

# Use of DPP-4 inhibitors in type 2 diabetes: focus on sitagliptin

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**Abstract:** Inhibition of dipeptidyl peptidase-4 (DPP-4) prevents the inactivation of glucagon-like peptide-1 (GLP-1). This increases circulating levels of active GLP-1, stimulates insulin secretion and inhibits glucagon secretion, which results in lowering of glucose levels and improvement of the glycemic control in patients with type 2 diabetes. This review summarizes experiences with DPP-4 inhibition in the treatment of type 2 diabetes, with a focus on sitagliptin. Sitagliptin has in several clinical studies been shown to improve metabolic control in type 2 diabetes, both when used as monotherapy and when used in combination with metformin, sulfonylurea, thiazolidinediones or insulin. The reduction in HbA<sub>1c</sub> is ≈0.6% to 1.0% from baseline levels of 7.5% to 8.7% over 6 to 12 months therapy. Sitagliptin has a favorable safety profile, is highly tolerable, and there is a minimal risk of hypoglycemia. Furthermore, sitagliptin is body weight neutral or induces a slight body weight reduction. Sitagliptin may be used in the early stages of type 2 diabetes in combination with metformin or other treatments in subjects with inadequate glycemic control on these treatments alone. Sitagliptin may also be used in monotherapy and, finally, sitagliptin may be used in combination with insulin in more advanced stages of the disease.

**Keywords:** glucagon-like peptide-1, dipeptidyl peptidase-4, type 2 diabetes, sitagliptin, treatment

## Introduction

Hyperglycemia is a key factor underlying complications of type 2 diabetes, and, therefore, reducing hyperglycemia is a critical aim of treatment of the disease. Improving hyperglycemia has thus been shown to reduce the risk of microvascular complications and may also reduce macrovascular complications.<sup>1,2</sup> The basis for treatment is lifestyle changes with increased physical activity and dietary modifications. If these treatments are not sufficient, pharmacological treatment with metformin is recommended.<sup>3</sup> However, due to the progressive nature of the disease, additional pharmacological treatment is often required. Several options exist: sulfonylureas, thiazolidinediones, meglitinides,  $\alpha$ -glucosidase inhibitors and insulin.<sup>3,4</sup> There are, however, limitations with these pharmacological treatments, such that even with aggressive treatment using these approaches, glycemic control often deteriorates. Furthermore, current therapy is often associated with adverse events. These adverse events include hypoglycemia with sulfonylureas and insulin, gastrointestinal discomfort with biguanides (such as metformin), and increased body weight, edema and cardiac insufficiency with thiazolidinediones.<sup>5-8</sup> Furthermore, the current therapies do not target all pathophysiological aspects of type 2 diabetes. Thus, dysregulation of glucose metabolism in type 2 diabetes is caused by a combination of insulin resistance, impaired insulin secretion, augmented glucagon

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secretion and reduced  $\beta$ -cell mass.<sup>9–12</sup> Whereas insulin resistance is treated by biguanides and thiazolidinediones, and insulin secretion is treated by sulfonylureas, no therapy treats the hypersecretion of glucagon and the reduced  $\beta$ -cell mass. There are thus several unmet needs in the treatment of diabetes which urge the development of novel treatment.

Recently, several new approaches have emerged to meet these challenges. These novel therapies include the amylin analog pramlintide and the GLP-1 receptor agonists, including exenatide and liraglutide.<sup>13–15</sup> Another novel class of compounds is inhibitors of the enzyme dipeptidyl peptidase-4 (DPP-4). The DPP-4 inhibitors, which prevent the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), increase the endogenous concentrations of these hormones which prolongs their actions and improves glycemia.<sup>16–20</sup> Several DPP-4 inhibitors have been developed and are in various stages of clinical development. Sitagliptin, vildagliptin and saxagliptin are approved for use in several countries.<sup>20</sup> This article reviews evidence for clinical use of DPP-4 inhibitors, with a focus on sitagliptin.

## Incretin-based therapy

GLP-1 is released from the gut following meal ingestion and GLP-1 in turn stimulates insulin secretion and inhibits glucagon secretion, which reduces glucose levels.<sup>16,17</sup> GLP-1 is, however, rapidly inactivated by the enzyme DPP-4, which cleaves the two N-terminal amino acids of the hormone making it largely inactive.<sup>16</sup> This process is efficient; the half-life of active GLP-1 is less than 2 minutes. Inhibition of DPP-4 prevents therefore the rapid inactivation of GLP-1. A major mechanism underlying the antidiabetic action of the DPP-4 inhibitors is thus the increased concentrations of active GLP-1 as has been demonstrated by vildagliptin following meal ingestion.<sup>21</sup> As a consequence, DPP-4 inhibition increases insulin secretion and inhibits glucagon secretion, which results in inhibition of hepatic glucose production,

as demonstrated for vildagliptin.<sup>21–23</sup> These actions reduce both fasting and prandial glucose levels and the 24-hour glucose profile, as has been shown for NVP-DPP728 and sitagliptin.<sup>24,25</sup> Rodent studies have also shown that DPP-4 inhibitors (vildagliptin and sitagliptin) increase islet mass and normalize islet cell topography in diabetes models in mice.<sup>26,27</sup> This would suggest that DPP-4 inhibition targets the important islet dysfunctions in type 2 diabetes. It should be emphasized, however, that no evidence of increased  $\beta$ -cell mass by DPP-4 inhibitors exists in humans.

