

# Dipeptidyl Peptidase-4 Inhibition in the Management of Type 2 Diabetes

a report by

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## Dipeptidyl Peptidase-4 in the Pathophysiology of Type 2 Diabetes

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that is expressed in many different tissues and cell types and that exists in two principal forms: a membrane-anchored complex, which is involved in transmembrane signalling independent of its enzymatic activity, and a circulating soluble protein with preserved enzymatic activity.<sup>1</sup> DPP-4 has mainly been investigated as the enzyme responsible for inactivation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These two gastrointestinal hormones, which are mainly secreted after meals, enhance glucose-dependent insulin secretion.<sup>1-3</sup> GLP-1 and GIP also stimulate  $\beta$ -cell proliferation, promote resistance to apoptosis and increase  $\beta$ -cell survival, thus increasing  $\beta$ -cell mass and function in the long term.<sup>1</sup> Furthermore, GLP-1 inhibits glucagon secretion and reduces food intake through the inhibition of gastric emptying and through a direct hypothalamic effect.<sup>1</sup> All of these actions of GIP and GLP-1 contribute to the physiological regulation of glucose homeostasis, particularly in the post-prandial state.

Type 2 diabetes is associated with a reduction of meal-induced active GLP-1 levels.<sup>4,5</sup> In type 2 diabetic patients, active GIP levels are not different from those of healthy controls,<sup>6</sup> but the sensitivity of insulin secretion to this hormone is reduced.<sup>6,7</sup> *In vivo*, both GLP-1 and GIP are rapidly inactivated through the cleavage of the N-terminal fraction of the peptide, mainly by DPP-4.<sup>1</sup> Chronic exposure to elevated glucose concentrations induces DPP-4 expression *in vitro*<sup>8</sup> and is associated with increased circulating enzyme activity in type 2 diabetic patients;<sup>9,10</sup> however, DPP-4 plasma activity is not increased in type 2 diabetic patients with mild hyperglycaemia.<sup>9</sup> The impairment of GLP-1 response to meals in type 2 diabetes is more probably due to reduced secretion rather than to increased degradation, although the induction of DPP-4 activity by high glucose levels could contribute to a further derangement in patients with very poor metabolic control.

## Dipeptidyl Peptidase-4 as a Therapeutic Target in Type 2 Diabetes

The inhibition of DPP-4 is an interesting target for the treatment of

type 2 diabetes. Among currently available hypoglycaemic drugs, only metformin has been shown to inhibit DPP-4 activity;<sup>11,12</sup> however, metformin is a weak DPP-4 inhibitor, capable of determining only a small increase of post-prandial GLP-1 levels.<sup>11</sup> The effect of metformin on DPP-4 contributes only marginally to the hypoglycaemic action of the drug, which is mainly determined by the inhibition of hepatic gluconeogenesis and the stimulation of insulin-induced glucose uptake in skeletal muscles.

Recently, several specific DPP-4 inhibitors that are bioavailable after oral administration have been developed for the treatment of type 2 diabetes.<sup>2</sup> These include sitagliptin, vildagliptin, saxagliptin, denagliptin and some other molecules with a less favourable kinetic profile, which were abandoned during the earlier phases of clinical development. Most of the available clinical data were obtained either with vildagliptin or sitagliptin.

Oral treatment with vildagliptin or sitagliptin induces a relevant inhibition (usually by about 80%) of circulating DPP-4 activity, which determines an increase of post-load active GLP-1 and GIP levels.<sup>13-15</sup> The action of these gastrointestinal hormones increases insulin secretion and  $\beta$ -cell function,<sup>13-20</sup> reducing glucagon levels at the same time.<sup>13,14</sup> As a consequence, treatment with oral DPP-4 inhibitors suppresses endogenous glucose production<sup>15</sup> and reduces both fasting and post-prandial glycaemia.<sup>13-15,20</sup>

