

Sitagliptin: first DPP-4 inhibitor to treat type 2 diabetes

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KEY POINTS

- sitagliptin (Januvia) is a DPP-4 inhibitor that blocks the breakdown of the incretin hormones GIP and GLP-1; it reduces fasting plasma glucose and decreases postprandial hyperglycaemia
- licensed to improve glycaemic control in type 2 diabetes in combination with metformin or a glitazone when diet and exercise plus either agent alone have not achieved adequate glycaemic control
- available as 100mg tablets; 28, £33.26
- as add-on therapy in patients with inadequate glycaemic control with metformin or pioglitazone, sitagliptin reduced HbA_{1C} by about 0.7 per cent compared with placebo
- as add-on therapy with metformin, sitagliptin and glipizide reduced HbA_{1C} and increased the proportion of patients with HbA_{1C} <7 per cent by similar amounts
- in clinical trials, sitagliptin was well tolerated; when added to pioglitazone, it was associated a higher incidence of gastrointestinal events than placebo
- long-term treatment with sitagliptin is associated with no weight gain and the incidence of serious hypoglycaemic events is very low



Sitagliptin (Januvia) is the first of a new class of drugs in the treatment of type 2 diabetes. Here, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Dr Krentz comments on its potential place in the treatment of type 2 diabetes.

Incretin hormones released by the intestine form part of the complex system that maintains glucose homeostasis. The two principal hormones are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).¹

Basal levels of GLP-1 and GIP are low but increase rapidly after ingestion of food; they are inactivated by the enzyme dipeptidyl-peptidase 4 (DPP-4).¹ Both GIP-1 and GIP stimulate insulin secretion; GLP-1 additionally stimulates insulin synthesis, inhibits glucagon secretion and reduces gastrointestinal motility. The effects on insulin and glucagon secretion

occur only when blood levels of glucose are elevated, preserving the glucagon response to hypoglycaemia.¹ Experimentally, GLP-1 has been shown to reduce calorie intake and both GIP and GLP-1 have trophic effects on pancreatic beta cells;¹ however, the clinical significance of these properties is uncertain. In patients with type 2 diabetes, the insulin response to GIP is impaired, while the response to GLP-1 is normal but blood levels are reduced.¹

The technology

Sitagliptin (Januvia) is an inhibitor of DPP-4. It is licensed for patients with type 2 diabetes mellitus to

improve glycaemic control in combination with metformin or a glitazone when diet and exercise plus either agent alone have not achieved adequate glycaemic control. It is administered orally at a dose of 100mg once daily at the same time as other oral hypoglycaemic agents.

In patients with type 2 diabetes given a glucose load, sitagliptin dose dependently inhibits DPP-4, increases insulin secretion, reduces glucagon secretion and decreases the glycaemic excursion.²

Sitagliptin is the second drug acting via the incretin system to be introduced. The first was exenatide (Byetta), a GLP-1 mimetic, which

is licensed for the treatment of type 2 diabetes mellitus in combination with metformin and/or sulphonylureas in patients who have not achieved adequate glycaemic control on maximally tolerated doses of these oral therapies, and is administered by twice-daily subcutaneous injection.

Clinical trials

Three double-blind, randomised trials provide the main evidence base for the efficacy of sitagliptin as add-on therapy to metformin^{3,4} or a glitazone (pioglitazone – Actos).⁵ All included patients who had previously been taking an oral hypoglycaemic agent and were switched to the study medication (metformin or pioglitazone) for a stabilisation period before randomisation. The primary endpoint in each study was the change from baseline in mean glycosylated haemoglobin (HbA_{1C}). The effects of both placebo⁵ and sitagliptin^{4,5} on HbA_{1C} were greatest in patients with baseline worst glycaemic control.

A total of 701 patients taking a stable dose of metformin (at least 1500mg per day) with inadequate glycaemic control (HbA_{1C} 7-10 per cent, mean 8 per cent) were randomised to placebo or sitagliptin 100mg per day.³ Diet and exercise were not included in the protocol. Pioglitazone was added if glucose levels exceeded a threshold initially of 15mmol per litre, decreasing to 11.1mmol per litre after 12 weeks.

