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

Antonio Ceriello\textsuperscript{1,2,*}, Nobuya Inagaki\textsuperscript{3}

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Keywords
Linagliptin, Pharmacodynamics, Pharmacokinetics

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INTRODUCTION
The global burden of type 2 diabetes mellitus continues to grow\textsuperscript{1}, 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 Asia\textsuperscript{1}. 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 hyperglycemia\textsuperscript{2}. 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)\textsuperscript{3}.

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
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 monotherapy8–10 and in combination with other antidiabetes agents11–18. 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 structure20,21. 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 volunteers23,24 and in patients with type 2 diabetes mellitus25–27. 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 administration21,22 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 agents22,28.

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 dose24,27, and 11–12 nmol/L at steady state25,27. The time taken to achieve maximum plasma concentration is approximately 1.5–2.0 h24,25,27. 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 (AUC0–inf) to be approximately 81.7–207 nmol h/L in patients with type 2 diabetes mellitus25,27. A large 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 animal31–33 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 exposure24,25.

Metabolism
Metabolism is a minor contributor to the overall disposition and elimination of linagliptin, which is mainly eliminated
unchanged through feces. Its main metabolite (CD 1790) accounts for approximately 18% of the molar linagliptin plasma exposure (AUC24) 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 glucagon38–40. 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
dependent insulin secretion\(^4\,4^3\), linagliptin therapy is associated with a low risk of hypoglycemia. This is supported by the findings of clinical trials of linagliptin, both alone\(^6\) and in combination with other non-sulfonylurea oral antidiabetes agents\(^1\,1^4\,1^8\), 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 therapy\(^4^4\).

**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 m\(^2\)) 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\(^4^5\,4^7\). 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 disease\(^4^8\). 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 ≥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 impairment\(^5^9\). Therefore, no dose adjustment of linagliptin or drug-related monitoring of eGFR is deemed necessary on the basis of renal function\(^2^8\,4^8\).

**Hepatic impairment**

In addition to renal dysfunction, patients with type 2 diabetes mellitus frequently show evidence of hepatic disease, including non-alcoholic fatty liver disease\(^6^0\) and cirrhosis\(^7\). 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 linagliptin\(^5^2\). 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 impairment\(^6^2\). 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\(^2^8\).

**DRUG INTERACTIONS**

Linagliptin is a weak-to-moderate inhibitor of cytochrome P450 enzymes\(^2\,2^1\). 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 is considered to be unlikely. Importantly, linagliptin has shown no clinically relevant PK interaction with commonly prescribed antidiabetes drugs, such as metformin\(^5^3\), pioglitazone\(^4^4\) and glyburide\(^5^5\).

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\(^2^8\,3^4\,5^6\). 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 index\(^7\). Asian individuals tend to show greater adiposity and a higher percentage of body fat for a given body mass index compared with Western populations\(^5^7\,5^8\). This feature is probably linked to the higher frequency of insulin resistance observed in Asian versus Caucasian populations\(^5^8\). Asian patients with type 2 diabetes mellitus are also at heightened risk of comorbidities, such as renal complications and cardiovascular disease\(^5^9\). 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 participants\(^6^0\). 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 populations\(^5^6\). 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 men. 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 linagliptin. 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 function. 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, which is comparable with the efficacy that has been observed in Caucasian populations. The PK profile of linagliptin in healthy Chinese volunteers has also been shown to be similar to that in other populations, including Japanese and Caucasian subjects.

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 (AUC0–24 and maximum plasma concentration) was approximately 40% higher among Chinese participants than previously reported in a similar study of Caucasian subjects, this is in line with the findings reported above for Japanese subjects, and is not considered to be clinically relevant.

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 linagliptin, and so dose adjustment is not required on the basis of bodyweight.