DPP-4 inhibition has been shown to be efficient in improving glycemia both as monotherapy and as add-on to metformin, sulfonylurea and thiazolidinediones in subjects with inadequate glycemic control. DPP-4 inhibition has also been shown to be safe, highly tolerated and body-weight neutral.<sup>18–20</sup> In fact, DPP-4 inhibition meets several of the challenges of the treatment of today – it improves glycemia with little risk for hypoglycemia, it does not increase body weight, it is safe with very little risk for adverse events, and, due to its targeting of the key islet defects, it has the potential to modify the disease process.

## Sitagliptin – pharmacokinetics and mechanisms of action

### Structure and pharmacokinetics

Sitagliptin is a triazolopiperazine derivative (Figure 1).<sup>10</sup> It is orally active and it selectively and reversibly inhibits DPP-4 compared to inhibition of other members of the DPP family. Thus, *in vitro* studies have shown that at 18 nmol/L, sitagliptin inhibits DPP-4 by 50% whereas 48  $\mu$ mol/L is required to inhibit DPP-8 by 50% and >100  $\mu$ mol/L is required to inhibit DPP-9 by 50%.<sup>28</sup> The pharmacokinetics of sitagliptin have been examined in both healthy subjects<sup>29</sup> and in subjects with type 2 diabetes<sup>30</sup> with no difference between these groups. Sitagliptin is rapidly absorbed after oral ingestion with an 87% bioavailability after intake of a

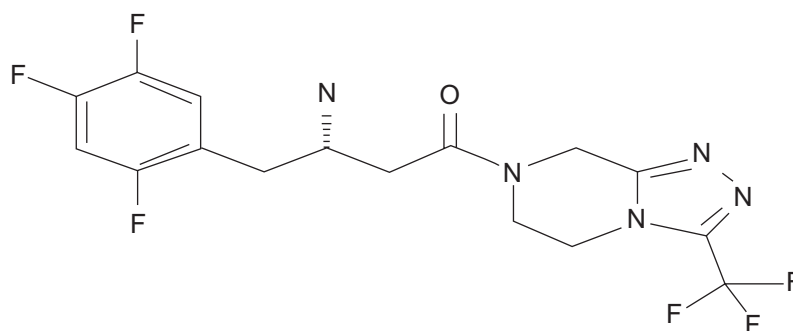


Figure 1 Structure of sitagliptin.

single 100 mg tablet.<sup>31</sup>  $C_{max}$  is observed within 1 to 2 hours and the half-life of the compound is  $\approx$ 12 hours.<sup>31</sup> Sitagliptin is minimally metabolized and  $\approx$ 80% of the compound is excreted unchanged in the urine.<sup>32</sup> Renal excretion is achieved through a combination of active secretion and glomerular filtration.<sup>29</sup> Renal insufficiency increases circulating levels of sitagliptin in that plasma levels of sitagliptin are increased by 2-fold in patients with moderate renal impairment (creatinine clearance 30–50 mL/min) and by 4-fold in patients with severe renal impairment (creatinine clearance  $<$ 30 mL/min), making dose adjustments recommended in these patients.<sup>33</sup> Hepatic insufficiency, obesity and old age do not seem to alter the pharmacokinetics of sitagliptin and no drug interactions have been observed for the compound.

## Mechanisms of action

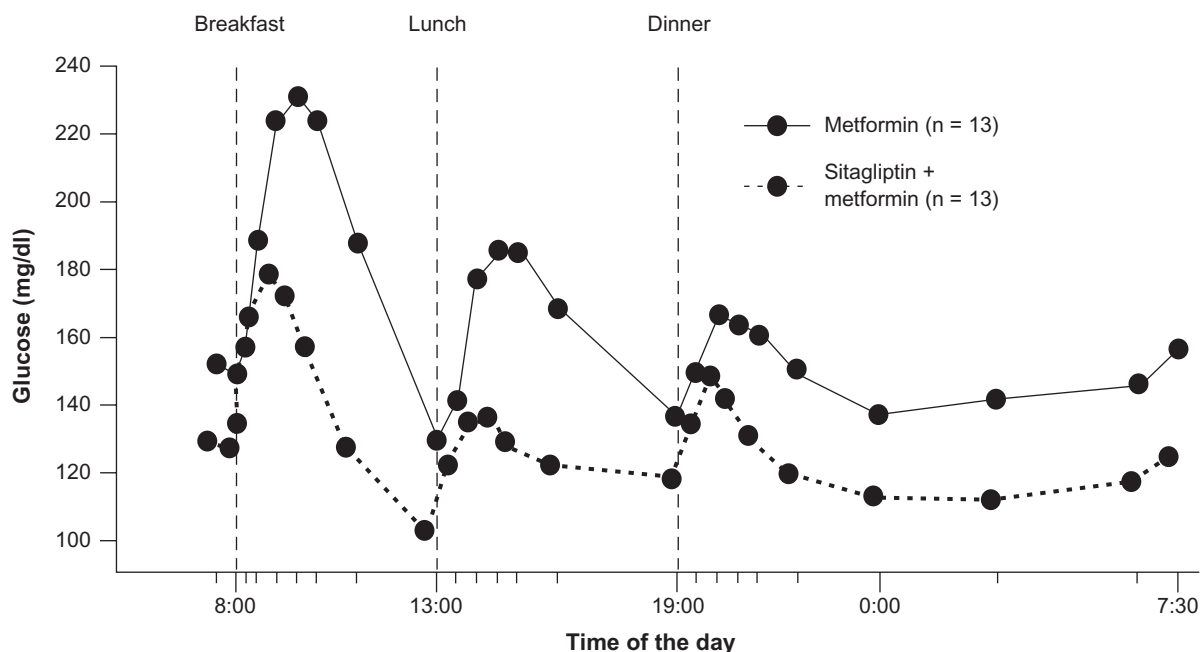
Sitagliptin rapidly inhibits DPP-4 after oral ingestion, and within 1 hour, DPP-4 activity, as determined in plasma, is inhibited by more than 90%.<sup>30</sup> The duration of DPP-4 inhibition is such that the drug can be dosed once daily. The inhibition of DPP-4 activity is dose-dependent and is sustained after multiple dosages, as demonstrated in studies up to 28 days.<sup>30,33,34</sup> Active GIP and GLP-1 levels are increased by sitagliptin by approximately 2- to 3-fold after meal ingestion or oral glucose.<sup>30,33,34</sup> This results in increased insulin secretion as judged from increased insulinogenic index<sup>35–40</sup>

