

NEW DRUG EVALUATION

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VILDAGLIPTIN

Vildagliptin, when added to metformin, a sulphonylurea, or a glitazone, produces a modest but statistically significant improvement in HbA_{1c}. It may be considered as an option for patients who fail to achieve glycaemic control despite an adequate trial of established first- and second-line oral antidiabetic drugs but there is currently little long-term safety or cardiovascular outcome data. Its appropriate place in treatment protocols is presently undetermined.

What is it?

Vildagliptin (Galvus[®]▼, Novartis) is the second dipeptidyl peptidase inhibitor drug available in the UK.¹ It is licensed for the treatment of type 2 diabetes in combination with a sulphonylurea (50 mg once daily), metformin or a glitazone (50 mg twice daily). It is not licensed for mono- or triple-therapy use.²

How effective is it?

Vildagliptin has been evaluated in six randomised, double-blind, controlled studies of 24 to 52 weeks duration relating to its licensed indication.^{3,8}

In combination with metformin

Vildagliptin 50 mg once or twice daily plus metformin (n = 143 in both groups) has been compared with placebo plus metformin (n = 130) in patients with a baseline HbA_{1c} between 7.5 and 11% (mean 8.4%) despite metformin therapy.³ After 24 weeks patients in the once daily group had a 0.5% mean reduction in HbA_{1c}, compared with a 0.9% reduction in the twice daily group and an increase of 0.2% in the placebo group (p < 0.001 for each active vs. placebo comparison).³

An active comparator study compared vildagliptin 50 mg twice daily (n = 295) with pioglitazone 30 mg once daily (n = 281), when added to pre-existing metformin therapy.⁴ Patients had a HbA_{1c} of 7.5 to 11% (mean 8.4%) despite a mean daily dose of > 2 g of metformin and treatment duration of nearly four years.⁴ Mean reduction in HbA_{1c} from baseline to 24 weeks was 0.9% and 1.0% respectively (difference not significant).⁴

In a 52 week study, vildagliptin 50 mg once daily plus metformin (n = 42) produced a 0.5% mean HbA_{1c} reduction from baseline compared with a 0.6% increase with placebo plus metformin (n = 29), between group difference 1.1% (p < 0.0001).⁵

In combination with a sulphonylurea

Vildagliptin 50 mg once or twice daily plus gliclazide 4 mg once daily (n = 132 in each group) has been compared with gliclazide 4 mg once daily plus placebo (n = 144) in one 24-week randomised controlled trial.⁶ From baseline to 24 weeks HbA_{1c} changed by - 0.6%, - 0.6% and + 0.1% respectively (p < 0.001 for each active

vs. placebo comparison).⁶ In this scenario, 100 mg vildagliptin daily provided little additional benefit compared with 50 mg daily.²

In combination with a glitazone

Vildagliptin 50 mg once or twice daily plus pioglitazone 45 mg once daily has been compared with placebo plus pioglitazone 45 mg once daily in a 24 week study (n = 124, 136, and 138 respectively).⁷ Patients had uncontrolled diabetes (HbA_{1c} 7.5 to 11%, mean 8.7%) despite at least four weeks treatment with rosiglitazone ≥ 4 mg daily or pioglitazone ≥ 30 mg daily.⁷ The vildagliptin 50 mg group demonstrated a mean reduction of 0.8% in HbA_{1c} compared with 1.0% for vildagliptin 100 mg, and 0.3% for placebo (p ≤ 0.001 for each active vs. placebo comparison).⁷

A 24 week study compared vildagliptin 100 mg daily monotherapy (n = 150) with pioglitazone 30 mg daily monotherapy (n = 157), vildagliptin 100 mg plus pioglitazone 30 mg daily (high dose dual therapy, n = 146), and vildagliptin 50 mg plus pioglitazone 15 mg daily (low dose dual therapy, n = 139).⁸ Patients had uncontrolled diabetes (HbA_{1c} 7.5 to 11%, mean 8.7%) not currently treated with oral antidiabetic drugs.⁸ From baseline to 24 weeks the vildagliptin monotherapy group demonstrated a reduction in HbA_{1c} of 1.1% compared with 1.4% for pioglitazone monotherapy (p < 0.001). Dual therapy demonstrated a 1.9% reduction in HbA_{1c} for the high dose dual therapy group (p = 0.039) and 1.7% in the low dose dual therapy group (p not stated).⁸

How safe is it?