In patients taking sitagliptin, mean HbA_{1C} decreased compared with placebo during the first 12 weeks, then stabilised. At 24 weeks, mean reductions in HbA_{1C} were 0.02 per cent with placebo and 0.67 per cent with sitagliptin ($p < 0.001$, see Figure 1); HbA_{1C} was reduced to <7 per cent in more patients taking sitagliptin (47 vs 18 per cent with placebo). This was associated

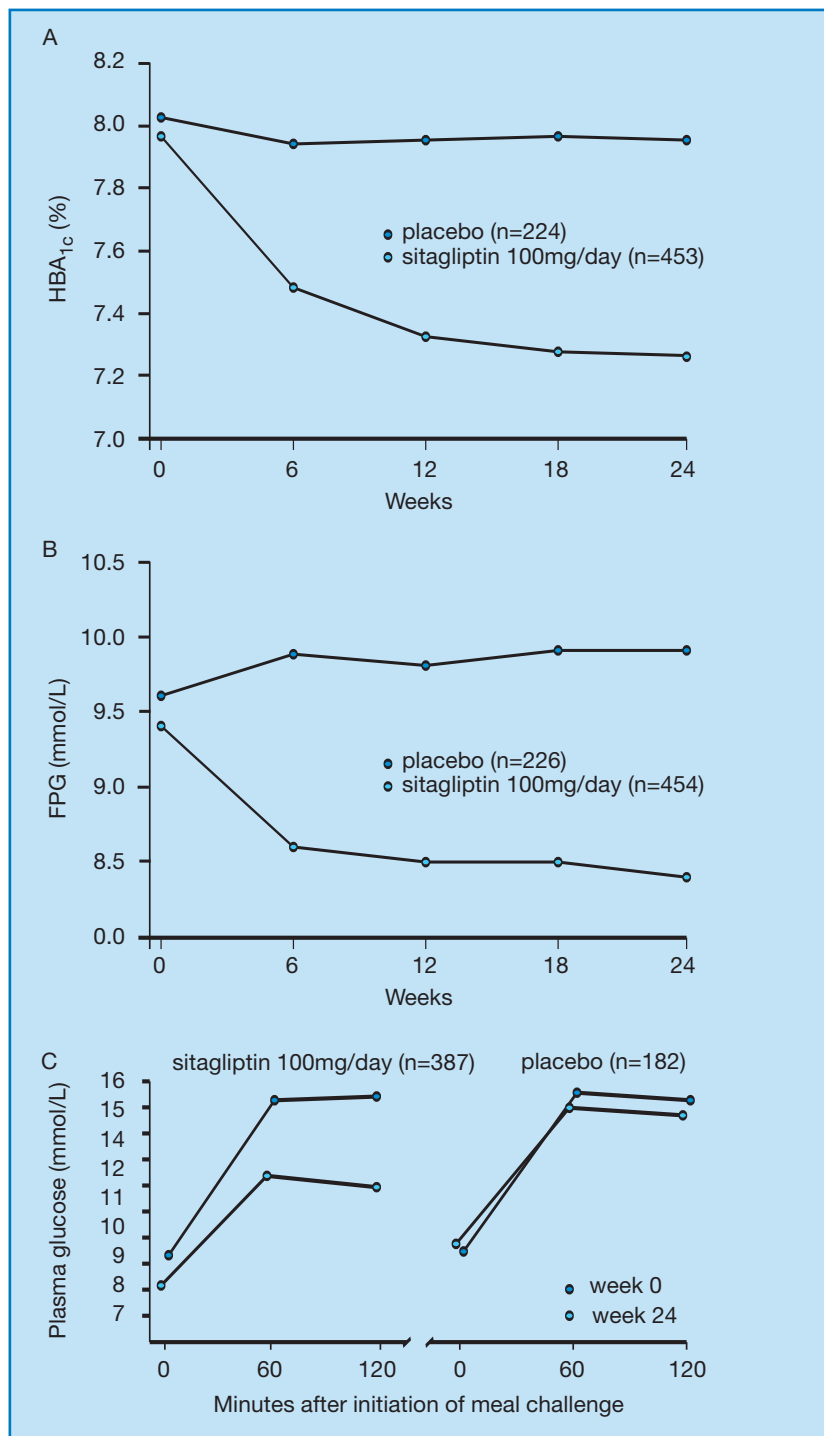


Figure 1. Changes in HbA_{1C}, fasting plasma glucose (FPG) and postprandial hyperglycaemia after sitagliptin or placebo as add-on therapy to metformin³

with increased insulin levels and improved beta-cell function and reductions in fasting plasma glucose and the postprandial hyperglycaemic response (see Figure 1).