Both GLP-1 and GIP have been found to inhibit  $\beta$ -cell apoptosis and stimulate differentiation of new  $\beta$ -cells from undifferentiated precursors in animal models.<sup>1</sup> Similar effects have been reported for long-acting GLP-1 analogues such as exenatide and liraglutide.<sup>2</sup> The antiapoptotic and pro-proliferative effects on pancreatic  $\beta$ -cells of these agents could be of great interest for the long-term management of type 2 diabetes. In fact, this disease is characterised by a progressive decline of  $\beta$ -cell mass and function, which is associated with deterioration of glycaemic control and which could be countered by the stimulation of GLP-1 and/or GIP receptors. It is very likely that DPP-4 inhibitors have effects on  $\beta$ -cell mass and function similar to those of GLP-1 analogues. In a study on a rodent model of type 2 diabetes (high-fat diet, low-dose streptozotocin-treated mice), a sitagliptin analogue was reported to preserve  $\beta$ -cell mass and function.<sup>21</sup> Clinical studies of appropriate duration to verify the long-term effects of DPP-4 inhibitors are not yet available. Although the favourable effects of vildagliptin on  $\beta$ -cell function are very well maintained after one year of treatment,<sup>17</sup> more evidence is needed in order to confirm the possible positive action of DPP-4 inhibitors on the natural history of type 2 diabetes.

Interestingly, unlike GLP-1 and its long-acting analogues,<sup>2</sup> DPP-4 inhibitors do not delay gastric emptying or nutrient absorption.<sup>22</sup> It can



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# Introducing JANUVIA® (sitagliptin) for patients who need additional control: The first in a new class of DPP-4 inhibitors for type 2 diabetes

Proven in clinical trials when added to  
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- Delivers substantial glucose control<sup>1,2</sup>
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Refer to Summary of Product Characteristics (SPC) before prescribing

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### PRESENTATION

100 mg film-coated tablet containing 100 mg of sitagliptin.

### USES

'Januvia' is indicated in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin when diet and exercise, plus metformin, do not provide adequate glycaemic control. For patients with type 2 diabetes mellitus in whom use of a PPAR $\gamma$  agonist (i.e. a thiazolidinedione) is appropriate, 'Januvia' is indicated in combination with the PPAR $\gamma$  agonist when diet and exercise plus the PPAR $\gamma$  agonist alone, do not provide adequate glycaemic control.

### DOSAGE AND ADMINISTRATION

One 100 mg tablet once daily, with or without food. Maintain the dosage of metformin or PPAR $\gamma$  agonist, and administer sitagliptin concomitantly. If a dose is missed, take as soon as the patient remembers. Do not take a double dose on the same day. **Patients with renal insufficiency:** no dosage adjustment required for mild renal insufficiency (creatinine clearance [CrCl]  $\geq 50$  ml/min). Not recommended in patients with moderate or severe renal insufficiency. **Patients with hepatic insufficiency:** no dosage adjustment necessary for patients with mild to moderate hepatic insufficiency. 'Januvia' has not been studied in patients with severe hepatic insufficiency. **Elderly:** no dosage adjustment necessary. Exercise care in patients  $\geq 75$  years of age as there are limited safety data in this group. **Children:** not recommended in children below 18 years of age.

### CONTRA-INDICATIONS

Hypersensitivity to active substance or excipients.

### PRECAUTIONS

**General:** do not use in patients with type 1 diabetes or for diabetic ketoacidosis. **Hypoglycaemia:** in trials of sitagliptin as monotherapy, or as part of combination therapy with metformin or pioglitazone, rates of hypoglycaemia reported with sitagliptin were similar to rates in patients taking placebo. Use of sitagliptin in combination with agents known to cause hypoglycaemia, such as sulphonylureas or insulin, has not been adequately studied. **Drug interactions** Effects of other medicinal products on sitagliptin Low risk of clinically meaningful interactions with metformin and ciclosporin. Meaningful interactions would not be expected with other p-glycoprotein inhibitors. The primary enzyme responsible for the limited metabolism of sitagliptin is CYP3A4, with contribution from CYP2C8. Effects of sitagliptin on other medicinal

products Digoxin: sitagliptin had a small effect on plasma digoxin concentrations, and may be a mild inhibitor of p-glycoprotein *in vivo*. No dosage adjustment of digoxin is recommended, but monitor patients at risk of digoxin toxicity if the two are used together. **Pregnancy and lactation:** Do not use during pregnancy or breast-feeding.

### SIDE EFFECTS

#### Refer to SPC for complete information on side effects

In clinical trials in over 2,700 patients, the rate of discontinuation due to adverse experiences considered drug-related was 0.8 % with 100 mg per day and 1.5 % with other treatments. No adverse reactions considered as drug-related were reported in patients treated with sitagliptin occurring in excess ( $>0.2$  % and difference  $>1$  patient) of that in patients treated with control.