and the homeostasis model of assessment of  $\beta$ -cell function (HOMA- $\beta$ ).<sup>36–46</sup> Improved  $\beta$ -cell function is also evident from reduced proinsulin to insulin ratio.<sup>38,41–44,47</sup> Sitagliptin also reduces glucagon levels,<sup>25,30</sup> although this needs to be examined in more detail. The improved islet function by sitagliptin results in reduction of both fasting glucose and prandial glucose as revealed in different studies in subjects with type 2 diabetes.<sup>25,36,48,49</sup> In fact, the entire 24-hour glucose profile is reduced by sitagliptin, as is evident from a study examining addition of sitagliptin to ongoing metformin therapy compared to metformin treatment alone (Figure 2).<sup>25</sup>

## Sitagliptin – clinical effects in monotherapy

### Placebo-controlled studies

Sitagliptin was initially evaluated as monotherapy for 12 weeks in dose-finding studies in drug-naïve patients with type 2 diabetes. At the dose of 100 mg, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was reduced by sitagliptin by 0.6% from a baseline of 7.7% in one study comprising 555 subjects<sup>50</sup> and by 0.8% from a baseline of 7.8% in another study of 743 subjects.<sup>45</sup> A subsequent placebo-controlled, multi-center 18-week study in 521 patients showed that sitagliptin at 100 mg or 200 mg once daily reduced HbA<sub>1c</sub> by 0.6% and 0.5%, respectively, from a baseline of 8.1%<sup>42</sup> and a 24-week study using sitagliptin at 100 mg or 200 mg daily in drug-naïve patients with a mean baseline



**Figure 2** 24-hour plasma glucose profile in patients with type 2 diabetes after four weeks treatment with sitagliptin (100 mg daily) added to ongoing treatment with metformin compared to patients continued with metformin alone. Reproduced with permission from Braz R, Xu L, Dalla Man C, et al. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and beta-cell function in patients with type 2 diabetes. *Diabet Obes Metab*. 2007; 9:186–193.<sup>25</sup> Copyright © 2007 Wiley-Blackwell.

HbA<sub>1c</sub> of 8.0% (n = 741) showed a reduction of 0.8% and 0.9%, respectively.<sup>41</sup> The improved glycemia during monotherapy with sitagliptin is sustained over at least 2 years, as shown in a 52-week study with an open label extension for another 52 weeks: sitagliptin at 100 mg had after 2 years reduced HbA<sub>1c</sub> by 0.7% from a baseline of 7.5%.<sup>51</sup> Sitagliptin has also been shown to efficiently improve glycemic control when used in monotherapy in a study comprising 530 Asian patients. Thus, one study showed that sitagliptin at 100 mg daily reduced HbA<sub>1c</sub> by 1.4% in Indians, by 1.4% in Koreans and by 0.7% in Chinese subjects with type 2 diabetes from baseline levels of 8.7% during 18 weeks treatment.<sup>35</sup> Furthermore, in a study in 151 Japanese patients, sitagliptin at 100 mg daily reduced HbA<sub>1c</sub> by 0.7% from a baseline of 7.5% over a study period of 12 weeks in subjects with type 2 diabetes.<sup>36</sup>

Since sitagliptin is cleared by the kidney, dose adjustments are required in subjects with moderate or severe renal insufficiency. One study examined the 54-week efficacy and safety of sitagliptin as monotherapy in subjects with type 2 diabetes with moderate (dose 50 mg daily) or severe (dose 25 mg daily) renal insufficiency. Mean baseline HbA<sub>1c</sub> was 7.7% and sitagliptin reduced HbA<sub>1c</sub> by 0.7%, ie, similar to those in other studies.<sup>52</sup> Furthermore, sitagliptin was safe and well tolerated in the subjects with renal insufficiency, with a lower risk of hypoglycemia relative to glipizide and with weight loss compared with weight gain with glipizide. Another study has examined the influence of sitagliptin in elderly patients. In this placebo-controlled study of 123 patients with type 2 diabetes above 65 years of age, sitagliptin at 100 mg over 24 weeks reduced HbA<sub>1c</sub> by 0.7% from a baseline of 7.8%.<sup>53</sup> Sitagliptin was well tolerated in the elderly with low degree of adverse events and hypoglycemia

occurring only in one subject, compared to two subjects treated with placebo.

