

NEW DRUG EVALUATION

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SAXAGLIPTIN

Saxagliptin, when used in combination with metformin, a sulphonylurea or a glitazone, produces modest improvements in glycaemic control. In line with current NICE guidance on the use of other DPP-4 inhibitors, add-on therapy with saxagliptin may be considered an option for patients who do not achieve glycaemic control despite an adequate trial of established first and second line regimens. There is currently no evidence to indicate that saxagliptin offers any significant advantages over other licensed DPP-4 inhibitors in terms of efficacy, safety or cost-effectiveness. Saxagliptin treatment should only be initiated by a clinician with a special interest in the management of type 2 diabetes.

Saxagliptin (Onglyza[®], Bristol Myers Squibb) is the third dipeptidyl peptidase (DPP-4) inhibitor to be launched in the UK. It is licensed for the treatment of type II diabetes in combination with either metformin, a sulphonylurea or a thiazolidinedione (glitazone) when, in combination with diet and exercise, these drugs do not provide adequate glycaemic control.¹ The recommended dose is 5 mg once daily, with or without food, at any time of day.¹ Saxagliptin is not licensed for use as monotherapy or as a component of triple therapy

How effective is it?

The efficacy of saxagliptin in combination with metformin, a sulphonylurea or a glitazone has been evaluated in four phase III, randomised, controlled, double-blind trials involving more than 3,000 patients in total.²⁻⁵ All four studies recruited patients with type II diabetes and poor glycaemic control, defined as HbA_{1c} between 7% and 12%. The primary endpoint in each study was the change in HbA_{1c} from baseline to 24 weeks.

In the largest trial, 1,306 treatment-naïve patients were randomised into four groups; saxagliptin 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo or metformin 500 mg + placebo (daily doses).² In patients receiving metformin, the dose was titrated to a maximum of 2,000 mg daily. At 24 weeks, patients receiving saxagliptin 5 mg or 10 mg + metformin 500 mg showed significantly greater reductions from baseline in HbA_{1c} compared with saxagliptin and metformin monotherapies (-2.5% and -2.5% vs. -1.7% and -2.0%, respectively, all $p < 0.0001$ vs. monotherapy).²

A study involving 768 patients assessed the efficacy of adding saxagliptin to submaximal doses of glibenclamide, compared with up-titration of glibenclamide monotherapy.³ Inclusion criteria required patients to be taking a submaximal dose of any sulphonylurea. Patients were randomised to receive saxagliptin 2.5 or 5 mg + glibenclamide 7.5 mg, or glibenclamide 10 mg + placebo. Blinded up-titration was allowed in the glibenclamide-only arm to a maximum total daily dose of 15 mg. At week 24 both saxagliptin groups showed significantly greater reductions from baseline in HbA_{1c}

compared with up-titrated glibenclamide. (-0.54% and -0.64% vs. +0.08%, respectively, both $p < 0.0001$ vs. monotherapy).³

A further trial in 743 patients assessed the efficacy of adding saxagliptin to stable doses of metformin. ($\geq 1,500$ mg/day to $\leq 2,550$ mg/day).⁴ Patients were randomised to one of four study groups; saxagliptin 2.5, 5, 10 mg once daily or placebo + stable dose metformin dose. At week 24, the groups treated with saxagliptin showed significantly greater reductions from baseline in HbA_{1c} compared with metformin monotherapy (-0.59%, -0.69% and -0.58% vs. +0.13%, respectively, all $p < 0.0001$ vs. placebo).⁴

A recently published study assessed the efficacy of adding saxagliptin to stable doses of glitazone (pioglitazone 30 or 40 mg, or rosiglitazone 4 or 8 mg). A total of 565 patients were randomised to receive saxagliptin 2.5, 5 mg or placebo + stable glitazone dose.⁵ At week 24, both saxagliptin groups showed significantly greater reductions from baseline in HbA_{1c} compared with glitazone monotherapy (-0.66%, $p = 0.0007$ and -0.94%, $p < 0.0001$, vs. -0.30%, respectively).⁵

How safe is it?

The most commonly reported AEs in patients treated with saxagliptin 5 mg include upper respiratory tract infection, urinary tract infection, gastroenteritis, sinusitis, headache and vomiting.³⁻⁵ Although there are no direct comparative data to assess how saxagliptin compares to established antidiabetic agents, one study provided data to compare the safety of saxagliptin and metformin monotherapy.² Overall there were few differences between the saxagliptin and metformin monotherapy groups. The most common AEs compared with metformin alone were nasopharyngitis (4.5% vs. 4%), headache (7.9% vs. 5.2%), diarrhoea (6.4% vs. 7.3%) and hypertension (4.8% vs. 3.4%).² Across all studies the majority of AEs were described as mild or moderate in intensity and self-limiting in nature. Saxagliptin when added to metformin, a sulphonylurea or a glitazone was not associated with a significantly increased incidence of hypoglycaemia, compared with either agent alone.²⁻⁵

All suspected adverse reactions to black triangle drugs such as saxagliptin should be reported to the MHRA via the Yellow Card Scheme (www.yellowcard.gov.uk).