**Combination with metformin:** Common ( $\geq 1/100$ ,  $<1/10$ ): nausea; Uncommon ( $\geq 1/1,000$ ,  $<1/100$ ): somnolence; upper abdominal pain, diarrhoea; blood glucose decreased, anorexia, weight decreased.

**Combination with a PPAR $\gamma$  agent (pioglitazone):** Common ( $\geq 1/100$ ,  $<1/10$ ): hypoglycaemia, flatulence, peripheral oedema. In addition, in studies of sitagliptin 100 mg alone compared to placebo, adverse reactions considered as drug-related reported in patients treated with sitagliptin in excess ( $>0.2$  % and difference  $>1$  patient) of that in patients receiving placebo are headache, hypoglycaemia, constipation, and dizziness. Also, adverse experiences reported regardless of causal relationship to medication and more commonly in patients treated with 'Januvia' included upper respiratory tract infection, nasopharyngitis, osteoarthritis and pain in extremity.

**PACKAGE QUANTITIES AND BASIC NHS COST** 28 Tablets: £33.26

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1. JANUVIA Summary of Product Characteristics.
2. Nauck M, Meininger G, Sheng D, et al for the 024 Study Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared to the sulphonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. *Diabetes Obes Metab.* 2007; 9:194-205.



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be speculated that the stimulation of GLP-1 receptors obtained with infusion of GLP-1, or subcutaneous injection of its analogues, at therapeutic doses is greater than that reached through DPP-4 inhibition; at the same time, the inhibition of the enzyme could affect other (as yet unidentified) hormones and/or neurotransmitters modulating gastrointestinal motility. The lack of effects of DPP-4 inhibitors on gastric emptying and nutrient absorption produces some relevant differences in the clinical profile in comparison with GLP-1 analogues, which will be discussed in greater detail below.

### A Brief Summary of Clinical Evidence

As many trials on DPP-4 inhibitors are currently ongoing, the body of available evidence on these drugs will be increased in a relevant manner in the next 2–3 years. A summary of clinical trials that have already been published as full papers is reported in *Table 1*; further studies have been presented at international meetings, but they are not yet available as complete publications.

### Monotherapy Studies

Several placebo-controlled trials have shown the efficacy of both sitagliptin<sup>18,23,24</sup> and vildagliptin<sup>20,25–27</sup> on glycated haemoglobin (HbA<sub>1c</sub>) and fasting and post-prandial glucose in type 2 diabetic patients. A dose–response relationship can be observed for both drugs, with the maximal efficacy at 50–100mg for vildagliptin<sup>25</sup> and at 100mg/day for sitagliptin.<sup>24</sup> Both drugs appear fit for a once-a-day administration,<sup>25</sup> although some of the trials with vildagliptin were performed with a twice-daily administration. The reduction of HbA<sub>1c</sub> obtained after six months of treatment with the active drugs in comparison with placebo is in the 0.5–0.9% range.<sup>18,26,27</sup> Few studies comparing vildagliptin with active drugs have been reported so far. In a short-term (12-week) study, the efficacy of sitagliptin was slightly lower than that of glipizide;<sup>24</sup> however, it should be considered that the effects of DPP-4 inhibitors on blood glucose seem to be somewhat slower than those of sulphonylureas,<sup>28</sup> and longer-term trials could yield different results. Conversely, the six-month efficacy of vildagliptin is similar to that of rosiglitazone<sup>29</sup> or pioglitazone.<sup>30</sup> A preliminary report comparing metformin with vildagliptin monotherapy at one year showed a slightly lower efficacy on HbA<sub>1c</sub>, but a greater tolerability, for vildagliptin.<sup>31</sup>

### Combination with Metformin

Adequately sized placebo-controlled trials have shown that both sitagliptin<sup>32</sup> and vildagliptin<sup>33</sup> reduce HbA<sub>1c</sub> by 0.6–1.1% when used as add-on therapies in patients failing with metformin monotherapy, with an effect that is sustained for up to one year.<sup>17</sup> In one 52-week trial comparing sitagliptin with glipizide, both in combination with metformin, the DPP-4 inhibitor was as effective as the sulphonylurea, but without hypoglycaemic risk and weight gain.<sup>28</sup>