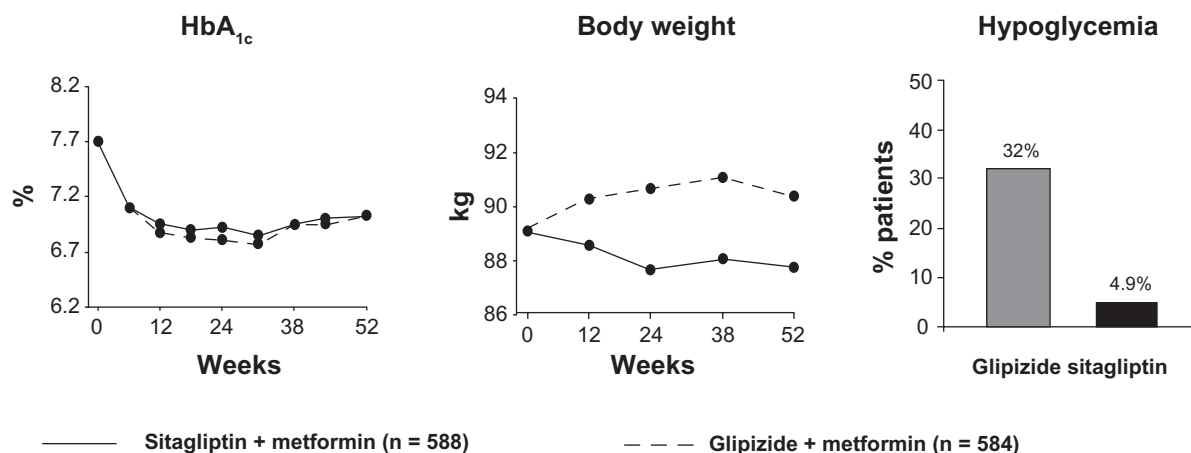
## Sitagliptin – clinical effects when used in combination with metformin

### Add-on to ongoing metformin

Sitagliptin has been shown to improve glycemic control when added to metformin in subjects with type 2 diabetes who are inadequately controlled when treated with metformin alone. One study showed that in patients with ongoing metformin treatment (n = 701) with a mean baseline HbA<sub>1c</sub> of 8.0%, sitagliptin at 100 mg daily during 24 weeks, reduced HbA<sub>1c</sub> by 0.7% when compared to subjects who maintained treatment with metformin alone.<sup>44</sup> Sitagliptin progressively reduced HbA<sub>1c</sub> levels during the first 12 weeks of treatment, and a sustained level was established thereafter. Also in Japanese patients, sitagliptin improves glycemic control when added to ongoing metformin treatment; the placebo-adjusted reduction in HbA<sub>1c</sub> by sitagliptin was 0.7%; baseline HbA<sub>1c</sub> was 7.8%.<sup>37</sup>

### Comparison with active comparator

One study compared the effect of sitagliptin (100 mg daily) with that of glipizide (up to 20 mg daily) when added to ongoing treatment with metformin for a study period of 52 weeks in a total of 1172 patients with type 2 diabetes with a mean baseline HbA<sub>1c</sub> of 7.5%.<sup>54</sup> HbA<sub>1c</sub> was reduced similarly by 0.7% in both groups (Figure 3). Sitagliptin (100 mg once daily) has also been compared with rosiglitazone (8 mg daily) when added to ongoing metformin in subjects with



**Figure 3** Mean HbA<sub>1c</sub>, mean body weight and percentage of patients with at least one event of hypoglycemia during 52 weeks treatment with sitagliptin (100 mg daily) or glipizide as add-on to metformin in patients with type 2 diabetes. Reproduced from Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabet Obes Metab*. 2007; 9:194–205.<sup>54</sup> Copyright © 2007 Wiley-Blackwell.

inadequate glycemic control with metformin alone (mean HbA<sub>1c</sub> 7.7%; n = 273). After 18 weeks, HbA<sub>1c</sub> was reduced by 0.7% by sitagliptin and by 0.8% by rosiglitazone; the difference was not significant.<sup>55</sup>

