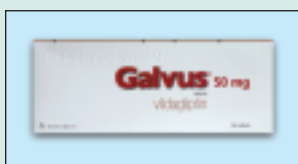


Vildagliptin: alternative add-on therapy for oral glycaemic control

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KEY POINTS

- vildagliptin is the second oral DPP-4 inhibitor to be introduced for the treatment of type 2 diabetes
- it is licensed as an add-on therapy when glycaemic control is poor after appropriate treatment with metformin, a sulphonylurea or a glitazone; it is not licensed as part of triple therapy
- vildagliptin is available as a single-component formulation of a 50mg tablet (Galvus) and in a combination of 50mg with metformin 850 or 1000mg (Eucreas)
- the dose is 50mg once or twice daily combined with metformin or a glitazone and 50mg once daily with a sulphonylurea
- in clinical trials lasting 24 weeks in overweight or obese patients with poor glycaemic control, adding vildagliptin to monotherapy with an oral hypoglycaemic reduced HbA_{1c} by approximately 0.5-1.0 per cent compared with up to 0.3 per cent with placebo
- vildagliptin is noninferior to pioglitazone as an add-on in reducing HbA_{1c}
- the maximum reduction in HbA_{1c} with vildagliptin occurs at 12-16 weeks
- vildagliptin does not affect body weight; treatment is well tolerated
- liver enzymes must be checked before treatment, every three months during first year of treatment, then periodically
- metformin plus vildagliptin should be considered when there is a risk of hypoglycaemia or unacceptable weight gain with a sulphonylurea, and where there is concern about weight gain, heart failure or bone fractures with a glitazone



Vildagliptin, an oral DPP-4 inhibitor, is licensed as an add-on therapy when adequate glycaemic control has not been achieved with metformin, a sulphonylurea or a glitazone. In our New products review Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Professor Ian Campbell comments on its place in type 2 diabetes therapy.

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

Basal levels of GIP and GLP-1 are low but increase rapidly after ingestion of food; they are inactivated by the enzyme dipeptidyl-

peptidase 4 (DPP-4).¹ Both GIP and GLP-1 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

There are now three drugs acting on the incretin system and licensed for type 2 diabetes: the injection-only incretin-mimetic exenatide (Byetta – for use with metformin and/or a sulphonylurea but not a glitazone), and the two orally active DPP-4 inhibitors sitagliptin (Januvia – for use with metformin and/or a sulphonylurea, or with a glitazone) and most recently vildagliptin.

