Linagliptin is one of the most recent additions to incretin-based therapies for Type 2 diabetes. Unlike other DPP-4 inhibitors, linagliptin is excreted chiefly via the enterohepatic system and can be used without dose adjustment in patients with renal or hepatic impairment.

In the American Diabetes Association and European Association for the Study of Diabetes guidelines, linagliptin and other incretin-based therapies are considered second-line agents after the first-line agent metformin. These agents can be used as first-line agents in people who did not tolerate metformin.

Like other incretin-based therapies, linagliptin is a multitasking agent that improves insulin secretion, reduces glucagon production, slows gastric emptying, promotes satiety and reduces appetite. Its advantages include a lack of severe hypoglycemia, weight neutrality and good overall tolerability.

The mean HbA1c reductions of 0.6–1% obtained with linagliptin and other DPP-4 inhibitors are modest. Clinically meaningful improvements with linagliptin in combination with metformin plus a sulfonylurea have been observed. Linagliptin, like other DPP-4 inhibitors, is a new and, thus, more costly agent compared with metformin and sulfonylureas.

The primary use of linagliptin will presumably be as an adjunct to other hypoglycemic agents.

Linagliptin has the highest potency for inhibiting the enzymatic activity of DPP-4 competitively and reversibly with an IC$_{50}$ of approximately 1 nM (compared with 1.75 nM for teneligliptin, 3.8 nM for anagliptin, 6.9 nM for alogliptin, 19 nM for sitagliptin, 62 nM for vildagliptin and 50 nM for saxagliptin).

Favorable data from animal models suggest that endogenous GLP-1 has a beneficial effect on β-cell mass. This finding has led to the speculation that GLP-1 and DPP-4 administration may have benefit in preserving endogenous insulin secretion in diabetic patients, but there have been no long-term studies as yet to confirm this possibility with any GLP-1 or DPP-4 agent.

The long-term risks of GLP-1 treatment have not yet been determined, particularly the risks of pancreatitis and pancreatic cancer.
Linagliptin is a highly selective inhibitor of the enzyme DPP-4. It is one of several agents of this class now available for treatment of Type 2 diabetes. This review is based on a PubMed search, clinical trials and personal experience with linagliptin. In addition, the US FDA approval folder on linagliptin was obtained under the Freedom of Information Act and analyzed. The pharmacokinetics and pharmacodynamics of linagliptin are reviewed. The glucose-lowering effect of this agent is discussed both as a monotherapy and in combination with metformin, sulfonylurea, pioglitazone and insulin. The potential adverse effects of linagliptin are summarized. Linagliptin is an additional choice in the group of DPP-4 inhibitors. Unlike other DPP-4 inhibitors, linagliptin is excreted chiefly via the enterohepatic system and can be used without dose adjustment in patients with renal or hepatic impairment. As a group, the DPP-4 inhibitors have a relatively modest glucose-lowering effect. The primary use of DPP-4 inhibitors is in combination with other hypoglycemic agents, mainly metformin. Their principal advantage is a low incidence of hypoglycemia, making these agents desirable in patients such as the elderly and those with cardiac disease. A greater use of linagliptin and other DPP-4 inhibitors will occur if long-term studies show extended retention of insulin secretory capacity and/or reduced cardiac events over time with these agents.

The choice of agents to improve blood glucose levels include metformin, sulfonylureas, dipeptidyl peptidase IV inhibitors, meglitinides, thiazolidinediones and various insulin formulations. Over the past few years, two new classes of agents based on the incretin system have come into clinical use. Incretins are hormones secreted by the digestive system in response to oral nutrient intake. Incretin action results in augmented insulin secretion over and above the response solely attributable to the rise in intravenous glucose concentration [1]. The two incretin hormones with the greatest effect on glucose control are GLP-1 and glucose-dependent insulinotropic peptide, also known as GIP. GIP and GLP-1 are both secreted within minutes of food consumption and act through distinct receptors [2]. Both peptides act on pancreatic β cells to stimulate insulin secretion dependent on blood glucose concentration; when glucose levels are normal, incretin-stimulated insulin secretion is suppressed. GIP is secreted proximally from the K cells of the gut in response to oral ingestion of food containing glucose and fat, and promotes glucose-dependent insulin secretion and energy storage by adipocytes [3]. Effects of GIP include incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, modulation of fatty acid synthesis [4] and promotion of β-cell proliferation and cell survival [5,6]. Plasma concentrations of GIP are reported to be normal or increased in diabetes [7,8]. The elimination rates of intact GIP as well as its primary metabolite, GIP3–42, are similar in Type 2 diabetic patients and healthy subjects [9], but GIP’s insulinotropic effect is deficient. This is believed to be due to the downregulation of GIP expression/activity [10,11] or the downregulation of GIP receptors. In addition, there is also a notion that impairment of β-cell function might be an important cause of impaired GIP-induced insulin secretion. This is supported by the fact that the magnitude of the reduction in GIP efficacy in patients with Type 2 diabetes appears to be comparable to the impairment in glucose-induced insulin secretion in such patients. Having said that, the reduction of the incretin effect in patients with diabetes may simply be due to the effect of chronic hyperglycemia, independent of any primary defect in GIP or GLP-1 action [12].

GLP-1 is a 37-amino acid peptide secreted from the L cells of the distal gut into the blood stream. GLP-1 produces a glucose-dependent increase in insulin secretion by the L cell. Other effects of GLP-1 include suppression of glucagon secretion, slowing of gastric emptying and promotion of satiety [13,14]. GLP-1 also stimulates differentiation and proliferation of β cells and inhibition of apoptosis. Postprandial GLP-1 release is approximately 25–30% lower in patients with Type 2 diabetes and those with impaired glucose tolerance [15]. In addition, the insulinotropic effect of GLP-1 is blunted in diabetes [16,17]. GLP-1 has additional actions beyond those of GIP on glucose sensors, as well as causing inhibition of gastric emptying, reduction of food intake and suppression of glucagon secretion [1]. GLP-1 infusions have been more effective than those of GIP in lowering plasma glucose in diabetes [18]. GLP-1 also promotes satiety, and sustained GLP-1 receptor activation is associated with weight loss in both preclinical and clinical...
studies [19]. Both GIP and GLP-1 are rapidly degraded by the enzyme DPP-4. Since GLP-1 has superior metabolic effects, pharmaceutical development has concentrated on this hormone rather than on GIP. Several studies have now shown that GLP-1 can lower glucose levels, even in patients with severe β-cell impairment, presumably as a result of lowered glucagon levels and other non-insulin-secretory mechanisms [20].