### Initial combination with metformin

One study has examined the initial combination of sitagliptin (100 mg daily) and metformin (1 or 2 g daily) compared to monotherapy treatment with sitagliptin or metformin alone for 24 weeks (n = 1091) in subjects with mean baseline HbA<sub>1c</sub> of 8.8%.<sup>43</sup> Approximately half of the patients were drug-naïve, whereas the other half had received oral agents before. There was a marked reduction in HbA<sub>1c</sub> after combination therapy (by 1.6% and 2.1% in the two groups differing in metformin dose, respectively).<sup>43</sup> This study continued as an open-label extension for 104 weeks, thus providing 2-year data on sitagliptin when given in combination with metformin. A total of 1091 patients were included at start of the study, 587 entered the extension and 402 were included in the final analysis. Reduction from baseline HbA<sub>1c</sub> was 1.4% and 1.7% in the two groups, respectively.<sup>51</sup>

### Sitagliptin – clinical effects in combination with agents other than metformin

#### Combination with pioglitazone

Sitagliptin has been evaluated as add-on to ongoing treatment with pioglitazone in one placebo-controlled, 6-month study.<sup>47</sup> The study evaluated addition of sitagliptin (100 mg daily) to pioglitazone at 30 or 45 mg daily versus continuation with pioglitazone alone in patients with a mean baseline HbA<sub>1c</sub> of 8.0% (n = 353). Sitagliptin reduced HbA<sub>1c</sub> by 0.7% versus pioglitazone alone.<sup>47</sup> Similar results of improved glycemic control when sitagliptin was added to ongoing pioglitazone treatment were also demonstrated in Japanese patients.<sup>39</sup>

#### Combination with glimepiride

Sitagliptin has as well been evaluated as add-on to ongoing treatment with glimepiride in a 6-month study of 441 patients with a mean baseline HbA<sub>1c</sub> of 8.3%. Sitagliptin (100 mg daily) reduced HbA<sub>1c</sub> by 0.7% when adjusted for changes in the group continuing with glimepiride alone.<sup>46</sup>

#### Combination with insulin

One study evaluated the influence of sitagliptin (100 mg daily) when added to ongoing insulin therapy in a total of 617 patients with type 2 diabetes.<sup>56</sup> Mean baseline HbA<sub>1c</sub> was 8.7% and following addition of sitagliptin to the ongoing insulin

therapy, HbA<sub>1c</sub> was reduced by 0.6% versus no change (0.0%) in patients who continued with insulin treatment alone.

### Sitagliptin – clinical effects when used in triple therapy Combination with metformin and sulfonylurea

A 6-month study evaluated addition of sitagliptin (100 mg daily) to a total of 441 patients with ongoing treatment with the combination of metformin and glimepiride with a baseline HbA<sub>1c</sub> of 8.3%.<sup>46</sup> It was found that HbA<sub>1c</sub> was reduced by 0.9% by sitagliptin compared to ongoing therapy with metformin and glimepiride.

### Combination with metformin and thiazolidinediones

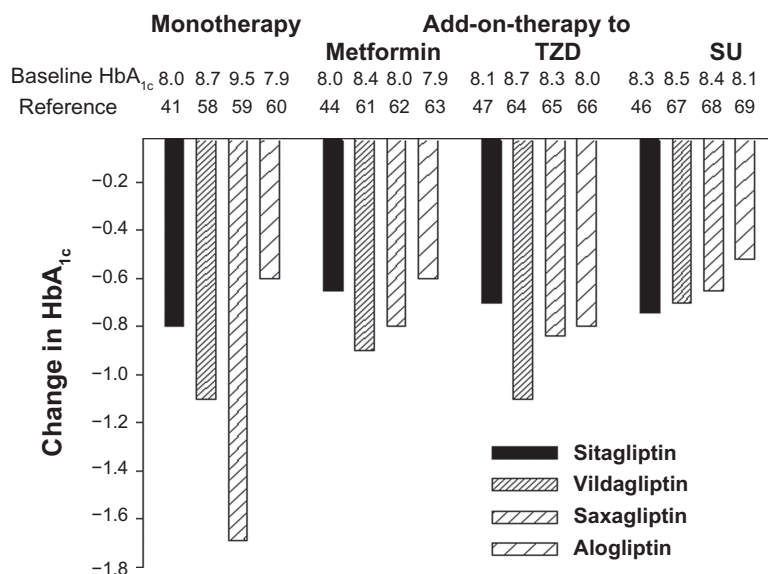
One study has examined the effect of addition of sitagliptin (100 mg daily) to ongoing therapy with metformin in combination with rosiglitazone in a total of 277 patients with type 2 diabetes with a mean baseline HbA<sub>1c</sub> of 8.8%.<sup>57</sup> The addition of sitagliptin reduced HbA<sub>1c</sub> by 0.9% versus a reduction by 0.2% in patients who continued on metformin and rosiglitazone.

### Clinical effects of sitagliptin – summary

The clinical trials show efficient and sustained (up to 2 years) improvement of glycemic control of sitagliptin both in monotherapy and in combination with metformin, glimepiride, pioglitazone and insulin and also improved effect when used in triple therapy together with metformin plus glimepiride or metformin plus rosiglitazone. In general, HbA<sub>1c</sub> was reduced by sitagliptin by ≈0.6% to 1.0% from baseline levels of 7.5% to 8.8%. An active comparative study has shown similar effect as glipizide when added to metformin.<sup>54</sup> The effect of sitagliptin seems to be similar to other DPP-4 inhibitors, although head-to-head-studies have not been undertaken.<sup>41,44,46,47,58–69</sup> Figure 4 shows the reduction in HbA<sub>1c</sub> during 24- to 26-week studies with four different DPP-4 inhibitors as monotherapy or in combination with metformin, a sulfonylurea or a thiazolidinedione. Initial HbA<sub>1c</sub> levels differed in the different studies; overall no clear difference between the various DPP-4 inhibitors is evident.