### 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).

**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). 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. From a clinical perspective, an important difference between linagliptin and other DPP-4 inhibitors is its mainly non-renal route of elimination, which means that unlike several other DPP-4 inhibitors, linagliptin does not require dose adjustment in the presence of renal impairment.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (mixed populations)</th>
<th>Estimate (Asian population)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Japanese</td>
<td>Chinese</td>
</tr>
<tr>
<td><strong>Cmax</strong> (nmol/L)</td>
<td>5.724</td>
<td>6.861†</td>
</tr>
<tr>
<td></td>
<td>8.325</td>
<td>10.462</td>
</tr>
<tr>
<td></td>
<td>9.627</td>
<td>4.061†</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td>1.524</td>
<td>15.041</td>
</tr>
<tr>
<td></td>
<td>1.825</td>
<td>2.068</td>
</tr>
<tr>
<td></td>
<td>2.027</td>
<td>–</td>
</tr>
<tr>
<td><strong>AUC0–24 (nmol h/L)</strong></td>
<td>10024</td>
<td>15923</td>
</tr>
<tr>
<td></td>
<td>11825</td>
<td>15062</td>
</tr>
<tr>
<td><strong>T1/2 (h)</strong></td>
<td>69.724</td>
<td>10523</td>
</tr>
<tr>
<td></td>
<td>12729</td>
<td>580–75.663†</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>8244†</td>
</tr>
<tr>
<td><strong>CL/F (mL/min)</strong></td>
<td>11.125</td>
<td>5.0–44.024†</td>
</tr>
<tr>
<td></td>
<td>12327</td>
<td>14.162</td>
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<tr>
<td></td>
<td>11.923</td>
<td>–</td>
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<tr>
<td></td>
<td>1.027</td>
<td>1.3–1.526†</td>
</tr>
<tr>
<td></td>
<td>1.525</td>
<td>–</td>
</tr>
<tr>
<td><strong>AUCss (nmol h/L)</strong></td>
<td>14827</td>
<td>894–37320†</td>
</tr>
<tr>
<td></td>
<td>19323</td>
<td>20462</td>
</tr>
<tr>
<td><strong>T1/2 ss (h)</strong></td>
<td>13125</td>
<td>14323</td>
</tr>
<tr>
<td></td>
<td>19427</td>
<td>10362</td>
</tr>
<tr>
<td><strong>Accumulation T1/2 (h)</strong></td>
<td>9527</td>
<td>223–2604†</td>
</tr>
<tr>
<td></td>
<td>11.425</td>
<td>10.523</td>
</tr>
<tr>
<td></td>
<td>100–38524†</td>
<td>197–94524†</td>
</tr>
<tr>
<td></td>
<td>133064†</td>
<td>–</td>
</tr>
<tr>
<td><strong>Renal elimination (%)</strong></td>
<td>&lt;12425</td>
<td>1.2–4.923, &lt;7204†</td>
</tr>
<tr>
<td></td>
<td>3.224</td>
<td>1.9–7.962†</td>
</tr>
<tr>
<td></td>
<td>5.424</td>
<td>–</td>
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<tr>
<td></td>
<td>6.225</td>
<td>–</td>
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</table>

Values are geometric mean. Superscript numbers refer to source references. In the pharmacokinetic study by Pichereau et al., 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., data shown are for subjects receiving linagliptin 0.5–10 mg daily. AUC0–24, area under the plasma concentration–time curve from zero to 24 h; AUCss, area under the plasma concentration–time curve at steady state; CL/F, apparent total clearance; CL/Fss, apparent clearance at steady state; Cmax, maximum plasma concentration; Cmaxss, maximum plasma concentration at steady state; PK, pharmacokinetic; T1/2, half-life; T1/2 ss, half-life at steady state; T2DM, type 2 diabetes mellitus; Tmax, time to reach maximum plasma concentration; Tmaxss, time to reach maximum plasma concentration at steady state.
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 mellitus. 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

<table>
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<th>Table 2</th>
<th>Main pharmacological differences between currently available dipeptidyl-peptidase-4 inhibitors</th>
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<tr>
<td>Characteristic</td>
<td>Sitagliptin^{69,82}</td>
</tr>
<tr>
<td>Therapeutic dose (mg)</td>
<td>100</td>
</tr>
<tr>
<td>Relative (fold) in vitro selectivity for DPP-4 vs DPP-8 or DPP-9</td>
<td>&gt;2,600^{73}</td>
</tr>
<tr>
<td>Fraction bound to plasma protein</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Renal excretion route</td>
<td>Major</td>
</tr>
<tr>
<td>Need for dose adjustment for renal impairment</td>
<td>Yes (moderate or severe)</td>
</tr>
<tr>
<td>Need for dose reduction with hepatic impairment (mild/moderate)</td>
<td>No (No experience in patients with severe hepatic impairment)</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>Low</td>
</tr>
<tr>
<td>Efficacy – HbA1c lowering</td>
<td>Similar efficacy</td>
</tr>
<tr>
<td>Overall safety</td>
<td>Good</td>
</tr>
</tbody>
</table>

- Most frequent AEs: URTI, nasopharyngitis, headache
- Risk of hospitalization for HFrEF, HR: 1.00 (95% CI, 0.83 to 1.20) vs placebo^{77}
- Postmarketing reports of acute pancreatitis, acute renal failure, hypersensitivity reactions, exfoliative skin conditions; also reports of arthralgia
- Common AEs: dizziness
- Risk of hospitalization for HFrEF, HR: 1.27 (95% CI, 1.07 to 1.51) vs placebo^{78}
- Postmarketing reports of acute pancreatitis, hypersensitivity reactions, and severe arthralgia
- Most frequent AEs: Nasopharyngitis, headache, URTI, abdominal pain, gastroesophageal reflux, rash
- Risk of hospitalization for HFrEF, 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
- Most frequent AEs: Nasopharyngitis, cough, rash, raised blood enzyme amylase, diarrhea
- Risk of HFrEF unknown; data from pooled analysis show hospitalization for HFrEF, 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 ≥5% of patients and more frequently than with placebo. Common AEs defined as a frequency of ≥1/100 to <1/10. CI, confidence interval; HbA1c, glycated hemoglobin; HFrEF, heart failure; HR, hazard ratio; URTI, upper respiratory tract infection; UUTI, urinary tract infection.
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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DISCLOSURE

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