GLP-1 effects can be provided therapeutically either by administering supplemental GLP-1 agonists to raise serum levels or by slowing degradation of endogenous GLP-1 with inhibitors of DPP-4. There are currently two GLP-1 analogs with resistance to DPP-4 degradation in clinical use, exenatide and liraglutide, with several more in development [21–25]. An extended-release exenatide preparation is used as a once-weekly injection [24]. Gastrointestinal issues related to the motility effects of GLP-1 are the most frequent adverse effects of the GLP-1 analogs. The most serious and growing concern related to the use of GLP-1 agents is the twofold increased incidence of pancreatitis associated with their use [25].

An alternative to supplementation of GLP-1 is to inhibit the rapid degradation of this hormone by DPP-4 [19,26,27]. Several DPP-4 inhibitors have been developed and have come into clinical use. The first approved DPP-4 inhibitor was sitagliptin [28]. Sitagliptin is effective as a monotherapy and in combinations with metformin [29–32] and various other hypoglycemic agents. Sitagliptin is generally well tolerated with an overall incidence of adverse events (AEs) comparable to placebo, a low incidence of gastrointestinal complaints and hypoglycemia, and a neutral effect on body-weight [32]. Vildagliptin is approved in Europe and Latin America, but not in the USA [33]. Vildagliptin is effective as a monotherapy and in combination with metformin and sulfonylureas [34–37]. Vildagliptin added to metformin therapy provides a modest reduction in HbA1c comparable to that of glimepiride, but without the significant weight gain and hypoglycemia that occurs with the sulfonylurea [36]. In a comparison study of vildagliptin versus metformin in drug-naïve Type 2 diabetic patients, metformin clearly had a superior glucose-lowering effect and greater associated weight loss [37]. Vildagliptin has also been associated with a low, but not insignificant, incidence of peripheral edema and liver enzyme elevation [201,202]. Saxagliptin is a DPP-4 inhibitor approved in 2010 and is available in the USA along with sitagliptin [38,39]. The combination of saxagliptin and metformin provided a sustained HbA1c reduction over 52 weeks and was noninferior to glipizide plus metformin, with reduced bodyweight gain and a significantly lower risk of hypoglycemia [40]. In several studies, saxagliptin provided an incremental benefit over placebo of approximately 0.9% when added to metformin, 0.5% when added to glyburide and 0.6% when added to pioglitazone [41–43]. Saxagliptin is metabolized to an active metabolite by CYP3A4/5 [44]. Therefore, levels of saxagliptin and its primary metabolite may be significantly modified when saxagliptin is coadministered with specific strong inhibitors (ketoconazole and diltiazem) or inducers (rifampicin) of CYP3A4/5 isoforms [45].

Alogliptin is another orally administered antidiabetic drug in the DPP-4 inhibitor class, developed by Takeda Pharmaceutical Company (Japan). Alogliptin was approved for use in Japan in April 2010. In 2013, the US FDA approved the drug in three formulations: as a standalone with the brandname Nesina®, combined with metformin using the name Kazano®, and when combined with pioglitazone as Oseni®. Alogliptin is associated with skin reactions, as are several other DPP-4 inhibitors [46].

The glucose-lowering effect of the currently available DPP-4 inhibitors appears to be less than those of the GLP-1 agonists, and these agents do not promote active weight loss [47,48]. Cutaneous hypersensitivity reactions occur in a small percentage of patients treated with the DPP-4 agents. There is increasing concern that DPP-4 inhibitors may also be associated with an increased incidence of pancreatitis [49].

Linagliptin (BI-1356, trade names Tradjenta® and Trajenta®) is a recently approved DPP-4 inhibitor developed by Boehringer Ingelheim (Ingelheim am Rhein, Germany) for treatment of Type 2 diabetes (Figure 1) [50,51]. Linagliptin (once daily) was approved by the FDA on 2 May

Figure 1. Linagliptin.
Linagliptin is differentiated from other DPP-4 inhibitors because it is primarily excreted unchanged via enterohepatic mechanisms, making it an agent of choice in those with renal impairment.

**Pharmacokinetics & pharmacodynamics of linagliptin**

Linagliptin is an orally available xanthine-based noncovalent inhibitor of DPP-4 with a molecular mass of 472.5 Da. Of all approved DPP-4 inhibitors, linagliptin has the highest potency for inhibiting the enzymatic activity of DPP-4 competitively and reversibly with an IC_{50} of approximately 1 nM (compared with 1.75 nM for teneligliptin, 3.8 nM for alogliptin, 6.9 nM for alogliptin, 19 nM for sitagliptin, 62 nM for vildagliptin and 50 nM for saxagliptin). The selectivity of linagliptin for DPP-4 is 10,000-fold higher than towards DPP-9. Linagliptin is concentration dependent, decreasing from approximately 99% at 1 nmol/l to 75–89% at ≥30 nmol/l, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. At high concentrations, where DPP-4 is fully saturated, 70% to 80% of linagliptin remains bound to plasma proteins and 20% to 30% is unbound in plasma. Plasma binding is not altered in patients with renal or hepatic impairment, and there is high-affinity binding to the target DPP-4 in different tissues, predominantly in the kidney [58]. Steady-state concentrations of linagliptin are reached within 2–5 days after once daily administration, with an elimination half-life between 113 and 130 hours. These pharmacokinetic data are valid for all ethnic groups studied [60,61].

**Metabolism**

In *vivo*, linagliptin is hardly metabolized and approximately 90% of the compound is excreted in an unchanged form by the hepatobiliary route via the feces [59,60]. The elimination is rather slow, with a half-life of 70–80 h. Approximately 1–6% of the dose is eliminated via the renal route and excreted in the urine when standard doses of 5 mg are given [62,63].

