safety [†]	Good	Good	Good	Good	Good
	<ul style="list-style-type: none"> • Most frequent AEs[‡]: URTI, nasopharyngitis, headache • Risk of hospitalization for HF, HR: 1.00 (95% CI, 0.83 to 1.20) vs placebo⁷⁷ • Postmarketing reports of acute pancreatitis, acute renal failure, hypersensitivity reactions, exfoliative skin conditions; also reports of arthralgia 	<ul style="list-style-type: none"> • Common AEs[§]: dizziness • Risk of HF unknown • Postmarketing reports of hepatitis, urticaria, pancreatitis, skin lesions; also reports of arthralgia 	<ul style="list-style-type: none"> • Most frequent AEs[‡]: URTI, UTI, headache • Risk of hospitalization for HF, HR: 1.27 (95% CI, 1.07 to 1.51) vs placebo⁷⁸ • Postmarketing reports of pancreatitis, hypersensitivity reactions, and severe arthralgia 	<ul style="list-style-type: none"> • Most frequent AEs[‡]: Nasopharyngitis, headache, URTI, abdominal pain, gastroesophageal reflux, rash • Risk of hospitalization for HF, HR: 1.07 (95% CI, 0.79 to 1.46)⁷⁹ • Postmarketing reports of acute pancreatitis, hypersensitivity reactions, and hepatic failure; also reports of arthralgia 	<ul style="list-style-type: none"> • Most frequent AEs[‡]: Nasopharyngitis, cough, rash, raised blood enzyme amylase, diarrhea • Risk of HF unknown; data from pooled analysis show hospitalization for HF, HR: 1.04 (95% CI, 0.43 to 2.47)⁸³ • Postmarketing reports of acute pancreatitis and hypersensitivity reactions, exfoliative skin conditions; also reports of arthralgia

[†]For all dipeptidyl-peptidase-4 (DPP-4) inhibitors listed, hypoglycemia is reported more frequently with concomitant sulfonylurea (SU) or insulin therapy. [‡]Most frequent adverse event (AEs) are those listed in prescribing information to occur in $\geq 5\%$ of patients and more frequently than with placebo. [§]Common AEs defined as a frequency of $\geq 1/100$ to $< 1/10$. CI, confidence interval; HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio; URTI, upper respiratory tract infection; UTI, urinary tract infection.

linagliptin is rapidly cleared from the body through bile and the gut. The PK characteristics of linagliptin have an impact on its clinical utility, such that an oral dose of 5 mg once daily is suitable for a broad range of patients with type 2 diabetes

mellitus⁸⁴. In contrast with most other DPP-4 inhibitors, the largely non-renal route of excretion of linagliptin allows treatment to be administered to patients with renal impairment, without the need for dose adjustment. Although linagliptin is

largely metabolized in the liver, dose adjustment is not required for patients with hepatic impairment. This feature might be related to its wide therapeutic window and the fact that exposure to linagliptin is not substantially altered by the presence of hepatic impairment. The 5-mg dose is also suitable for patients of Asian ethnicity; small changes in PK parameters observed when linagliptin is given to Japanese and Chinese patients have not been shown to have clinically relevant effects. Despite the fact that many clinical trials of linagliptin have been carried out in largely Caucasian populations, these findings provide reassurance that the PK/PD properties of linagliptin are not altered to a clinically relevant extent in patients of Asian ethnicity.

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