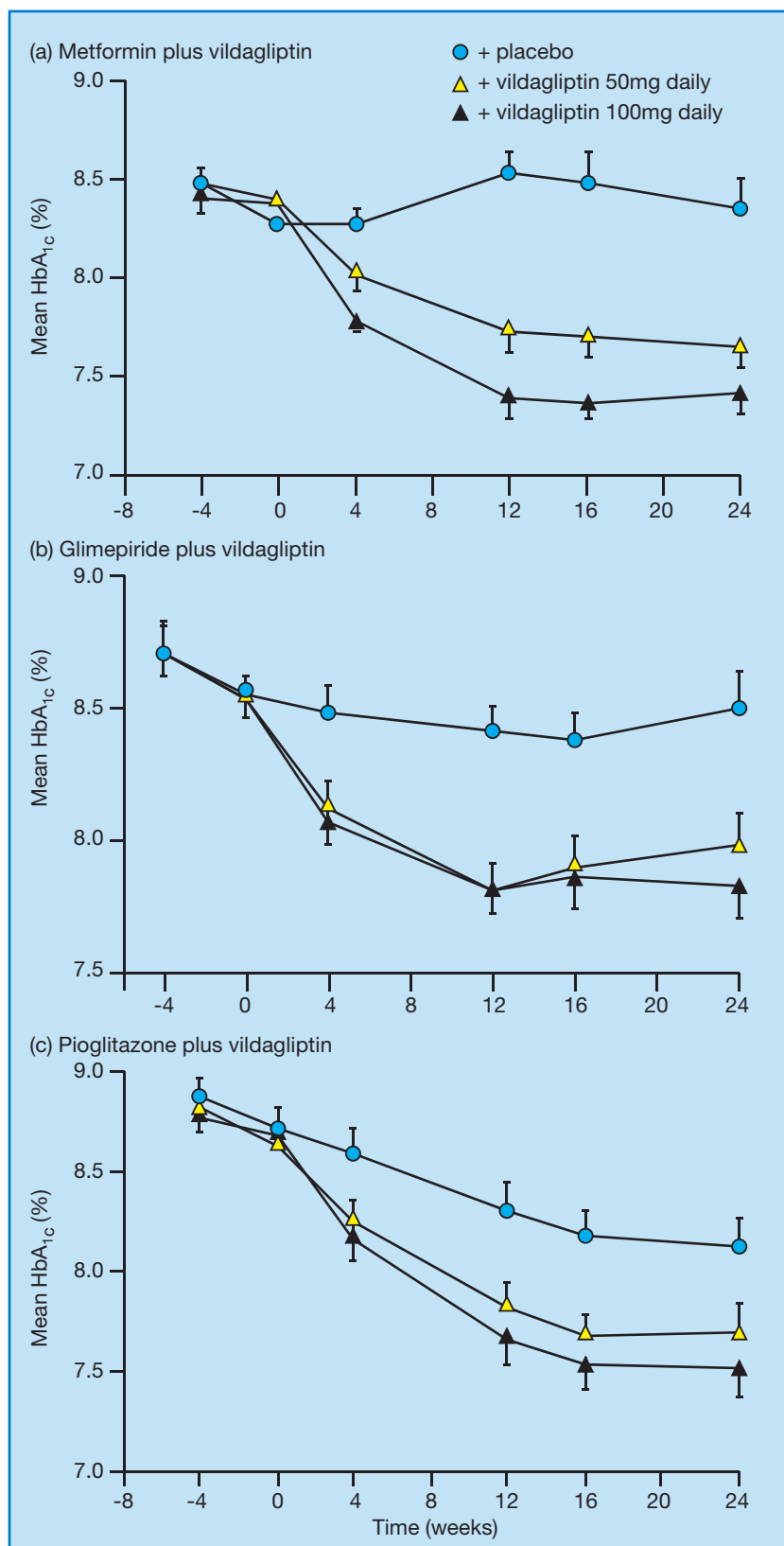


Figure 1. Change in mean HbA_{1c} after addition of placebo or vildagliptin 50mg once or twice daily to (a) metformin,² (b) glimepiride³ or (c) pioglitazone⁴

The technology

When added to inadequate treatment (see below) with metformin, glimepiride or pioglitazone (Actos), vildagliptin reduced post-prandial glucose levels and improved beta-cell function.²⁻⁴ It also reduced fasting plasma glucose (FPG) levels, though the difference was statistically significant compared with placebo only in patients taking metformin.

Vildagliptin is available as a single-component formulation of a 50mg tablet (Galvus) and in a combination of 50mg with metformin 850 or 1000mg (Eucreas). It is licensed for use with metformin, a sulphonylurea (but not both) or a glitazone when adequate doses of these agents fail to achieve glycaemic control in patients with type 2 diabetes. The recommended dose is 50mg morning and evening with metformin or a glitazone, and with a sulphonylurea 50mg in the morning.

No dose adjustment is indicated for older patients or in patients with mild renal impairment. Vildagliptin is contraindicated in patients with moderate to severe renal or hepatic impairment.

Clinical trials

Vildagliptin has been evaluated as add-on treatment after monotherapy with metformin,² glimepiride³ or pioglitazone⁴ has not achieved target HbA_{1c}. It has been compared with pioglitazone as additional treatment to metformin.⁵

The protocols in the three add-on trials²⁻⁴ were similar and all were double blind. Patients with HbA_{1c} 7.5-11.0 per cent after at least three months' treatment with the baseline drug were randomised to placebo or vildagliptin 50mg once or twice daily. The primary endpoint was the change in HbA_{1c} after 24 weeks. Secondary end-

points were FPG, changes in lipids and body weight.