After oral administration of a single 5-mg dose to healthy subjects, the T_{max} of linagliptin occurred at approximately 1.5 h; the mean plasma AUC was 139 nmol·h/l and the C_{max} was 8.9 nmol/l. Plasma concentrations of linagliptin decline in a biphasic manner with a long terminal half-life (>100 h) related to the saturable binding of linagliptin to DPP-4. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of linagliptin 5 mg, is approximately 12 h. After once-daily dosing, steady-state plasma concentrations of linagliptin 5 mg are reached by the third dose, and the C_{max} and AUC increased by a factor of 1.3 at steady state compared with the first dose. The intra- and inter-subject coefficients of variation for linagliptin AUC were small (12.6 and 28.5%, respectively). The plasma AUC of linagliptin increases in a less than dose-proportional manner in the dose range of 1–10 mg. The pharmacokinetics of linagliptin are similar in healthy subjects and in patients with Type 2 diabetes. Linagliptin exposure (AUC and C_{max}) increases less than
proportionally with the dose. The accumulation half-life is short (8.6–23.9 h), resulting in rapid attainment of a steady state (2–5 days) and little accumulation. All linagliptin that is absorbed into the body binds to the DPP-4 enzyme. The free linagliptin is eliminated relatively rapidly (a rough measure is the accumulation half-life). With a therapeutic 5-mg dose at steady state, the DPP-4 enzyme is fully saturated and, at the Cmax, free linagliptin is available, but directly before the next dose (minimum concentrations) all free linagliptin (non-DPP-4 bound) is eliminated. If a dose is missed, elimination of linagliptin bound to the DPP-4 enzyme starts; although this is a slow process (here, the terminal half-life is the relevant measure). The long terminal half-life (113–131 h) provides sustained inhibition of DPP-4 activity. Inhibition of plasma DPP-4 activity correlates well with linagliptin plasma concentrations, resulting in DPP-4 inhibition of >90% in the two highest dose groups; even 24 h post dose, DPP-4 inhibition is >80%. Following an oral glucose tolerance test 24 h after the last dose, statistically significant reductions of glucose excursions were observed with linagliptin (2.5-, 5- and 10-mg doses) compared with placebo [64]. Since the goal is full DPP-4 inhibition over the entire dosing interval, a 24 h period was determined to be the optimal dosing frequency.

Efficacy of linagliptin

The efficacy of linagliptin was assessed alone (as a monotherapy) and in combination with other commonly used antidiabetic agents.

- Linagliptin monotherapy
  Del Prato et al. evaluated linagliptin 5 mg as a monotherapy for 24 weeks in patients with Type 2 diabetes who were either treatment naive or who had received one oral antidiabetes drug [73]. The mean HbA1c decreased significantly with 5-mg linagliptin (-0.69%; p < 0.0001) after 24 weeks. In patients with baseline HbA1c ≥9.0%, the adjusted reduction in HbA1c was 1.01% (p < 0.0001). After 24 weeks, when compared with placebo, linagliptin decreased fasting plasma glucose by 1.3 mmol/l (p < 0.0001) and 2-h post prandial glucose by 3.2 mmol/l (p < 0.0001). Statistically significant differences were observed for the proinsulin:insulin ratio (p = 0.025) and in parameters for β-cell function, the Homeostasis Model Assessment-%B (HOMA B) (p = 0.049) and the disposition index (p = 0.0005) compared with placebo. The improvement in HbA1C compared with placebo was independent of gender, age, race, prior

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Coadministered drug</th>
<th>Dosing of coadministered drug</th>
<th>Dosing of linagliptin (mg q.d.)</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graefe-Mody et al. (2009)</td>
<td>Metformin</td>
<td>850 mg t.i.d.</td>
<td>10</td>
<td>No interaction</td>
<td>[66]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2011)</td>
<td>Glyburide</td>
<td>1.75 mg (single dose)</td>
<td>5</td>
<td>No interaction</td>
<td>[65]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2010)</td>
<td>Pioglitazone</td>
<td>45 mg q.d.</td>
<td>10</td>
<td>No interaction</td>
<td>[67]</td>
</tr>
<tr>
<td>Friedrich et al. (2011)</td>
<td>Digoxin</td>
<td>0.25 mg q.d.</td>
<td>5</td>
<td>No interaction</td>
<td>[70]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2010)</td>
<td>Simvastatin</td>
<td>40 mg q.d.</td>
<td>10</td>
<td>No interaction</td>
<td>[69]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2011)</td>
<td>Warfarin</td>
<td>10 mg (single dose)</td>
<td>5</td>
<td>No interaction</td>
<td>[71]</td>
</tr>
<tr>
<td>Friedrich et al. (2011)</td>
<td>Ethinylestradiol and levonorgestrel</td>
<td>ethinylestradiol 0.03 mg and levonorgestrel 0.150 mg q.d.</td>
<td>5</td>
<td>No interaction</td>
<td>[72]</td>
</tr>
</tbody>
</table>

q.d.: Once daily; t.i.d.: Three-times daily.
antihyperglycemic therapy, baseline BMI and standard indices of insulin resistance. There was no excess of hypoglycemic episodes in the linagliptin arm compared with placebo. In another randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin, it was shown that GLP-1 plasma concentrations in the linagliptin group increased up to fourfold during meal tests [61]. The glucagon plasma concentrations were consecutively lowered by 24%. These effects led to a significant reduction of the meal-related glucose excursions caused by linagliptin. At the end of 4 weeks, the placebo-subtracted changes of HbA1c were -0.31, -0.37 and -0.28% for the doses of 2.5, 5 and 10 mg of linagliptin, respectively. Kawamori R et al. carried out a randomized trial in Japanese patients with Type 2 diabetes [74]. Daily doses of either 5 or 10 mg of linagliptin were compared with placebo (for 12 weeks) or the disaccharidase inhibitor 0.2 mg of voglibose three-times daily (for 26 weeks). The adjusted mean (95% CI) treatment differences at week 12 were -0.87% (-1.04 to -0.70; p < 0.0001) and -0.88% (-1.05 to -0.71; p < 0.0001) for linagliptin 5 and 10 mg versus placebo. There was a decrease in HbA1c of 0.32% (linagliptin 5 mg; p < 0.0003) and 0.39% (linagliptin 10 mg; p < 0.0001) compared with voglibose. Linagliptin was better tolerated than voglibose. Barnett and coworkers investigated the safety and tolerability of linagliptin in comparison with placebo for the first 18 weeks and glimepiride 1–4 mg for the next 34 weeks [75]. In the initial 18 weeks, the changes in HbA1c were -0.39 and +0.21% in the linagliptin and placebo groups, respectively, with a mean difference of 0.6% in total (95% CI: -0.88 to -0.32; p < 0.0001). At the end of 52 weeks, the mean changes in HbA1c were -0.44 and -0.72% in the linagliptin and glimepiride groups, respectively. However, linagliptin was shown to be associated with less hypoglycemia (2.2 vs 7.8%) and no weight gain (mean change from baseline of -0.2 and +1.3 kg, respectively) compared with the glimepiride group. Therefore, as a monotherapy, linagliptin is associated with a modest reduction in HbA1c (from 0.3 to 0.6%) depending on the dose and duration of treatment, and is associated with less hypoglycemia and no weight gain.