Fewer patients taking sitagliptin required pioglitazone (4.5 vs 13.5 per cent).

A double-blind extension phase of this study included 544 patients

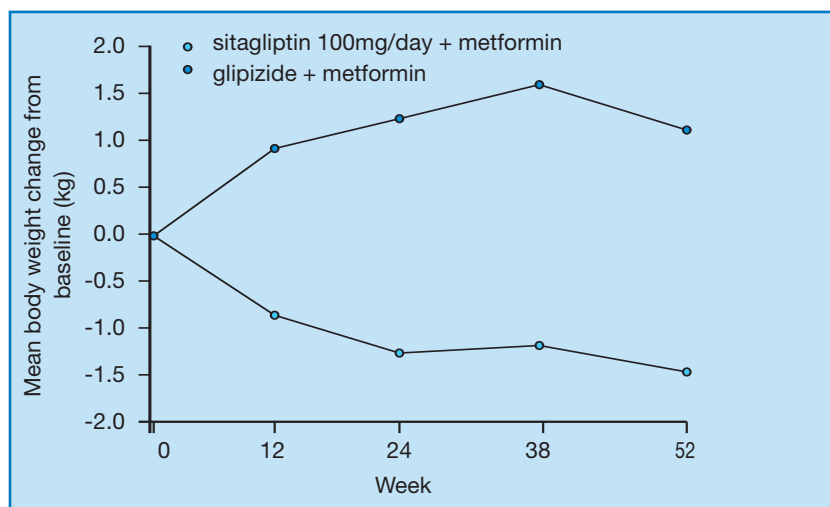


Figure 2. Weight change with sitagliptin and glipizide added to metformin over 52 weeks⁴

who had not required additional pioglitazone; those originally assigned to placebo were switched to glipizide.⁶ After a further 30 weeks, HbA_{1C} increased slightly (by 0.07 per cent) in patients taking sitagliptin and decreased by 0.4 per cent with glipizide (total reduction over 54 weeks: 0.7 per cent with sitagliptin and 0.9 per cent with placebo/glipizide). By week 54, HbA_{1C} was <7 per cent in 51 per cent of patients taking sitagliptin and 61 per cent of those assigned to placebo/glipizide.

In a second trial, after beginning a programme of diet and exercise, 353 patients taking a stable dose of pioglitazone (30 or 45mg per day) with HbA_{1C} 7-10 per cent (mean 8.0-8.1 per cent) were randomised to placebo or sitagliptin 100mg per day.⁵ Metformin was added if glycaemic thresholds were not met during the study.

After 24 weeks, HbA_{1C} was 0.15 per cent lower with placebo and 0.85 per cent lower with sitagliptin ($p < 0.001$); HbA_{1C} was reduced to <7 per cent in more patients taking sitagliptin (45 vs 23 per cent with placebo). Compared with placebo, sitagliptin was associated with reduced fasting plasma glu-

cose, but there was no difference in fasting insulin levels (though fasting proinsulin levels were lower), and beta-cell function was improved. Fewer patients taking sitagliptin required additional treatment with metformin (6.9 vs 14.0 per cent).

Sitagliptin was compared with glipizide (5-20mg per day, mean 10.3mg per day) as add-on therapy in a noninferiority trial in 1172 patients with HbA_{1C} 6.5-10 per cent (mean 7.5 per cent) while taking a stable dose of metformin of at least 1500mg per day.⁴ Counselling on exercise and diet was provided. Patients who failed to achieve increasingly tight glycaemic thresholds (fasting plasma glucose decreasing from >14.4mmol per litre at week 6 to >11.1mmol per litre after 30 weeks) were excluded.

In total, 793 patients completed 52 weeks' treatment and were included in the per protocol analysis (secondary analyses including all treated patients did not differ substantially). More patients taking sitagliptin were excluded due to lack of efficacy (15 vs 10 per cent) and exclusions were more frequent among patients with higher baseline hyperglycaemia. Mean HbA_{1C}

was reduced by 0.67 per cent in both groups, which met the criterion for noninferiority. However, dose optimisation of glipizide was limited by the study design, possibly reducing potential differences between the treatments.⁷

The maximum reduction in HbA_{1C} occurred at 30 weeks (and was greater with glipizide), then increased in both groups. After 52 weeks, HbA_{1C} was <7 per cent in 63 per cent of patients taking sitagliptin and 59 per cent taking glipizide, and <6.5 per cent in 29 per cent in both groups. Glipizide increased fasting insulin levels and beta-cell function by more than sitagliptin but there was no difference in fasting plasma glucose.