At baseline mean HbA_{1c} was 8.4-8.7 per cent, mean FPG 9.7-10.5mmol per litre, mean body mass index (BMI) 31-33, mean age 54-58 years and mean duration of diabetes was approximately five to eight years.

In 416 patients failing on metformin monotherapy (mean dose 2.1g per day), vildagliptin 50mg once or twice daily reduced HbA_{1c} by significantly more than placebo: -0.5 and -0.9 per cent respectively *vs* +0.2 per cent (see Figure 1).² The proportions of patients achieving target HbA_{1c} (<7 per cent) decreased with worsening baseline glycaemic control – from 50 and 54 per cent with vildagliptin *vs* 14 per cent with placebo at baseline HbA_{1c} <7.9 per cent, to 7.7 and 16 *vs* 2 per cent at baseline HbA_{1c} >8.5 per cent.

In 408 patients taking sulphonylureas with poor baseline glycaemic control, the mean duration of treatment was approximately four years. The doses were not reported and may have been low – minimum glibenclamide or glipizide ≥7.5mg per day, gliclazide ≥2mg per day;³ it is therefore unclear whether these patients truly represent sulphonylurea failure before all were switched to gliclazide 4mg per day.

Although vildagliptin 50mg was administered once and twice daily, the higher dose was not more effective and only data for the licensed dose of 50mg once daily are reported here.

Vildagliptin reduced mean HbA_{1c} by 0.58 per cent compared with an increase of 0.07 per cent with placebo (see Figure 1). The reduction in HbA_{1c} was greater in older patients (<65 *vs* ≥65 years) and, by contrast with metformin and pioglitazone therapy, also among patients with poorer base-

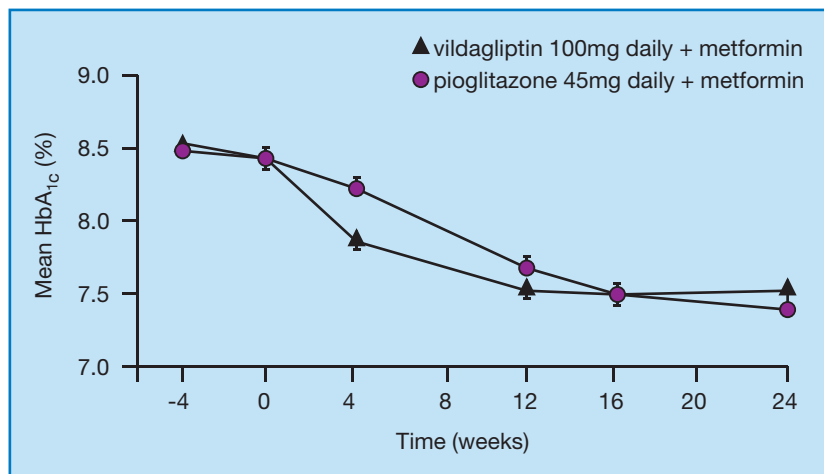


Figure 2. Similar changes in mean HbA_{1c} after addition of vildagliptin 50mg twice daily or pioglitazone 45mg daily to metformin 2g daily⁵

line glycaemic control (HbA_{1c} above *vs* 9 per cent or below). Target HbA_{1c} <7 per cent was achieved in 21 per cent of patients taking vildagliptin and 12 per cent with placebo.

In another trial 398 patients with poor glycaemic control after treatment with rosiglitazone ≥4mg per day or pioglitazone ≥30mg per day were switched to pioglitazone 45mg per day before being randomised to receive placebo or vildagliptin 50mg once or twice daily.⁴ Vildagliptin reduced HbA_{1c} significantly more than placebo: -0.8 and -1.0 respectively *vs* -0.3 per cent (see Figure 1). The proportions of patients achieving HbA_{1c} <7 per cent were 29 and 36 *vs* 15 per cent with placebo; these proportions were approximately doubled in patients with good baseline glycaemic control (HbA_{1c} ≤8 per cent).

In each of these trials, the maximum reduction in HbA_{1c} occurred 12-16 weeks after beginning treatment with vildagliptin (see Figure 1).