### Linagliptin in combination with metformin

Taskinen et al. assessed the efficacy and safety of linagliptin administered as add-on therapy in 701 patients with inadequate glycemic control on metformin [76]. The linagliptin add-on showed significant reductions compared with placebo in adjusted mean changes from baseline of HbA1c (-0.49 vs 0.15%), fasting plasma glucose (-0.59 vs 0.58 mmol/l) and 2-h postprandial glucose (-2.7 vs 1.0 mmol/l; all p < 0.0001). Hypoglycemic events occurred rarely with an incidence of 0.6% in linagliptin-treated patients and 2.8% in the placebo-treated patients. In both arms, body weight did not change significantly (-0.4 kg in the linagliptin arm vs -0.5 kg in the placebo arm). Haak et al. investigated the efficacy and safety of initial combination therapy with linagliptin plus metformin versus linagliptin or metformin monotherapy in 791 patients with Type 2 diabetes for 24 weeks [77]. The study had a total of six treatment arms with two arms being treated with a free combination of linagliptin (2.5-mg linagliptin plus 500-mg metformin, both twice-daily, or 2.5-mg linagliptin plus 1000-mg metformin, both twice daily). The other four arms were monotherapy arms with linagliptin 5-mg once daily, metformin 500 or 1000 mg twice daily, or placebo. Mean reductions in HbA1c from baseline (8.7%) to week 24 were 1.7, 1.3, 1.2, 0.8 and 0.6% (all p < 0.0001) for linagliptin plus high-dose metformin, linagliptin plus low-dose metformin, high-dose metformin, low-dose metformin and linagliptin, respectively. Hypoglycemia occurred at a similar low rate with linagliptin plus metformin (1.7%) and with

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Coadministered drug</th>
<th>Dosing of coadministered drug</th>
<th>Dosing of linagliptin</th>
<th>Effect on linagliptin exposure</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graefe-Mody et al. (2009)</td>
<td>Metformin</td>
<td>850 mg t.i.d.</td>
<td>10 mg q.d.</td>
<td>No interaction</td>
<td>[66]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2010)</td>
<td>Pioglitazone</td>
<td>45 mg q.d.</td>
<td>10 mg q.d.</td>
<td>No interaction</td>
<td>[67]</td>
</tr>
<tr>
<td>Graefe-Mody et al. (2011)</td>
<td>Glyburide</td>
<td>1.75 mg (single dose)</td>
<td>5 mg q.d.</td>
<td>No interaction</td>
<td>[65]</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>200 mg b.i.d.</td>
<td>5 mg (single dose)</td>
<td>Increases AUC and C&lt;sub&gt;max&lt;/sub&gt; threefold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg q.d.</td>
<td>5 mg q.d.</td>
<td>Decreases AUC and C&lt;sub&gt;max&lt;/sub&gt; by 40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AUC: Area under the curve; b.i.d.: Twice daily; C<sub>max</sub>: Maximum concentration; q.d.: Once daily; t.i.d.: Three-times daily.
metformin alone (2.4%). AE rates were comparable across treatment arms. No clinically significant changes in bodyweight were noted. Gallwitz et al. compared linagliptin to glimepiride as an add-on therapy to metformin in a 2-year randomized, double-blind study [78]. Patients not well controlled on metformin monotherapy with a baseline HbA1c of 7.7% either received 5-mg linagliptin once daily (n = 764) or glimepiride 1–4 mg daily (n = 755). At week 104, adjusted mean changes in HbA1c from a baseline of 7.7% were -0.16% with linagliptin and -0.36% with glimepiride in the full analysis set. The mean dose of glimepiride was 3 mg daily. The hypoglycemia incidence was much lower with linagliptin than with glimepiride (7.5 vs 36.1%; p = 0.0001). Bodyweight decreased on average by 1.4 kg in the linagliptin group, but increased by 1.3 kg in the glimepiride cohort. Cardiovascular events occurred in 12 (2%) patients treated with linagliptin versus 26 (3%) patients on glimepiride, a significant 50% reduction in the relative risk for a combined cardiovascular end point (risk ratio: 0.46; 95% CI: 0.23–0.91; p = 0.0213).

- **Initial combination with pioglitazone**
  Gomis R et al. assessed the efficacy, safety and tolerability of linagliptin (5 mg) administered in combination with pioglitazone (30 mg) in 389 subjects with inadequately controlled Type 2 diabetes [68]. At the end of the 24 weeks of study, there was a reduction of HbA1c of 1.06% in the combination therapy group compared with 0.56% in pioglitazone monotherapy patients. In parallel with the HbA1c reductions, fasting plasma glucose reductions were significantly greater for linagliptin plus pioglitazone (-1.8 mmol/l) than for placebo plus pioglitazone (-1.0 mmol/l), a treatment difference of -0.8 mmol/l (95% CI: -1.2 to -0.4; p = 0.0001). The rate of hypoglycemic events was low (1.2%), all of which were in the linagliptin group, with no severe hypoglycemia reported. The parameters of β-cell function improved.

- **Combination with sulfonylurea**
  Lewin et al. evaluated the addition of linagliptin to inadequately controlled Type 2 diabetes with sulfonylurea monotherapy in a placebo-controlled randomized trial [79]. At the end of 18 weeks, the linagliptin add-on group had a change in HbA1c of -0.47% (-0.70 to -0.24; p < 0.0001). When compared with that of the placebo add-on group, subjects in the linagliptin group achieved the target HbA1c of <7.0% after 18 weeks (15.2% in the linagliptin group vs 3.7% in the placebo group; odds ratio [OR]: 6.5; 95% CI: 1.7–24.8; p = 0.007). Similarly, patients in the linagliptin group achieved a mean HbA1c reduction of ≥0.5% compared with those in the placebo group (57.6 vs 22.0%; OR: 5.1; 95% CI: 2.7–9.6; p < 0.0001). The overall frequency of AEs was similar between the linagliptin and placebo groups (42.2 vs 42.9%). The incidence of hypoglycemic events did not differ significantly between the two groups (5.6 vs 4.8%).