Adverse effects

When added to metformin, the incidence of adverse events associated with sitagliptin was similar to that with placebo.³ Added to pioglitazone, sitagliptin was associated with significantly more discontinuations due to adverse events (5.7 vs 1.1 per cent) and more adverse gastrointestinal events (13.7 vs 6.2 per cent).⁵ Hypoglycaemia occurred in two patients taking sitagliptin (1.1 per cent), neither requiring assistance.⁵

Although the incidence of adverse events associated with glipizide and sitagliptin was similar overall, more patients reported hypoglycaemia with glipizide (32 vs 4.9 per cent); assistance was required by 15 patients taking glipizide (2.6 per cent) and two taking sitagliptin (0.4 per cent).⁴ In the extension trial, the incidence of hypoglycaemia (not defined) was 1 per cent with sitagliptin and 16 per cent with glipizide.

In these trials, sitagliptin had a modest or no effect on plasma lipids compared with placebo or glipizide.^{3,4,5} There was no difference in weight gain between

placebo and sitagliptin,⁵ but glipizide was associated with weight gain of 1.1kg over 52 weeks compared with a weight loss of 1.5kg with sitagliptin (see Figure 2).⁴ In the extension study (total treatment duration 54 weeks),⁶ sitagliptin was associated with mean weight loss of 0.9kg compared with a gain of 1.5kg with placebo/glipizide.

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

Type 2 diabetes is characterised metabolically by a progressive loss of insulin secretion from islet beta cells in the presence of whole-body insulin resistance, the latter often aggravated by obesity. Improving the endogenous insulin response through a glucose-dependent mechanism is an attractive therapeutic approach. In contrast to secretagogues such as sulphonylureas and meglitinides stimulating insulin secretion via physiological pathways should reduce hyperglycaemia while minimising the risks of weight gain and iatrogenic hypoglycaemia.

It has long been known that gastrointestinal polypeptide hormones secreted in response to ingestion of a meal augment postprandial insulin secretion. This is known as the incretin effect and accounts for about 70 per cent of postprandial insulin secretion in

healthy subjects. The two most important incretin hormones are GLP-1 and GIP and both enhance glucose-stimulated insulin secretion. GLP-1, but not GIP, also retards gastric emptying, has a central appetite-suppressant effect and impairs inappropriate glucagon secretion from islet cells. All of these properties are favourable attributes for a putative anti-diabetic drug.

Inappropriate glucagon secretion has an underappreciated role in the development of the hyperglycaemia of type 2 diabetes. No conventional therapies have the capacity to directly reduce glucagon secretion.

For reasons that remain to be clarified, the incretin effect is almost completely absent in patients with type 2 diabetes. This reflects reduced GLP-1 secretion and reduced insulinotropic activity of GIP. GLP-1 and GIP are subject to rapid degradation by the ubiquitous enzyme DPP-4.

Novel therapies that exploit the incretin effect of GLP-1 include the injectable incretin mimetic exenatide and the oral DPP-4 inhibitor sitagliptin. Orally active pharmacological inhibitors of DPP-4 increase plasma levels of endogenous GLP-1 two- to threefold. The primary target of action of these drugs is postprandial hyperglycaemia, although fasting glucose concentrations are also reduced.

Sitagliptin, the first DPP-4 inhibitor, is licensed in the UK for use as a second-line agent in patients failing to achieve glycaemic goals on metformin or a glitazone. Registration trials have shown that sitagliptin improves glycaemic control and insulin secretion and reduces glucagon secretion.

As already discussed, sitagliptin is weight neutral and well tolerated with an incidence of hypoglycaemia similar to placebo. The DPP-4 inhibitors are now being used in clinical prac-

tice and are likely to be useful for patients with obesity-associated type 2 diabetes. Long-term efficacy and safety data are required but, to date, no concerns have been reported.

Cost, inevitably, will be an important consideration and it seems likely

that DPP-4 inhibitors will be used initially in patients for whom avoidance of further weight gain or hypoglycaemia are particularly important.

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and honorary senior clinical lecturer at Southampton University; he was previously received research funding and has acted in an advisory capacity to several manufacturers of oral antidiabetic agents, including Merck Sharp & Dohme
