Vildagliptin for the management of type 2 diabetes

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Vildagliptin (Galvus) is a new therapeutic option for patients with type 2 diabetes who are inadequately controlled on monotherapy with metformin or a sulfonylurea. It offers the advantage of improving glycaemic control with a low risk of hypoglycaemia and is not associated with weight gain.

What is vildagliptin?

Vildagliptin (Galvus) is an oral medication used to improve glycaemic control in patients with type 2 diabetes. It works as a dipeptidyl peptidase-4 (DPP-4) inhibitor (see Figure). This means that the DPP-4 enzyme cannot degrade the incretin hormones, glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), which are produced in response to oral food intake. An increase in GLP-1 levels produces a glucose-dependent increase of insulin secretion and reduces glucagon secretion from pancreatic β- and α-cells, respectively.

Vildagliptin reduces blood glucose levels and is most beneficial in reducing postprandial blood glucose elevations in patients with type 2 diabetes.

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When is it used?

Vildagliptin has slightly less efficacy compared with sulfonylureas or pioglitazone when used as monotherapy. It is best used as add-on therapy in patients already taking medication for type 2 diabetes and who have inadequate glycaemic control (see the box on page 74).

Data from double-blinded, randomised, controlled trials have shown the benefits of adding vildagliptin to pre-existing oral hypoglycaemic agents (see Table).[1-3]

Several studies have compared the efficacy of vildagliptin with sulfonylureas in improving glycaemic control in patients with type 2 diabetes who are inadequately controlled with metformin alone.[4,5] Vildagliptin, gliclazide and glimepiride have comparable efficacy when added to metformin monotherapy. However, vildagliptin is associated with fewer hypoglycaemic episodes and does not cause weight gain compared with gliclazide and glimepiride.[4,5]

A comparison between vildagliptin and pioglitazone as add-on therapy to metformin has also been made.[6,7] There appears to be equal efficacy in the ability to lower HbA_{1c} levels with both medications but there is no weight gain

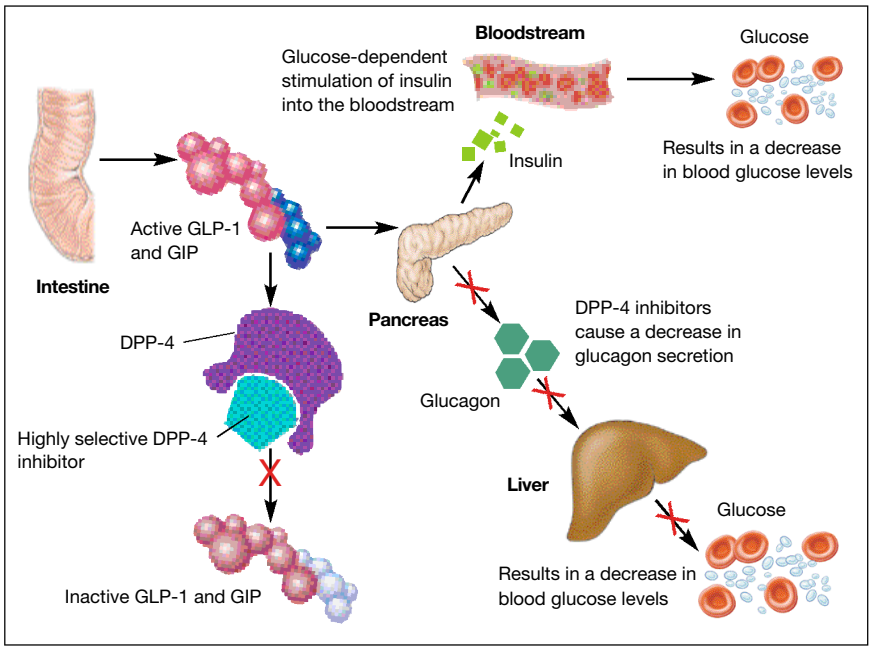

Figure. Concentrations of active GLP-1 and GIP hormones are increased by DPP-4 inhibition, thereby increasing and prolonging the actions of these hormones.

ABBREVIATIONS: DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = gut-derived glucagon-like peptide-1.