- **Metformin & sulfonylurea add on**
  A multicenter, 24-week, randomized, double-blind, parallel-group study in 1058 patients comparing linagliptin (5 mg once daily) with placebo as an add-on therapy in patients treated with metformin and a sulfonylurea was reported by Owens et al. [80]. After 24 weeks of double-blind treatment, patients receiving add-on linagliptin had a significantly greater reduction in HbA1c (with a placebo-corrected adjusted mean change of -0.62%; 95% CI: -0.73 to -0.50; p < 0.0001) as well as fasting plasma glucose (placebo-corrected adjusted mean change from baseline at week 24: -0.7 mmol/l; 95% CI: -1.0 to -0.4; p < 0.0001). Among patients with a baseline HbA1c ≥7.0%, significantly more patients in the linagliptin group achieved HbA1c <7.0% by 24 weeks (29.2 vs 8.1%; OR: 5.5; p < 0.0001) and significantly more patients in the linagliptin group achieved a reduction in HbA1c of ≥20.5% (58.2 vs 30.2%; OR: 3.4; p < 0.0001). Symptomatic hypoglycemia occurred in 16.7 and 10.3% of the linagliptin and placebo groups, respectively, but severe hypoglycemia was less frequent in the linagliptin group than in the placebo group (2.7 vs 4.8% of participants experiencing a hypoglycemic episode, respectively).

- **Insulin add-on**
  Linagliptin was studied as an add-on therapy in a placebo-controlled, 52-week study of 1261 patients treated with basal insulin alone or in combination with metformin and/or pioglitazone [81]. The background dose of basal insulin was kept stable for up to 24 weeks, but later it was slightly adjusted (week 52: linagliptin +2.6 IU/day and placebo +4.2 IU/day; p < 0.003). The placebo-adjusted mean reduction in HbA1c from baseline to week 24 was...
was observed in the linagliptin add-on therapy risk of hypoglycemia or additional weight gain -10.4 ± 4.7 mg/dl (p = 0.0280). No additional baseline in fasting plasma glucose at week 24 was adjusted mean ± standard error change from placebo; OR: 2.06; p = 0.0071). The placebo -reduction of ≥ group were more likely to achieve an HbA1c SGLT2 inhibitor add on patients, respectively.

- Combination of metformin & pioglitazone (triple therapy)
Linagliptin, in combination with metformin and pioglitazone, improved glycemic control without weight gain or hypoglycemia in patients with inadequately managed Type 2 diabetes in a randomized, placebo-controlled trial [83]. Either linagliptin 5 mg (n = 183) or placebo (n = 89) was added to the metformin and pioglitazone combination. The placebo-adjusted mean ± standard error change from baseline in HbA1c was -0.58 ± 0.13% (p < 0.0001). In patients with baseline HbA1c≥7.0%, 32.4% in the linagliptin add-on group and 13.8% in the placebo add-on group achieved HbA1c <7.0% (OR: 2.94; p = 0.0033). Patients in the linagliptin add-on group were more likely to achieve an HbA1c reduction of≥0.5% (65.4% linagliptin vs 49.4% placebo; OR: 2.06; p = 0.0071). The placebo-adjusted mean ± standard error change from baseline in fasting plasma glucose at week 24 was -10.4 ± 4.7 mg/dl (p = 0.0280). No additional risk of hypoglycemia or additional weight gain was observed in the linagliptin add-on therapy group when compared with placebo.

- SGLT2 inhibitor add on
Friedrich et al. investigated potential drug–drug interactions between linagliptin and the novel SGLT2 inhibitor BI10773 (empagliflozin) in healthy volunteers at doses of 5-mg linagliptin daily and 50-mg BI10773 daily [84]. The administration of linagliptin had no effect on the extent of absorption of BI10773; although there was a slight, clinically nonsignificant reduction in the absorption rate. Co-administration of BI10773 had no effect on the extent or rate of absorption of linagliptin. BI10773 alone and in combination with linagliptin led to a clinically relevant excretion of glucose in urine due to the action of the SGLT2 inhibitor. DPP-4 inhibition was similar following linagliptin administration with BI10773 or alone. Both BI10773 and linagliptin were well tolerated.

---

**Effects on lipids**
As an add-on therapy to metformin and sulfonylurea, linagliptin has had no significant effects on lipid profiles [81]. In one study, hyperlipidemia was reported in 2.7% of subjects with linagliptin added to pioglitazone as compared with 0.8% for those in the placebo arm [68]. The lipid changes seen in the overall program were not clinically significant.

**Effects on weight**
Of note, in clinical trials, metformin, GLP-1 analogs, α-glucosidase inhibitors and DPP-4 inhibitors have been associated with stable weight or weight loss, whereas thiazolidinedione, sulfonylureas and glinides have been associated with weight gain [85]. There have been no statistically significant weight changes noted when linagliptin is used as a monotherapy or as an add-on to metformin with or without a combined sulfonylurea [73,75–78]. Minor increases in weight were seen when linagliptin was added to pioglitazone, with an adjusted mean difference between groups of 1.1 kg (95% CI: 0.2–2.0; p = 0.014) [68].

**Effects on pancreatic β-cell function**
In a randomized trial carried out by Del Prato et al., statistically significant differences were observed in the proinsulin:insulin ratio (p = 0.025) and in parameters of β-cell function, the HOMA B (p = 0.049) and the disposition index (p = 0.0005) as compared with placebo [73]. Similar findings of improvement in β-cell function and postprandial glucose were confirmed in a pooled analysis of six randomized, placebo-controlled trials [86]. In these trials, there was a total of 2960 subjects, 53.8% had over a 5-year duration of diabetes, and subjects had a mean ± standard deviation age of 56.5 ± 10.2 years, BMI of 29.2 ± 5.1, HbA1c of 8.2 ± 0.9%, fasting plasma glucose of 167.1 ± 44.9 mg/dl, and exposure to linagliptin of 163 ± 33 days. The mean ± standard deviation baseline HOMA B and postprandial glucose for linagliptin vs placebo were 54.6 ± 101.6 versus...
of treatment, the placebo-adjusted mean ± standard error change from baseline in HOMA B with linagliptin was 16.5 ± 4.6 mU/l/mmol/l (p = 0.0003). Similarly, after 24 weeks of treatment, the placebo-adjusted mean change in post prandial glucose for linagliptin was -53.7 ± 8.6 mg/dl (p < 0.0001).