### Combination with Thiazolidinediones

In patients inadequately controlled by pioglitazone monotherapy, the addition of vildagliptin<sup>34</sup> or sitagliptin<sup>35</sup> reduces post-prandial glucose and HbA<sub>1c</sub>; the reduction of HbA<sub>1c</sub> in comparison with placebo is approximately 0.4–0.7%. A low-dose combination of vildagliptin and pioglitazone could have some advantages in efficacy over full-dose monotherapy with either agent as initial therapy in type 2 diabetic patients who are unsatisfactorily controlled by non-pharmacological interventions.<sup>30</sup>

### Combination with Insulin

One 24-week placebo-controlled trial on an adequately sized sample of type 2 diabetic patients on insulin monotherapy showed that the addition of vildagliptin improved metabolic control while reducing the incidence of hypoglycaemia.<sup>36</sup>

### Safety and Tolerability

DPP-4 inhibitors appear to be extraordinarily well tolerated. Unlike traditional secretagogues (sulphonylureas and glinides), they seem unable to induce hypoglycaemia, even at the highest doses; in fact, in randomised clinical trials, the incidence of hypoglycaemia is not different from that of placebo. In insulin-treated patients, the addition of DPP-4 inhibitor could even reduce the incidence of hypoglycaemic episodes.<sup>36</sup> These results are consistent with the action of GLP-1 and GIP, which are not capable of stimulating insulin synthesis and release when ambient glucose is lower than normal.<sup>1,37</sup>

Treatment with DPP-4 inhibitors does not determine any relevant gastrointestinal side effects. In this respect, DPP-4 inhibitors appear to have a greater tolerability than GLP-1 analogues, which can induce nausea and vomiting.<sup>2</sup> Treatment with sitagliptin or vildagliptin is not associated with weight loss (as with GLP-1 analogues) or weight gain (as with sulphonylureas and glinides). In fact, to date no specific adverse event has been associated with DPP-4 inhibitors.

DPP-4 is capable of hydrolysing the N-terminus of many other peptides different from GLP-1. Substrates of this enzyme include pituitary adenylylate cyclase-activating polypeptide (PACAP), vasoactive intestinal peptide (VIP), gastrin-releasing peptide (GRP), growth hormone-releasing hormone (GHRH), glucagon-like peptide-2 (GLP-2), peptide YY, neuropeptide Y and B-type natriuretic peptide.<sup>1,38</sup> Some of the peptides inactivated by DPP-4 have a physiological role in the regulation of cardiovascular function. Despite this fact, DPP-4 inhibitors have never been shown to affect any haemodynamic parameter. Although some studies on longer term cardiac safety are still ongoing, available data from clinical trials seem to exclude any relevant adverse effect on the heart.

When expressed at the surface of immunocompetent cells, with the name of CD26, DPP-4 contributes to the activation and proliferation of T cells and therefore to the modulation of immunogenic responses.<sup>3</sup> This function of DPP-4 has given rise to some worries about possible adverse effects of its inhibitors on immunogenic responses,<sup>1</sup> although no immunodepressant effect has ever been shown in clinical trials.

### Extra-glycaemic Effects of Dipeptidyl Peptidase-4 Inhibitors

Some data suggest that DPP-4 inhibitors could have favourable – although small – effects on lipid metabolism. Sitagliptin has been reported to reduce triglyceride levels in monotherapy<sup>24</sup> and in addition to metformin<sup>32</sup> or pioglitazone;<sup>35</sup> vildagliptin does not seem to affect triglycerides in the fasting state,<sup>26,34</sup> while it could reduce their postprandial levels.<sup>39</sup>

GLP-1 receptors are present at the surface of myocardiocytes, where they contribute to the regulation of glucose metabolism. GLP-1 receptor agonists have been reported to improve cardiac function after myocardial infarction in humans.<sup>2</sup> The possibility that DPP-4 inhibitors share this interesting effect still needs to be proved.