Case study. Management of a woman with type 2 diabetes experiencing hypoglycaemic episodes

Mrs Jones was diagnosed with type 2 diabetes five years ago. Although she attempted diet and exercise modifications, she required medication soon after the diagnosis to help improve her glycaemic control. She did not tolerate metformin and so commenced gliclazide, which was subsequently up-titrated to maximal therapeutic dose over the following years.

Recently her glycaemic control has worsened with HbA_{1c} levels of 7.5%. Since diagnosis, she has experienced several moderate hypoglycaemic episodes and she is concerned about more frequent episodes. She has normal renal and liver function. You discuss treatment options and she agrees to commence dual therapy with gliclazide 160 mg twice daily and vildagliptin 50 mg daily.

Mrs Jones returns to see you 12 weeks later and reports no side effects and no hypoglycaemic episodes. Her liver function tests remain normal and her HbA_{1c} level is now close to 7%.

associated with the addition of vildagliptin compared with pioglitazone.

Review of the literature found no studies investigating the efficacy of adding vildagliptin as a third agent in patients already taking dual therapy with metformin and a sulfonylurea.

There is limited evidence comparing the efficacy of vildagliptin with other DPP-4 inhibitors. A small study compared vildagliptin with sitagliptin in 38 patients and suggested fewer blood glucose excursions over a 48-hour period in the vildagliptin group.[8] A clinical trial is in progress comparing the safety and tolerability of the medications.

In March 2010, vildagliptin was approved by the TGA. The approved use is as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone if diet, exercise and the single agent do not result in adequate glycaemic control.

Vildagliptin is subsidised by the PBS (authority required; streamlined) for patients taking pre-existing metformin or a sulfonylurea who have HbA_{1c} levels greater than 7% within the previous four months and if a combination of metformin and a sulfonylurea is contraindicated or not tolerated. It is not subsidised for use in combination with both metformin and a sulfonylurea (triple oral therapy), as monotherapy, or in combination with a thiazolidinedione (glitazone).

How is it used?

Vildagliptin is an oral preparation and the maximal dose should not exceed 100 mg per day.

When vildagliptin is used as add-on therapy to metformin or pioglitazone (not subsidised), either 50 mg daily or 50 mg twice daily can be used. When vildagliptin is added to sulfonylurea therapy, 50 mg once daily in the morning is sufficient because there appears to be no added benefit when compared with a 100 mg daily dose. It can be administered with or without a meal.

What needs monitoring?

Renal function should be known before initiating vildagliptin treatment in a patient. There is insufficient evidence to support using vildagliptin in patients with an estimated glomerular filtration rate of less than 60 mL/min/m^2. This

Table. Benefits of adding vildagliptin to pre-existing oral hypoglycaemic agents[1-3]

Results of the 24-week study period	Metformin[1]		Pioglitazone[2]		Glimepiride[3]	
Dose of vildagliptin added	+ 50 mg daily	+ 50 mg twice daily	+ 50 mg daily	+ 50 mg twice daily	+ 50 mg daily	+ 50 mg twice daily
Mean baseline HbA_{1c} (%)	8.4	8.4	8.6	8.7	8.5	8.6
Mean reduction in HbA_{1c} from baseline (%)	0.5	0.9	0.8	1.0	0.6	0.6
Reduction in HbA_{1c} compared with placebo (%)	0.7	1.1	0.5	0.7	0.6	0.7
Achieving HbA_{1c} targets of <0.7%	46%	60%	54%	68%	47%	51%

differs from the DPP-4 inhibitor sitagliptin, an oral preparation taken once daily that can be used in patients with chronic kidney disease and in those who are haemodialysis-dependent providing there is a dose reduction (25 mg instead of 100 mg daily).

Vildagliptin should not be used in patients with hepatic impairment, including patients with pre-existing alanine transaminase or aspartate transaminase levels of more than 2.5 times the upper limit of normal. Liver function tests should be performed at initiation of treatment and then at three-monthly intervals during the first year of treatment. If alanine transaminase or aspartate transaminase levels increase above three times the upper limit of normal then vildagliptin should be discontinued. In comparison, hepatic impairment does not limit the use of sitagliptin in patients with type 2 diabetes.

