

NEW DRUG EVALUATION

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SITAGLIPTIN

Sitagliptin is the first in a new class of once daily, oral anti-hyperglycaemic agents. When added to ongoing metformin or pioglitazone therapy, it significantly improved HbA_{1c} in type-2 diabetic patients who failed to achieve adequate glycaemic control with these agents as monotherapy, and it was found to be non-inferior to glipizide when added to metformin. Sitagliptin treatment was not associated with significantly increased incidences of hypoglycaemia or gastrointestinal adverse events. Sitagliptin as add-on therapy to metformin or a glitazone may be considered as an option for patients who fail to achieve glycaemic control despite an adequate trial of established first and second-line regimens. Comparative and long-term safety and efficacy data are lacking.

What is it?

Sitagliptin (Januvia[®], MSD Ltd) is the first in a new class of oral, once daily anti-hyperglycaemic agents (dipeptidyl peptidase type 4 (DPP-4) inhibitor).¹ It is licensed for the treatment of patients with type 2 diabetes to improve glycaemic control in combination with metformin or a glitazone, when diet and exercise, plus metformin or a glitazone do not provide adequate glycaemic control. The recommended dose is 100mg once daily; the dosage of metformin or glitazone should be maintained, and sitagliptin administered concomitantly. Sitagliptin is not currently licensed for use in triple therapy.

How effective is it?

Four randomised, double-blind trials have assessed the efficacy of sitagliptin in combination with metformin or a glitazone in patients with type 2 diabetes who despite treatment had inadequate glycaemic control (glycosylated haemoglobin (HbA_{1c}) $\geq 6.5\%$ and $\leq 11\%$).²⁻⁵ In all four studies patients underwent a dose titration/stabilisation and/or placebo run-in period. The main efficacy measure was the change in HbA_{1c} from baseline. Secondary endpoints included; proportion of patients achieving HbA_{1c} $< 7\%$.

A 24-week study assessed the efficacy of adding Sitagliptin to ongoing metformin therapy.² Patients were randomised (2:1) to receive sitagliptin 100mg/day (n=464) or placebo (n=237), in addition to metformin (≥ 1500 mg/day). Rescue therapy with pioglitazone was allowed for patients not meeting glycaemic goals. After 24 weeks sitagliptin plus metformin was associated with significant reductions in HbA_{1c} compared to placebo plus metformin (placebo-subtracted mean change from baseline -0.65% [95% CI -0.77% to -0.53%], $p < 0.001$). A significantly greater proportion of patients achieved an HbA_{1c} $< 7\%$ with sitagliptin than with placebo (47% vs. 18.3%, $p < 0.001$).

Significantly fewer patients receiving sitagliptin than those receiving placebo required pioglitazone rescue therapy (4.5% vs. 13.5%, $p < 0.001$).

A second 24-week study randomised 1,091 patients to sitagliptin 100mg/day, metformin 1g or 2g/day, sitagliptin 100mg/day plus either 1g or 2g/day metformin, or placebo.³

All active treatments produced significant reductions in HbA_{1c} from baseline compared to placebo (0.83% for sitagliptin alone, 0.99% and 1.3% for metformin 1g and 2g, and 1.57% and 2.07% for sitagliptin plus 1g and 2g metformin respectively, $p < 0.001$ for combination vs. respective monotherapy).

A further 24-week study assessed the efficacy of adding sitagliptin to ongoing pioglitazone therapy.⁴ Patients were randomised (1:1) to receive sitagliptin 100mg/day (n=175) or placebo (n=178), in addition to pioglitazone (30mg/day or 45mg/day). Rescue therapy with metformin was allowed for patients not meeting glycaemic goals. The placebo-subtracted mean change from baseline was -0.70 [95% CI -0.85% to -0.54%], $p < 0.001$) for sitagliptin plus pioglitazone. A significantly greater proportion of patients achieved an HbA_{1c} $< 7\%$ with sitagliptin than with placebo (45% vs. 18.3%, $p < 0.001$). Significantly fewer patients receiving sitagliptin required rescue therapy (6.9% vs. 14.0%, $p < 0.05$).

A 52-week non-inferiority trial compared the addition of sitagliptin or glipizide to metformin.⁵ Patients were randomised to sitagliptin 100mg daily (n=588), or glipizide up to 10mg BID (n=584). The mean change from baseline HbA_{1c} using sitagliptin plus metformin was shown to be non-inferior to glipizide plus metformin (-0.67% for both groups). The proportion of patients achieving an HbA_{1c} $< 7\%$ was similar between the two groups (63% vs. 59%, respectively). Sitagliptin was associated with a small weight loss (-1.5 kg) compared to a small weight gain ($+1.1$ kg) in those receiving glipizide in this study ($p < 0.001$).

How safe is it?