Preclinical safety

- Carcinogenesis, mutagenesis & impairment of fertility

Linagliptin did not increase the incidence of tumors in male and female rats in a 2-year study at doses of 6, 18 and 60 mg/kg [80]. The highest dose of 60 mg/kg is approximately 418-times the clinical dose of 5 mg/day based on AUC exposure. Linagliptin did not increase the incidence of tumors in mice in a 2-year study at doses up to 80 (males) and 25 mg/kg (females), or approximately 35- and 270-times the clinical dose based on AUC exposure. Higher doses of linagliptin in female mice (80 mg/kg) increased the incidence of lymphoma at approximately 215-times the clinical dose based on AUC exposure. Linagliptin was not mutagenic or clastogenic, with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes and an in vivo micronucleus assay. In fertility studies in rats, linagliptin had no adverse effects on early embryonic development, mating, fertility or bearing live young up to the highest dose of 240 mg/kg (approximately 943-times the clinical dose based on AUC exposure) [80].

- Potential pleiotropic effects of linagliptin

Linagliptin improves wound healing in the rodent model of ob/ob mice. Strong expression of DPP-4 in skin from healthy and diabetic (ob/ob) mice, and keratinocytes has been shown using immunohistochemistry [88]. Upon full-thickness excision wounding in healthy mice, DPP-4 expression decreases over a period of 3 days after injury and the enzyme remains absent in the late phase of wound repair. By contrast, in acute wounds of diabetic mice, DPP-4 expression is absent. DPP-4 protein, however, is expressed in the late phase of wound repair. This inverse regulation of DPP-4 protein in diabetic versus nondiabetic skin seems to indicate a functional basis of the potentially positive action of linagliptin in general wound healing processes [88]. In animal models of inflammatory bowel diseases, it was shown that DPP-4 inhibitors have anti-inflammatory properties, probably mediated via T-cell regulation or the inhibition of degradation of GLP-2, which favors proliferation and repair of the colonic mucosa [92]. Klein et al. investigated the anti-inflammatory effects of linagliptin in artificially induced (with dextran sulfate sodium [DSS]) colitis in Balb/c mice [90]. Linagliptin significantly reduced proinflammatory cytokines, elevated active GLP-2 levels and reduced clinical changes (colon length, histology and stool consistency) in DSS-treated animals. Klein et al. also investigated the effect of linagliptin on liver tissue composition in diet-induced obese mice [99]. Treatment of the animals with linagliptin improved glycemic parameters and reduced the liver fat content measured by magnetic resonance spectroscopy. Changes in liver fat content were visible as early as 2 weeks of treatment. The histological examination revealed significantly less hepatic steatosis and inflammation in the linagliptin group. The correlation between liver lipid content and hepatic triglyceride levels was $r^2 = 0.565$ (p = 0.0001). In an artificial myocardial ischemia model in rats, linagliptin significantly reduced the proportion of infarcted tissue relative to the total area at risk, as well as the absolute infarction size, an effect mediated by a significant elevation of endogenous GLP-1 plasma concentrations as a result of DPP-4 inhibition. Left ventricular left end diastolic and systolic pressure, as well as all echocardiography parameters, were similar between groups, with a significant improvement in isovolumetric contractility indices [91].

Clinical safety studies

In the cumulative studies performed, linagliptin was well tolerated and not associated with specific side effects in doses up to 120-fold the therapeutic dose of 5 mg [87]. The most frequently reported AEs for linagliptin versus placebo were headache (21 vs 38%), influenza-like illness (11 vs 4%) and nausea (4 vs 6%). Nasopharyngitis, which has been associated with other DPP-4 inhibitors [92], was reported in 5.8% of linagliptin patients versus 5.5% of placebo patients in a pooled analysis of placebo-controlled trials that included the four pivotal trials. Cough, hyperlipidemia and weight increase were the only AEs reported in at least 2% of patients treated with linagliptin and at a rate at least twofold greater than with placebo. Hyperlipidemia was
reported in 2.7 and 0.8%, and weight increase in 2.3 and 0.8% of the linagliptin and placebo groups, respectively, when linagliptin was used as an add-on to pioglitazone. When linagliptin was used as add-on to metformin and sulfonylurea, cough was reported in 2.4% of patients in the linagliptin group and 1.1% of patients in the placebo group [88]. Hypoglycemia is an outcome of special interest with therapies for Type 2 diabetes mellitus, since the aim of therapy is to reduce blood glucose, but excessive reductions will lead to hypoglycemia. Although the expected incidence of hypoglycemia with DPP-4 inhibitors is low because their effect is glucose dependent [93], linagliptin was closely monitored for risk of hypoglycemia, using the classification proposed by the American Diabetes Association [94]. The overall hypoglycemia incidence was not increased during linagliptin treatment in the studies as long as linagliptin was not given in a combination with a sulfonylurea [87,203]. An analysis of vital signs and relevant biomarkers across 12 placebo-controlled trials, including the four pivotal trials, has shown no clinically meaningful changes in vital signs (blood pressure and pulse rate) in linagliptin-treated subjects [87,203]. Few changes have been seen in laboratory parameters. An increase in uric acid was found in 2.7% of patients receiving linagliptin compared with 1.3% in the placebo group [203]. Schernthaner et al. conducted a pooled analysis from eight randomized clinical Phase III trials lasting ≥24 weeks to assess the safety and tolerability of linagliptin [95,204]. A total of 2523 patients received linagliptin 5 mg once daily and 1049 patients received placebo. The incidence was calculated with descriptive statistics for the overall population and for subgroups of elderly and renally impaired patients. The overall incidence of AEs or serious AEs with linagliptin was similar to placebo (AEs: 55.8 vs 55.0%; and serious AEs: 2.8 vs 2.7%). Overall, aggregated infection incidence was similar in the linagliptin and placebo groups (19.5 and 21.4%, respectively). Similar or reduced incidence of AEs versus placebo were seen with linagliptin for upper respiratory tract infection (3.3 vs 4.9%), headache (2.9 vs 3.1%), urinary tract infection (2.2 vs 2.7%), blood and lymphatic disorders (1.0 vs 1.2%), hypersensitivity (0.1 vs 0.1%), hepatic enzyme increase (0.1 vs 0.1%) and serum creatinine increase (0.0 vs 0.1%). There was a slight increased frequency of nasopharyngitis (5.9 vs 5.1%) and cough (1.7 vs 1.0%) with linagliptin. Hypoglycemia incidence was 8.2% for linagliptin and 5.1% for placebo; incidence was higher in patients with a background of sulfonylurea therapy (20.7 and 13.3%, respectively). In patients not receiving concomitant sulfonylurea, the hypoglycemic incidence with linagliptin was very low in both the total population (<1%), and elderly and renally impaired patients (both <1%).