Common side effects

Of 6135 patients taking vildagliptin, 69% reported an adverse event.[9] Most of these were mild and transient and did not require discontinuation of the drug. The most commonly reported side effects were headache, tremor and dizziness.

Patients should be warned of the potential towards hypoglycaemia when vildagliptin is used as add-on therapy, particularly in combination with a sulfonylurea. When added to metformin or pioglitazone, hypoglycaemia is very uncommon.

Important precautions and interactions

No serious adverse reactions such as permanent drug-induced liver injury, pancreatitis, immune-mediated reactions or hypersensitivity reactions have been reported with the use of vildagliptin.[9] In comparison, pancreatitis and severe hypersensitivity reactions have been reported with the use of sitagliptin.

Vildagliptin has been found to elicit dose-dependent necrotic skin lesions in monkeys but not in humans.

A recent meta-analysis pooling data from 7508 patients taking vildagliptin did not find an increased risk of acute coronary syndrome, transient ischaemic attack, stroke or cardio-cerebrovascular death.[10] The studies included within this meta-analysis followed patients from 12 to 52 weeks from commencement of vildagliptin.

There is limited evidence regarding the longer-term safety of vildagliptin and other DPP-4 inhibitors, including cardiovascular and cerebrovascular outcomes. There have been no significant drug interactions reported.

Summary

Vildagliptin is a new therapeutic option for patients inadequately controlled on monotherapy with metformin or a sulfonylurea. It offers the advantage of improving glycaemic control with a low risk of hypoglycaemia and no association with weight gain. It lowers both fasting and postprandial blood glucose levels and reduces HbA_{1c} levels by approximately 0.5 to 1% over several months. It is generally well tolerated. MT

References

1. Bosi E, Camisasca RP, Collober C, Rochotte, E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Care 2007; 30: 890-895.
2. Garber AJ, Schweizer A, Baron MA, Rochotte E, Dejager S. Vildagliptin in combination with pioglitazone improves glycaemic control in patients with type 2 diabetes failing thiazolidinedione monotherapy: a randomized, placebo-controlled study. Diabetes Obes Metab 2007; 9: 166-174.
3. Garber AJ, Foley LE, Banerji MA, et al. Effects of vildagliptin on glucose control in patients with type 2 diabetes inadequately controlled with a sulphonylurea. Diabetes Obes Metab 2008; 10: 1047-1056.
4. Ferrannini E, Fonseca V, Zinman B, et al. Fifty-two-week efficacy and safety of vildagliptin vs. glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009; 11: 157-159.
5. Filozof C, Gautier JF. A comparison of efficacy and safety of vildagliptin and gliclazide in combination with metformin in patients with type 2 diabetes inadequately controlled with metformin alone: a 52-week, randomized study. Diabet Med 2010; 27: 318-326.
6. Bolli G, Dotta F, Rochotte E, Cohen SE. Efficacy and tolerability of vildagliptin vs. pioglitazone when added to metformin: a 24-week, randomized, double-blind study. Diabetes Obes Metab 2008; 10: 82-90.
7. Bolli G, Dotta F, Colin L, Minic B, Goodman M. Comparison of vildagliptin and pioglitazone in patients with type 2 diabetes inadequately controlled with metformin. Diabetes Obes Metab 2009; 11: 589-595.
8. Marfella R, Barbiera M, Grella R, Rizzo M, Nicoletti GF, Paolisso G. Effects of vildagliptin twice daily vs. sitagliptin once daily on 24-hour acute glucose fluctuations. J Diabetes Complications 2010; 24: 79-83.
9. Ligueros-Saylan M, Foley JE, Schweizer A, Couturier A, Kothny W. An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of phase II and III clinical trials. Diabetes Obes Metab 2010; 12: 495-509.
10. Schweizer A, Dejager S, Foley JE, Couturier A, Ligueros-Saylan M, Kothny W. Assessing the cardio-cerebrovascular safety of vildagliptin: meta-analysis of adjudicated events from a large phase III type 2 diabetes population. Diabetes Obes Metab 2010; 12: 485-494.

COMPETING INTERESTS: Dr Glastras: None. Dr Fulcher has been an invited speaker on behalf of Novartis Pharmaceuticals.