Sitagliptin added to either metformin or pioglitazone was not associated with significantly increased incidences of hypoglycaemia or overall gastrointestinal adverse events.^{2,4} The most common adverse effects occurring at a higher incidence compared to placebo were nasopharyngitis, urinary tract infection, arthralgia, back pain and cough when taken in combination with metformin,^{2,3} and abdominal pain, upper respiratory infection, headache and oedema when taken in combination with pioglitazone.⁴ Sitagliptin was associated with a significantly lower incidence of

hypoglycaemia compared to glipizide.⁵ Although sitagliptin therapy resulted in a small weight loss in one study, it is generally associated with weight-neutrality.

What other options are there?

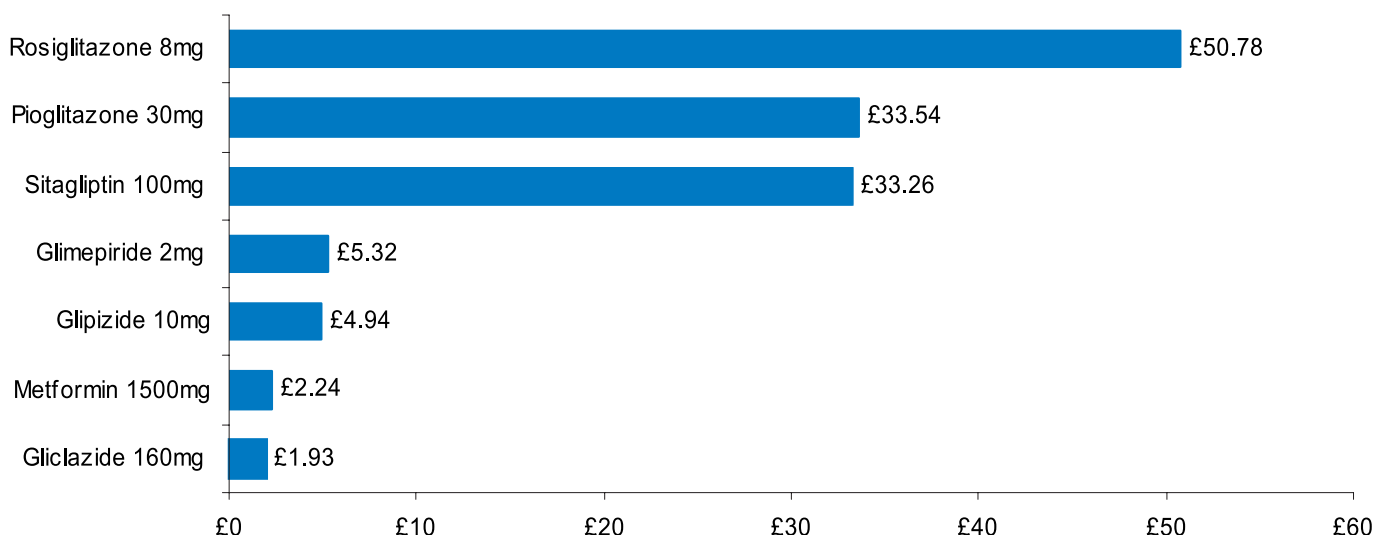
Drug treatment should only be used to augment the effects of a diet and exercise programme and not to replace them. NICE guidance for type 2 diabetes recommends metformin and sulphonylureas as the first-line therapy for all patients.⁶ A combination of the two drugs should then be used as second-line therapy.⁶ The use of glitazones is only recommended for those who are unable to take metformin and a sulphonylurea in combination because of intolerance or a contraindication to one of the agents.⁷ Although NICE guidelines acknowledge that triple combination therapy (sulphonylurea, metformin and a glitazone) is widely practised in the UK, the licence at that time did not allow the Institute to recommend the use of glitazones, as monotherapy, as triple combination therapy, or

in combination with insulin.⁷ In obese patients who fail to achieve glycaemic control on maximal dose oral antidiabetic agents, exenatide in combination with metformin, or a sulphonylurea may be considered as an alternative to insulin therapy.^{8,9} NICE guidance on type 2 diabetes is currently being updated and new indications for glitazones as monotherapy and triple therapy will be considered. The new guidance is due to be published in 2008.¹⁰

When should it be used?

Sitagliptin in combination with metformin or a glitazone may be considered an option for those patients who fail to achieve glycaemic control despite an adequate trial of established first and second-line oral regimens. There is no evidence to support use as triple therapy. Furthermore, comparative data with existing recommended combination regimens and long-term safety data are lacking, and the effects of sitagliptin on morbidity and mortality have not yet been demonstrated.

How much does it cost?



N.B. Daily doses shown for general comparison only and do not imply therapeutic equivalence.

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KEY RCT - randomised controlled trial; G - guideline.