### Sitagliptin – safety and tolerability Adverse events

The extensive experience with DPP-4 inhibition that now exists in clinical trials shows high tolerability and safety.



**Figure 4** Changes in HbA<sub>1c</sub> during 24–26 weeks treatment with four different DPP-4 inhibitors in clinical trials, as monotherapy or as add-on to metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU). Baseline HbA<sub>1c</sub> levels above column.

This is evident from results in several studies with a number of different DPP-4 inhibitors, which show that the number of adverse events is not increased in study groups treated with DPP-4 inhibitors compared to placebo groups, and the drop out rates from studies due to adverse events are low. This is evident also for sitagliptin,<sup>35–57</sup> and notably also in elderly patients<sup>53</sup> and in patients with moderate or severe renal insufficiency.<sup>52</sup> A meta-analysis has been published in regard to adverse events with sitagliptin in 12 large, double-blind studies with durations from 18 weeks to 2 years.<sup>70</sup> The meta-analysis comprised a total of 3415 patients treated with sitagliptin (100 mg daily) and 2724 controls, who were treated either with other antihyperglycemic agents or placebo. The overall incidence of adverse events in these studies was 63% in patients given sitagliptin versus 63% in controls, ie, the same degree of total number of events. Serious adverse events were also similar in the two groups (7%) as was the number of patients who discontinued therapy (35% vs 36%) or withdrew from the studies due to adverse events (3% vs 4%). Some adverse events occurred, however, during the treatment with sitagliptin, although the pattern differed between different studies. When used as add-on to metformin adverse events were absent more frequently with sitagliptin versus metformin alone. When used as initial combination with metformin or as add-on to thiazolidinedione, the most frequent adverse events occurring more commonly in the sitagliptin group were headache and upper respiratory tract infection (5%–6% vs 3%–5% with metformin or thiazolidinedione alone),

and most frequent adverse events for sitagliptin when combined with sulfonylurea were hypoglycemia (12% vs 2%), nasopharyngitis (6% vs 5%) and headache (6% vs 2%). Furthermore, sitagliptin seems to be safe from a cardiovascular point of view, since adverse events suggestive of cardiac disorders (such as acute coronary syndrome, acute myocardial infarction or angina pectoris) were absent more frequently in patients treated with sitagliptin versus comparators or placebo.<sup>70</sup>

Following the reports of acute pancreatitis in subjects treated with exenatide or sitagliptin, concern has been raised that incretin based therapy is associated with increased risk of acute pancreatitis. This is difficult to establish because there is a generalized increased risk of acute pancreatitis in patients with diabetes, obesity or hyperlipidemia. A claims-based drug surveillance system has, however, shown that the risk for pancreatitis is not higher when patients are treated with sitagliptin (or exenatide) than when treated with metformin or sulfonylurea.<sup>71</sup> Also a few serious hypersensitivity reactions have been reported during treatment with sitagliptin. Therefore, although being extremely well tolerated in studies up to 2 years, long-term surveillance is of importance for the detection of potential adverse events that might occur at later stages or infrequently during treatment with sitagliptin.

## Hypoglycemia

Hypoglycemia is rare (<3%) during treatment with DPP-4 inhibitors as monotherapy or in combination with metformin or thiazolidinediones.<sup>35–38,41–45,47,53</sup> The low degree of

hypoglycemia is especially seen when compared with the risk of hypoglycemia during treatment with sulfonylurea (Figure 4). This is explained by the glucose-dependency of the islet effects of GLP-1; hence when glucose levels are reduced the effects of GLP-1 in stimulating insulin secretion and inhibiting glucagon secretion vanish. In contrast, hypoglycemia was shown to be more common when sitagliptin was added to ongoing glimepiride; the incidence of hypoglycemia was 12% versus 2% in the group given glimepiride alone.<sup>46</sup> The potential risk for hypoglycemia when combining sitagliptin and sulfonylureas may be due to an uncoupling mechanism of sulfonylureas of the glucose dependency of the islet actions by GLP-1.<sup>72</sup> This risk needs, however, to be evaluated in more detail. If increased frequency of hypoglycemia when combining sitagliptin with a sulfonylurea is confirmed, a clinical consequence is that the dose of sitagliptin or sulfonylureas should be reduced when these are used in combination. Similarly, when combined with insulin, there was an increased risk for hypoglycemia by sitagliptin.<sup>56</sup>

In spite of the very low risk of hypoglycemia during treatment with DPP-4 inhibition, a concern might be that if hypoglycemia nevertheless evolves, DPP-4 inhibition might compromise the counterregulation, if it is associated with inhibition of glucagon secretion also under these conditions. A recent study addressed this by examining the glucagon response to hypoglycemia in patients treated with the DPP-4 inhibitor vildagliptin.<sup>73</sup> It was found that contrary to the inhibition of glucagon secretion after meal ingestion by vildagliptin, ie, when glucose levels are elevated, the glucagon response to hypoglycemia was not inhibited.<sup>72</sup> This preserved glucagon secretion during hypoglycemia in patients treated with vildagliptin suggests that DPP-4 inhibition prevents hypoglycemia. This prevention may be due to improved glucose sensing in the  $\alpha$ -cells such that DPP-4 inhibition, through GLP-1, restores and improves the action of glucose on glucagon secretion, ie, it augments the inhibition of glucagon secretion at high glucose but exaggerates the stimulation of glucagon secretion at low glucose. A similar study with sitagliptin is warranted to examine whether sitagliptin, like vildagliptin, would prevent hypoglycemia.