A noninferiority trial compared vildagliptin 50mg twice daily with pioglitazone 30mg per day as add-on therapy in 576 patients with poor glycaemic control despite 43 months' treatment with metformin

(mean 2.0g per cent day).⁵ After 24 weeks, there was no significant difference in HbA_{1c} reduction (0.88 *vs* 0.98 per cent with pioglitazone), though with pioglitazone change was slower (see Figure 2) and was more marked in obese patients, whereas vildagliptin's effects were greater in nonobese patients.

Meta-analysis

A meta-analysis of 11 randomised trials of sitagliptin and 14 of vildagliptin found similar reductions in HbA_{1c}. Neither was superior to other hypoglycaemic agents and neither was associated with weight gain.⁶

Adverse effects

There was little difference between vildagliptin and placebo in the frequency or nature of adverse effects reported in these trials. Vildagliptin had little effect on body weight compared with an increase with pioglitazone.^{4,5} Changes in lipids were modest and not clinically significant. Hypoglycaemia was rare and no more frequent than with placebo at the licensed doses. The meta-analysis found an increased risk of all-cause infection with sitagliptin (relative risk, RR,

1.15; CI 95% 1.02-1.31) but not with vildagliptin (RR 1.04; CI 95% 0.87-1.24).⁶

The most frequent adverse effects associated with vildagliptin reported in all clinical studies were tremor, headache and dizziness (plus metformin or sulphonylurea); nausea (plus metformin); asthenia (plus sulphonylurea); and weight increase and peripheral oedema (plus glitazone).⁷

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

Place in therapy

With any new medication, I ask myself three questions: is it effective, is it safe and what advantage is there in prescribing it?

Efficacy

The available data for vildagliptin show similar efficacy to sitagliptin

with an average reduction in HbA_{1c} of 0.5-1.0 per cent compared with up to 0.3 per cent with placebo in clinical trials. It is therefore licensed as an add-on therapy to metformin, a sulphonylurea or a glitazone but, unlike sitagliptin, the other gliptin, it does not have a licence for triple oral hypoglycaemic agent (OHA) therapy.

Safety

There are special precautions for the use of vildagliptin. As there is limited experience of the drug in moderate to severe renal impairment, the drug is not recommended in these situations. There are rare reported cases of hepatic dysfunction (including hepatitis), therefore the drug

should not be used in patients with hepatic impairment, including any patient with pretreatment ALT (alanine aminotransferase) or AST (aspartate aminotransferase) >3xULN (upper limit of normal). Liver function tests are required to be done prior to therapy with vildagliptin and thereafter should be checked at

three-monthly intervals during the year, and periodically thereafter.

Skin disorders, including blistering and ulceration, have been reported in monkeys and, although not seen in human clinical trials, it is recommended that monitoring for skin disorders is required.

The Federal Drug Administration (FDA) has not granted approval for vildagliptin in the USA until further safety data are available. There are no similar restrictions for sitagliptin use.

Advantage

What is the place of vildagliptin in type 2 diabetes therapy? The gliptins were not reviewed in the recent National Institute for Health and Clinical Excellence (NICE) guidance update on the management of type 2 diabetes.^{1,2}

Vildagliptin, like sitagliptin, will compete with the sulphonylureas and glitazones as a combination OHA with metformin, and is to be considered when there is a risk of hypoglycaemia or unacceptable weight gain with a sulphonylurea, and where there is concern about weight gain, heart failure or bone

fractures with a glitazone. The potential benefits of being weight neutral and to have a very low risk of hypoglycaemia would have to be considered for each individual patient.

Unlike the GLP-1 injectable analogue exenatide, there is much less weight reduction with vildagliptin. NICE recommends exenatide only when insulin would be otherwise started, obesity is a specific problem (BMI >35kg per m²) and the need for high-dose insulin is likely. If improved blood glucose control is not obtained and body weight not lost, exenatide should not be continued beyond 12 months.²

As mentioned above, no guidance for vildagliptin (and sitagliptin) was given in the NICE document, and at the present time the gliptins are looking for a place

in the type 2 diabetes treatment algorithm. Vildagliptin, along with sitagliptin, is being reviewed by NICE as part of the 'newer agents for blood glucose control' guideline, expected in early 2009.

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