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. There are well established treatment protocols and guidelines for treating diabetes using established oral antidiabetic drugs. Metformin and sulphonylureas remain first choice pharmacological options in most patients.⁶ A combination of the two drugs should be used as second-line therapy. Initiation of treatment should be the responsibility of clinicians experienced in the treatment of type II diabetes.

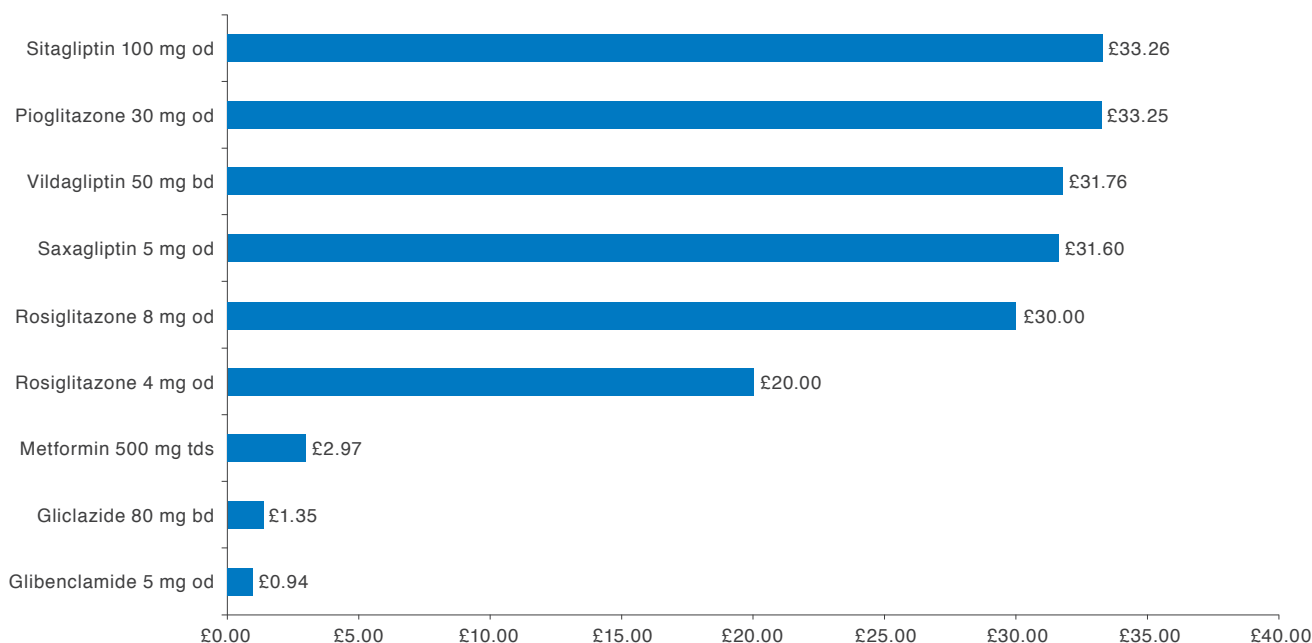
When should it be used?

NICE guidance covering other DPP-4 inhibitors (vildagliptin and sitagliptin) but not saxagliptin recommends that a DPP-4

inhibitor may be considered instead of a sulphonylurea as second-line therapy to first-line metformin if glycaemic control is inadequate and the patient is considered at risk of hypoglycaemia or its consequences; or if a sulphonylurea is otherwise unsuitable.⁶ A DPP-4 inhibitor may be considered as add-on therapy to a sulphonylurea if glycaemic control is inadequate and metformin is contraindicated or not tolerated. A DPP-4 inhibitor may be preferable to a glitazone if further weight gain is undesirable or if a glitazone is contraindicated or not tolerated.⁶ DPP-4 inhibitor therapy should only be continued following a beneficial metabolic response to therapy (a reduction of at least 0.5% in HbA_{1c} in six months).⁶ There is currently no evidence to indicate that saxagliptin offers any significant advantages over the other DPP-4 inhibitors in terms of efficacy, safety or cost-effectiveness,^{7,8} and long-term data are limited. Saxagliptin treatment should only be initiated by a clinician with a special interest in the management of type 2 diabetes.

How much does it cost?

Cost for 28 days treatment (Drug Tariff and eMIMS, January 2010)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence. Average daily quantity (ADQ) values are used where appropriate

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