## Sitagliptin – other potential effects

### Body weight

Many studies show that sitagliptin is body weight neutral.<sup>41–47,51,54,57</sup> Therefore, when compared to thiazolidinediones, sulfonylureas and insulin, DPP-4 inhibition shows advantage compared to the increase in body weight which

is associated with these other treatments. This is clearly evident when compared with glipizide, which increased body weight, whereas sitagliptin was body weight neutral over a study period of 52 weeks (Figure 4<sup>54</sup>).

### Lipids

In clinical studies with sitagliptin, there has been either no significant change in lipids<sup>42,47</sup> or small beneficial effects on blood lipids.<sup>44,45</sup> The two studies reporting effects showed that when sitagliptin was added to metformin, total cholesterol was reduced by 3% to 6%, triglycerides were reduced by 17%, non-high-density lipoprotein (HDL)-cholesterol was reduced by 10% to 19% and HDL-cholesterol was increased by 2%.<sup>44,45</sup> Potential long-term effects of sitagliptin on lipids remain to be established.

## Sitagliptin – regulatory aspects

Sitagliptin (Januvia®; Merck) was approved by the Food and Drug Administration (FDA) in October 2006 and by the European Medicines Agency (EMA) in April 2007. It is at present approved in 85 countries throughout the world. It is indicated for use as monotherapy and in combination therapy. As monotherapy, the indication in the US is as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes, whereas in the EU, it is indicated as monotherapy in patients who have inadequate glycemic control with diet and exercise and in whom metformin is inappropriate due to contraindications or intolerance. Sitagliptin is also indicated, both in the US and in EU, in combination therapy with metformin, a sulfonylurea or a thiazolidinedione in patients who have inadequate control with these agents used as single agents plus diet and exercise. Recently, sitagliptin was also approved to be used in combination with insulin. Sitagliptin is also indicated as triple therapy in combination with metformin plus a sulfonylurea or metformin plus a thiazolidinedione in patients who have inadequate glycemic control with the two agents.

The recommended dose for sitagliptin is 100 mg daily as a single tablet. When used as add-on to metformin or thiazolidinediones, the doses of these agents can be maintained, whereas when added to a sulfonylurea it is recommended that the dose of the sulfonylurea is reduced. Sitagliptin exists also as a combination tablet with metformin. The tablets contain 50 mg sitagliptin and 850 mg metformin (Janumet®). The recommended dose of these tablets is twice daily, which is equivalent to 100 mg sitagliptin daily.

In the US the dose of sitagliptin is recommended to be lowered in subjects with renal insufficiency: 50 mg

daily in moderate renal insufficiency (creatinine clearance 30–50 mL/min), and 25 mg daily in severe renal insufficiency (creatinine clearance <30 mL/min). In the EU, sitagliptin is not recommended in subjects with renal insufficiency.

## Conclusions and clinical positioning of sitagliptin

DPP-4 inhibition as a novel therapy of type 2 diabetes improves islet function due to the increased concentrations of active GLP-1, which stimulates insulin secretion and inhibits glucagon secretion. Since these effects target main pathophysiologic defects in type 2 diabetes, DPP-4 inhibition is a treatment targeting pathophysiologically relevant aspects of the disease. The therapy therefore holds the promises of improving basis of the disease and may therefore be the solution to several of the currently unmet needs for treatment of the disease. Clinical trials also show the efficacy of the strategy, and the safety profile shows low risk for adverse events or hypoglycemia. DPP-4 inhibition is therefore a novel and promising paradigm for treatment of type 2 diabetes.

Sitagliptin is a DPP-4 inhibitor which has shown good clinical effect in reducing glycemia both as monotherapy and in combination with other oral agents and with insulin. Sitagliptin may be of greatest value as add-on to ongoing metformin in patients with inadequate glycemic control when treated with metformin alone or as monotherapy in subjects in whom metformin is contraindicated or in subjects with adverse events from metformin. Initial combination with DPP-4 inhibitors and metformin in drug-naïve patients requiring pharmacological treatment for glycemic control, would be another place of the therapy. The reason for this is that sitagliptin improves pathophysiological defects which are seen early during the progression of diabetes, mainly the islet dysfunction, in association with safety and high tolerability. In particular, the occurrence of hypoglycemia is rare, which makes it of special interest in early stages as well as in elderly patients.

