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). 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). 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.

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.

**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 (Galvs) 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 HbA1c 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 HbA1c.
- The maximum reduction in HbA1c 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.

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.
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. 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, glimepiride or pioglitazone has not achieved target HbA1c. It has been compared with pioglitazone as additional treatment to metformin.

The protocols in the three add-on trials were similar and all were double blind. Patients with HbA1c 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 HbA1c after 24 weeks. Secondary end-
points were FPG, changes in lipids and body weight.

At baseline mean HbA1c 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 HbA1c 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 HbA1c (<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 HbA1c <7.9 per cent, to 7.7 and 16 vs 2 per cent at baseline HbA1c >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, glimepiride ≥2mg per day;3 it is therefore unclear whether these patients truly represent sulphonylurea failure before all were switched to glimepiride 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 HbA1c by 0.58 per cent compared with an increase of 0.07 per cent with placebo (see Figure 1). The reduction in HbA1c was greater in older patients (<65 vs ≥65 years) and, by contrast with metformin and pioglitazone therapy, also among patients with poorer baseline glycaemic control (HbA1c above vs 9 per cent or below). Target HbA1c <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 HbA1c significantly more than placebo: -0.8 and -1.0 respectively vs -0.3 per cent (see Figure 1). The proportions of patients achieving HbA1c <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 (HbA1c ≤8 per cent).

In each of these trials, the maximum reduction in HbA1c occurred 12-16 weeks after beginning treatment with vildagliptin.

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 HbA1c 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 HbA1c. 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).

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).

References

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 HbA1c 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 glitzone. 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.

**References**


By Ian Campbell, consultant physician at Victoria Hospital, Kirkcaldy, and honorary professor in the Department of Biological Sciences, Bute Medical School, University of St Andrews