Preclinical studies carried out with other DPP-4 inhibitors such as vildagliptin and saxagliptin have raised concerns due to necrotic skin lesions observed in monkeys [95,96,205]. No such lesions have appeared in the linagliptin trials, although there is an increased incidence of hypersensitivity-related reactions, including cutaneous manifestations, which also occur with other DPP-4 inhibitors. The FDA has requested a long-term postmarketing study assessing the impact of hypersensitivity and skin reactions. The FDA has also developed an elaborate procedure for evaluating potential cardiovascular risk of diabetes drugs [97]. For the DPP-4 class as a whole, there is no suggestion of a detrimental effect. Epidemiologic evidence obtained from health insurance data showed no excess risk of all-cause hospital admission or death compared with other glucose-lowering agents among newly treated patients with Type 2 diabetes [98]. Gallwitz et al. conducted a 2-year study comparing linagliptin with a sulfonylurea in terms of cardiovascular events as a safety outcome [78]. In this study, adults with Type 2 diabetes mellitus receiving ongoing stable metformin (21500 mg/day for ≥10 weeks) were randomized to double-blind linagliptin 5 mg/day (n = 764) or glimepiride 1–4 mg/day (n = 755), and prospectively followed for pre-specified cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalized unstable angina). The linagliptin group showed a significant reduction in the rate of cardiovascular events (relative risk: 0.46; 95% CI: 0.23–0.91; p = 0.02). These results have been further supported by a meta-analysis of eight randomized, double-blind controlled trials with a total of 5239 patients [99]. Of these, 3319 patients received linagliptin while 1920 patients received a comparator compound (977 received placebo, 781 glimepiride 1–4 mg/day and 162 voglibose). The overall, adjudicated primary cardiovascular events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving a comparator compound,
yields a significantly lower hazard ratio for the linagliptin group. The FDA has asked for further confirmatory long-term cardiovascular studies. Boehringer Ingelheim has proposed the CAROLINA study [206], a large trial with a planned recruitment of 6000 patients comparing linagliptin with glimepiride for cardiovascular outcomes. Boehringer Ingelheim has proposed a different study CARMELINA [201], which is now recruiting subjects, to compare the addition of linagliptin vs placebo with ongoing therapy with the end points of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke and hospitalization for unstable angina pectoris.

**Concern regarding pancreatitis & pancreatic cancer**

Initially, one of the great excitement about incretin-based therapies was that GLP-1 appeared to stimulate β-cell regeneration. In preclinical studies in animal models, incretin-based therapies were associated with β-cell hypertrophy, β-cell proliferation, a reduction in β-cell apoptosis and an increase in neogenesis from islet elements, with overall β-cell regeneration and increased mass. A pancreatic autopsy study reported that there was a fourfold increase in both α- and β-cell mass in people who had diabetes and were receiving incretin-based therapies when compared with that of nondiabetic patients and diabetic patients who had been receiving other therapies [100]. Recently, Butler et al. stated that incretin-based therapies are associated with increased acute pancreatitis, chronic pancreatitis, and pancreatic and medullary carcinoma of the thyroid [49]. In a counterpoint, Nauck argued that the benefits of incretin therapy far outweigh the risks [101]. He added that although serum lipase is elevated in patients who are taking incretin-based therapies, this does not necessarily indicate pancreatitis.

**Special populations**

**Renal impairment**

Linagliptin is primarily excreted through the hepatobiliary route, with only minor renal contribution. A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg) in patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 ml/min), moderate (30 to <50 ml/min) and severe (<30 ml/min), as well as patients with end-stage renal disease on hemodialysis [102]. In addition, patients with Type 2 diabetes mellitus and severe renal impairment (<30 ml/min) were compared with Type 2 diabetes mellitus patients with normal renal function. Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of approximately 1.7-fold was observed compared with controls. Exposure in Type 2 diabetes mellitus patients with severe renal impairment was increased by approximately 1.4-fold. Steady-state predictions for AUC of linagliptin in patients with end-stage renal disease indicated comparable exposure to that of patients with moderate or severe renal impairment. Linagliptin is not eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis.

Data were pooled from three randomized studies from the global Phase III program of linagliptin (5 mg daily) in patients with Type 2 diabetes to compare steady-state trough concentrations of linagliptin [103]. Linagliptin plasma concentrations were available for 969 patients who were determined by estimated glomerular filtration rate to have normal renal function (n = 438), or mild (n = 429), moderate (n = 44) or severe (n = 58) renal impairment. In patients with normal renal function, the geometric mean linagliptin trough concentration (coefficient of variation) was 5.93 nmol/l (56.3%). In patients with mild, moderate or severe renal impairment, geometric mean concentrations were 6.07 nmol/l (62.9%), 7.34 nmol/l (58.6%) and 8.13 nmol/l (49.8%), respectively. The efficacy and safety of linagliptin was evaluated in Type 2 diabetes mellitus patients with severe renal impairment in a 12-week double-blind study versus placebo [104]. Most patients (80.5%) received insulin as background therapy, alone or in combination with other oral agents such as sulfonylurea and pioglitazone. There was a further 40-week treatment period during which dose adjustments in antidiabetes background therapies were allowed. Linagliptin provided significant improvements in HbA1c (-0.59% compared with placebo after 12 weeks, from a mean baseline HbA1c of 8.2%). After 52 weeks, the observed difference in HbA1c over placebo was -0.72%. Bodyweight did not differ significantly between the groups. The observed incidence of hypoglycemia in patients treated with linagliptin was higher than placebo due to an increase in asymptomatic
hypoglycemic events. However, no severe hypoglycemic events were reported. Based on the collective findings, the FDA determined that no dose adjustment of linagliptin was necessary in renal impairment [87].