DPP-4 inhibition may be of greatest impact as add-on to metformin in patients with inadequate control of glycemia when treated with metformin alone. The clinician may in such a situation select between a DPP-4 inhibitor and a sulfonylurea. It is therefore of interest that when directly comparing sitagliptin versus glipizide when added to metformin in such patients, the reduction in HbA<sub>1c</sub> was the same over a 6 month but yet important differences existed.<sup>54</sup> Thus, whereas glipizide increased body weight, sitagliptin reduced body weight, and whereas glipizide resulted in several events

of hypoglycemia, this was rare with sitagliptin (Figure 4<sup>54</sup>). A similar finding was recently reported also for vildagliptin after 1 year of treatment when added to metformin versus glimepiride.<sup>74</sup> Hence, although long term comparisons are required, DPP-4 inhibition offers a better outcome than sulfonylurea when added to metformin over a duration of 6 months to 1 year.

Sitagliptin may also be exchanged for sulfonylurea or thiazolidinediones in combination with metformin in subjects with intolerance to sulfonylurea or thiazolidinediones or with inadequate glycemic control with these combinations. This might also be a useful indication, considering the limitation when using sulfonylureas or thiazolidinediones in terms of adverse events. Furthermore, DPP-4 inhibition has also an important place as add-on to sulfonylurea or thiazolidinediones in subjects with inadequate glycemic control when treated with these agents alone. A potential future combination is DPP-4 inhibition plus insulin, in more advanced stages of the disease. Hence, DPP-4 inhibition may be used both in early stages of the diseases, as monotherapy or in combination therapy, as well as in more advanced stages of the disease. This is in line with a recent algorithm for glycemic control as stated by an American Association of Clinical Endocrinologists/American College of Endocrinology Consensus Panel.<sup>75</sup>

The evidence for the beneficial effect of sitagliptin is its efficacy in improving glycemic control in studies over 6 to 12 months in association with safety and low risk of adverse events. The long-term durability is now important to consider and of high importance for the future long-term value of this class of compounds. Whether sitagliptin may have additional beneficial effects on islet mass, as has been shown in rodents,<sup>26</sup> remains to be established in humans.

In the clinical context, sitagliptin offers similar indication as the other DPP-4 inhibitors and the GLP-1 receptor agonists. Sitagliptin is very similar to the other DPP-4 inhibitors on the market, vildagliptin and saxagliptin,<sup>20</sup> and no long-term head-to-head study exists yet for these; it is therefore not possible yet to differentiate between them. Of the GLP-1 receptor agonists (GLP-1 mimetics), exenatide (Byetta®; Amylin and Eli Lilly) and liraglutide (Victoza®; Novo Nordisk) have been approved for therapy and several others are in clinical development, such as lixisenatide, albiglutide and taspoglutide. They are DPP-4 resistant compounds which are based either on modification of the GLP-1 molecule or based on the peptide exendin-4.<sup>76</sup> The GLP-1 mimetics are given through the subcutaneous route either once or twice daily or with longer intervals, such as once

weekly. The efficacy of these compounds seems to be similar as that of the DPP-4 inhibitors. The main differences are that GLP-1 receptor agonists reduce body weight, whereas DPP-4 inhibitors are body weight neutral; that GLP-1 mimetics are injectables, whereas DPP-4 inhibitors are active after oral administration; and that DPP-4 inhibitors are virtually free from adverse events, whereas GLP-1 mimetics are associated with nausea.

Sitagliptin, like the other DPP-4 inhibitors, has a higher cost per day of clinical use than sulfonylureas, which is an economic drawback for the DPP-4 inhibitors. However, a health economic model analysis has shown that addition of sitagliptin to metformin was cost saving compared to sulfonylurea or a thiazolidinedione in patients with inadequate glycemic control on metformin alone.<sup>77</sup> Nevertheless, more studies are required on this issue.

For future studies, it is important to examine the durability and long-term effects and safety of sitagliptin. Studies are also required to compare the long-term effects in head-to-head studies with other DPP-4 inhibitors and with GLP-1 mimetics. Moreover, outcome studies in relation to co-morbidity, such as cardiovascular diseases, are required. Recently, Merck and Co. has initiated a clinical cardiovascular study with sitagliptin entitled “A randomized placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with sitagliptin in patients with type 2 diabetes mellitus and inadequate glycemic control on mono- or dual combination oral antihyperglycemic therapy” (TECOS).<sup>78</sup> This is a long-term event-driven study with the primary objective of evaluating cardiovascular endpoints in high-risk populations; results are expected in 2014. Furthermore, more mechanistic studies are required to establish more detailed information on how sitagliptin affects islet function, including effects on glucagon secretion, and also effects on incretin hormone secretion and metabolism; most mechanistic studies on DPP-4 inhibition exist for vildagliptin.<sup>79</sup> Studies directed at establishing potential contribution of the incretin hormone GIP, the level of which also is increased by DPP-4 inhibition. Finally, since sitagliptin relies on incretins which are released after meal ingestion, it is important to study their effects in relation to ingestion of various meal ingredients, since it is known that macronutrients have different effects on the release and concentrations of incretin hormones.<sup>80</sup> Therefore, although much information exists on clinical effects and mechanisms of DPP-4 inhibition, more information is required for a fuller understanding of this promising concept to treat subjects with type 2 diabetes.

## Disclosure

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