The overall incidence of any adverse effect with vildagliptin is similar to that observed in the active control groups of the comparator studies.^{3,8} In the 52 week study one case of atrioventricular block and one case of peripheral oedema were considered to be related to vildagliptin.⁵ A small number of clinically non-significant episodes of hypoglycaemia were also observed.^{3,5,6} In combination with pioglitazone, vildagliptin appears to increase the incidence of some adverse effects irrespective of the dose of vildagliptin.⁷ The most common adverse effects were peripheral oedema, arthralgia, dizziness, weight gain, infections and headache.^{7,8}

What other options are there?

There are well established treatment protocols and guidelines for treating diabetes using established therapeutic groups i.e. metformin, sulphonylureas (e.g. gliclazide) and glitazones (rosiglitazone and pioglitazone).^{9,10} Sitagliptin has been available in the UK since April 2007 and has the same mode of action and licensed indications as vildagliptin. They appear to have similar efficacy and safety profiles, and both are considered to be weight-neutral, although no comparative studies of the two drugs have been published.¹

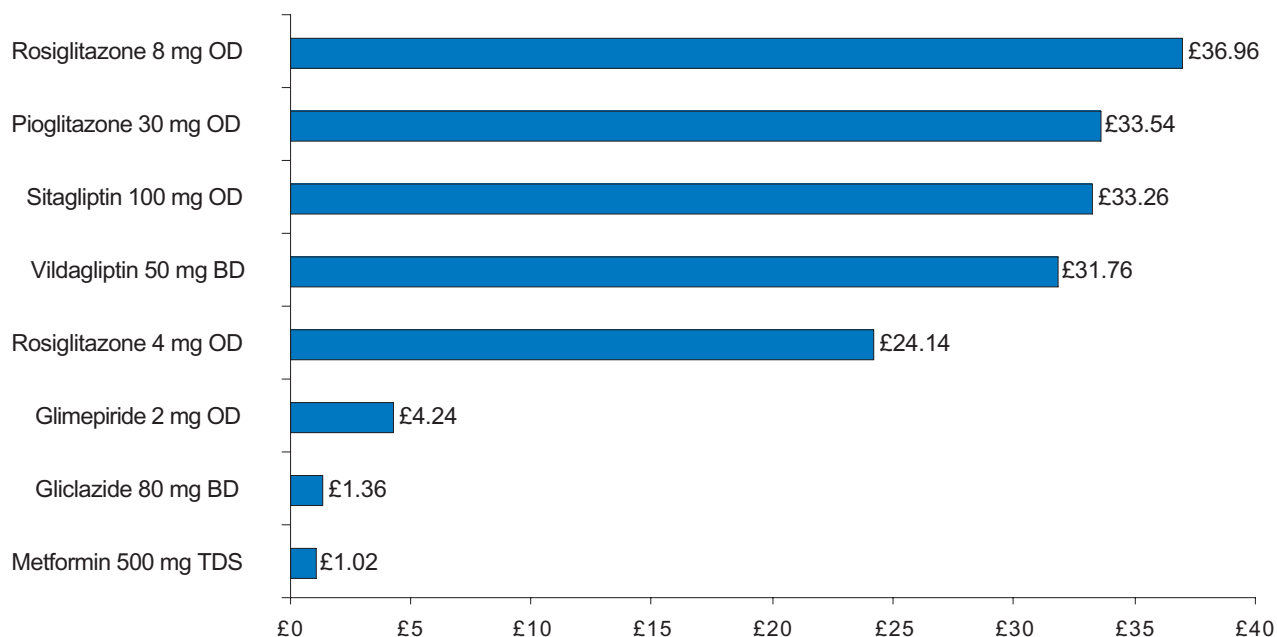
When should it be used?

There is a paucity of comparative data with common combination regimens and no long-term safety data. The effects of vildagliptin on

morbidity and mortality have not been demonstrated. Studies of vildagliptin in combination with established oral antidiabetic drugs as dual therapy have demonstrated clinically modest but statistically significant improvements in HbA_{1c} compared to metformin, sulphonylurea, or glitazone alone^{3,5-8} but the exact place of vildagliptin in treatment protocols is undetermined at the present time. It may be considered as an option for patients who fail to achieve glycaemic control despite an adequate trial of established first- and second-line oral antidiabetic drugs but there is currently little long-term safety or cardiovascular outcome data. Initiation of treatment should remain with clinicians experienced in the treatment of type 2 diabetes.

How much does it cost?

Cost for 28 days treatment (Drug Tariff and NHS dm+d, March 2008)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, G - guideline, R - review

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