## Dipeptidyl Peptidase-4 Inhibitors and Glucagon-like Peptide-1 Analogues

Both GLP-1 analogues and DPP-4 inhibitors enhance  $\beta$ -cell function and inhibit glucagon secretion through the stimulation of GLP-1 receptors. Despite this similarity, the profile of action of the two classes of drugs is markedly different. The first – and most obvious – difference is the route of administration (oral for DPP-4 inhibitors and subcutaneous for GLP-1 agonists). The lack of effects of DPP-4 inhibitors on gastric emptying<sup>22</sup> can be considered either an advantage or a disadvantage over GLP-1 analogues: on one side, agents inhibiting gastric motility, such as GLP-1 and its analogues, induce satiety and determine weight loss, while DPP-4 inhibitors are weight-neutral. On the other hand, treatment with GLP-1 receptor agonists is associated with nausea and vomiting, while DPP-4 inhibitors are much better tolerated.

The fact that DPP-4 inhibitors, despite the increase of GLP-1 levels, do not delay gastric emptying and do not suppress food intake is not easy to explain. It can be speculated that the reduced inactivation of other peptides different from GLP-1 induced by DPP-4 inhibitors antagonised some of the effects of GLP-1; for example, inhibition of inactivation of hypothalamic neuropeptide Y or peptide YY could counterbalance the anorectic action determined by the increase of active GLP-1 levels.<sup>37</sup>

## Clinical Use of Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes

Current guidelines recommend the use of metformin as first-line treatment of type 2 diabetes.<sup>40,41</sup> Although DPP-4 inhibitors could have a similar efficacy on HbA<sub>1c</sub> and a greater tolerability than metformin monotherapy,<sup>31</sup> currently available evidence is not sufficient to support their use as first-line agents in drug-naïve patients. In fact, data on long-term hypoglycaemic efficacy<sup>42</sup> and results in the prevention of cardiovascular disease<sup>43</sup> obtained with metformin should be replicated with other drugs before biguanide is replaced as first-line agent. Conversely, monotherapy with DPP-4 inhibitors could be an interesting option in patients intolerant to metformin.

A recent treatment algorithm for type 2 diabetes issued by the American Diabetes Association (ADA) and the European Association for

**Table 1: Summary of Main Controlled Clinical Trials with Vildagliptin and Sitagliptin**

| Ref. | Drug         | Comparator               | Combination  | Duration |
|------|--------------|--------------------------|--------------|----------|
| 20   | Vildagliptin | Placebo                  | None         | 12 weeks |
| 25   | Vildagliptin | Placebo                  | None         | 12 weeks |
| 24   | Sitagliptin  | Placebo                  | None         | 12 weeks |
|      |              | Glipizide                |              |          |
| 23   | Sitagliptin  | Placebo                  | None         | 18 weeks |
| 26   | Vildagliptin | Placebo                  | None         | 24 weeks |
| 27   | Vildagliptin | Placebo                  | None         | 24 weeks |
| 18   | Sitagliptin  | Placebo                  | None         | 24 weeks |
| 29   | Vildagliptin | Rosiglitazone            | None         | 24 weeks |
| 31   | Vildagliptin | Metformin                | None         | 52 weeks |
| 33   | Vildagliptin | Placebo                  | Metformin    | 24 weeks |
| 32   | Sitagliptin  | Placebo                  | Metformin    | 24 weeks |
| 28   | Sitagliptin  | Glipizide                | Metformin    | 52 weeks |
| 34   | Vildagliptin | Placebo                  | Pioglitazone | 24 weeks |
| 35   | Sitagliptin  | Placebo                  | Pioglitazone | 24 weeks |
| 30   | Sitagliptin  | Pioglitazone monotherapy | Pioglitazone | 24 weeks |
| 36   | Vildagliptin | Placebo                  | Insulin      | 24 weeks |

the Study of Diabetes (EASD) recommends the addition of sulphonylureas, thiazolidinediones or insulin when metformin monotherapy is insufficient to maintain an adequate metabolic control.<sup>41</sup> DPP-4 inhibitors should be carefully considered as a valid alternative to those approaches. In fact, sitagliptin and vildagliptin are similarly effective as sulphonylureas and thiazolidinediones, without their side effects (hypoglycaemia, weight gain and fluid retention). In comparison with sulphonylureas, they could also show a greater efficacy on post-prandial hyperglycaemia.<sup>28</sup>

Triple oral therapy with DPP-4 inhibitors, metformin and thiazolidinediones could be an interesting combination, but it has not been studied so far. Conversely, the addition of DPP-4 inhibitors to metformin and other secretagogues (sulphonylureas or glinides) does not seem a very rational approach. The combination of DPP-4 inhibitors with insulin, although promising, needs to be investigated more thoroughly. ■

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