- **Hepatic impairment**
  An open-label, parallel-group, single-center study enrolled patients with mild (n = 8), moderate (n = 9) or severe (n = 8) hepatic impairment and healthy subjects (n = 8). Groups were matched for age, weight and gender. Treatment of patients with mild, moderate or severe hepatic impairment with 5 mg of linagliptin for 7 days did not result in an increase in linagliptin levels compared with patients with normal hepatic function [105]. The FDA has concluded that no dose adjustment is warranted in patients with liver disease [87].

- **Geriatric population**
  No dose adjustment is recommended based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis [203]. Barnett et al. assessed the effectiveness of linagliptin 5 mg in elderly patients (≥70 years) with Type 2 diabetes with HbA1c of ≥7% in a 24-week randomized, placebo-controlled trial [106]. At week 24, placebo-adjusted mean change in HbA1c with linagliptin was -0.64% (95% CI: -0.81 to -0.48; p < 0.0001) [106]. Overall safety, tolerability and hypoglycemia events were the same in the two groups. In a study of insulin-treated patients over the age of 70 years, there was no increased risk of hypoglycemia [82].

- **Pediatric population**
  Boehringer Ingelheim intends to pursue the indication for pediatric use and studies are currently being designed.

**Conclusion**

DPP-4 is a membrane-associated protein present in many tissues, including the kidneys, intestine, hepatocytes, vascular endothelium and lymphocytes [107]. DPP-4 has a relatively non-specific enzymatic action involving cleavage of oligopeptides, including a variety of regulatory peptides such as YY (involved in gastrointestinal functions), neuropeptide Y (involved in regulation of food intake) and BNP (involved in vasodilation and natriuresis). Given the fairly ubiquitous nature of DPP-4-related functions, it is reassuring that the side effect profiles of the currently available DPP-4 inhibitors have been relatively benign. The unfortunate saga of the thiazolidinediones, with their known effect of fluid retention, which leads to heart failure in susceptible patients as well as the possible acceleration of coronary artery disease, has raised concerns about unfavorable long-term cardiac effects of all antidiabetes medications. The FDA has noted that linagliptin is not as effective as metformin or glimepiride as a monotherapy [87]. However, the potential advantage of this agent, similar to other DPP-4 inhibitors, is its glucose-dependent insulin stimulation mechanism, which reduces the risk of hypoglycemia. One of the considerable advantages of linagliptin and other incretin-based therapies is the minimal risk of hypoglycemia, which is one of the most important barriers in efforts to achieve normoglycemia in diabetes management. In the ACCORD study, improvement in HbA1c levels in the intensively treated groups was associated with a 2.5-fold increase in hypoglycemic events [108,109]. The ACCORD trial was terminated due to increased cardiovascular mortality in the intensively treated groups. The increased mortality in that group could have been a result of the unfavorable effect of hypoglycemia in susceptible patients, such as those with underlying coronary disease [110]. There was no systematic attempt in the ACCORD study to avoid hypoglycemia. It is conceivable that the use of agents such as linagliptin and other DPP-4 inhibitors could allow the benefits of glucose lowering to proceed without increasing the risk of hypoglycemia. In patients with congestive heart failure, renal failure and liver disease, hypoglycemia can be more severe and refractory to treatment. In the elderly, hypoglycemic events increase the risk of injurious falls as well as coronary events. Linagliptin and other DPP-4 inhibitors could potentially replace sulfonylureas in these vulnerable patients.

Linagliptin, as a result of its enterohepatic excretion, has the particular advantage of dose invariance in renally impaired patients, unlike the other DPP-4 inhibitors. In these patients, metformin is contraindicated and sulfonylurea treatment can provoke long-lasting refractory hypoglycemia. Pioglitazone causes fluid retention, risking congestive heart failure in nephropathy patients. Based on these considerations, linagliptin is a preferred agent in Type 2 diabetics with renal complications.
Linagliptin for the treatment of Type 2 diabetes

**Future perspective**

To date, there is a lack of long-term safety data with the DPP-4 inhibitors, especially those related to generalized DPP-4 inhibition. Studies of longer duration and careful postapproval surveillance are needed, and have been requested by the FDA. Studies are now underway to assess the safety of linagliptin, particularly in subjects with multiple cardiovascular risks. These large-scale long-duration studies will not only characterize the long-term safety of linagliptin, but should also shed light on possible β-cell preservation. Further data to support the concept of β-cell preservation would markedly enhance the desirability of the use of linagliptin and other DPP-4 inhibitors. Initial data also suggest fewer cardiac events in linagliptin-treated patients compared with other comparators. Confirmation in long-term studies (MARLINA [202], CARMELINA and CAROLINA) would strongly support the use of this agent as an initial treatment for Type 2 diabetes.

**Acknowledgements**

As the sponsor of linagliptin, Boehringer Ingelheim (Ingelheim am Rhein, Germany) was given the opportunity to review for factual accuracy at the request of the journal’s editors.

**Financial & competing interests disclosure**

M Rendell has been an investigator on several linagliptin studies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

**References**

Papers of special note have been highlighted as:

- of interest
- of considerable interest


Viewpoint that raises concern about the long-term potential risks of incretin therapy.


Long-term study that directly compared linagliptin and glimepiride as long-term treatment of Type 2 diabetes.


Good analysis of second-line options available after metformin in Type 2 diabetes.


Emphasizes the risks of hypoglycemia in treating diabetes.


Explains the current strategies to allow new diabetes treatments to come to the market.


Emphasizes that the benefits of incretin treatment outweigh the risks.


Results from the ACCORD trial have emphasized the risks of hypoglycemia on cardiovascular outcomes.

Websites


CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes. http://clinicaltrials.gov/ct2/show/NCT01243424?term=NCT01243424&rank=1

CARMELINA: Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus at High Vascular Risk. http://clinicaltrials.gov/ct2/show/NCT01897532?term=NCT01897532&rank=1


Authoritative US FDA analysis of linagliptin.