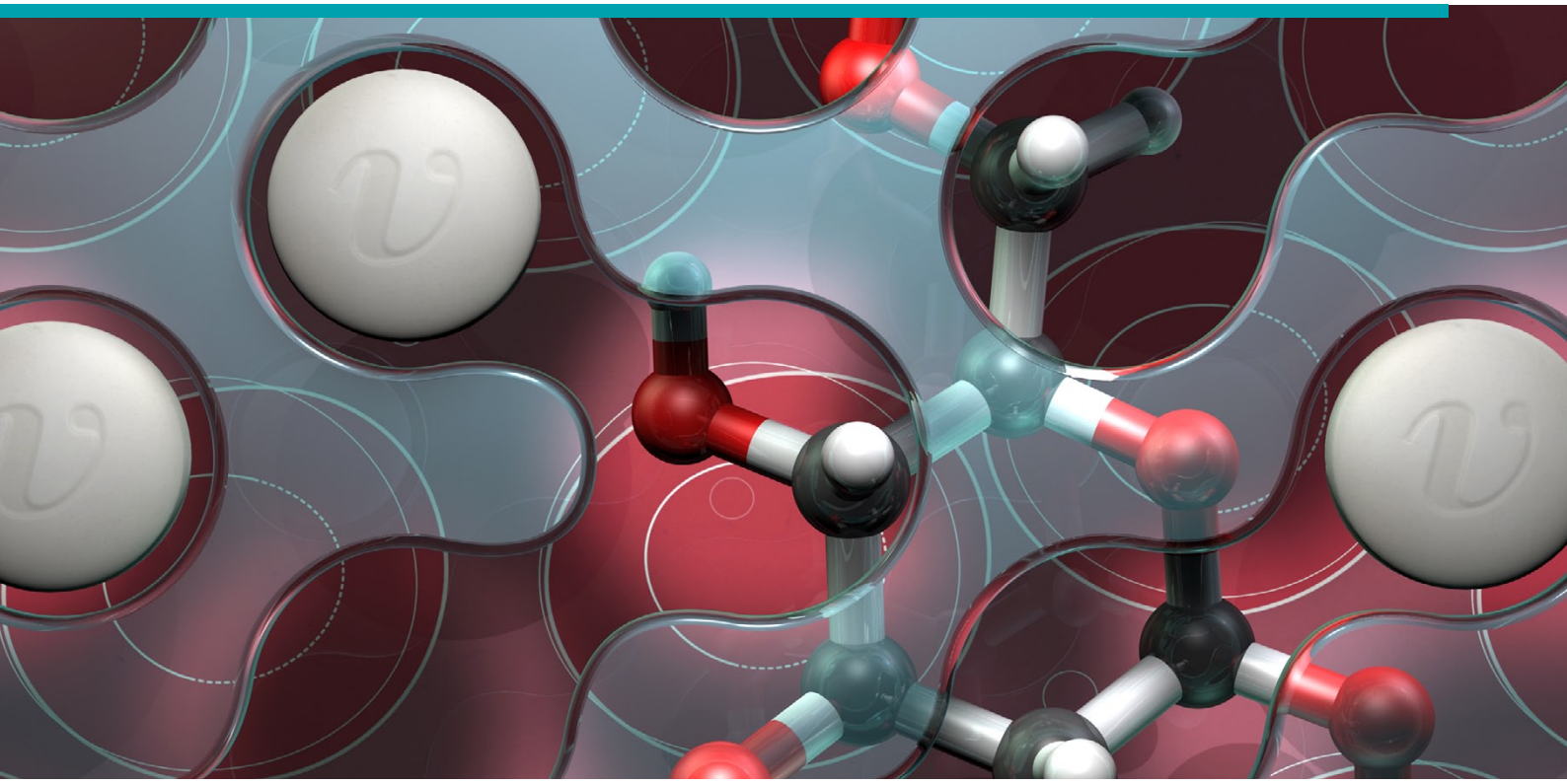


Vildagliptin: a new treatment for type 2 diabetes

Vildagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor available fully subsidised from 1 October, 2018. DPP-4 inhibitors have been approved for the treatment of type 2 diabetes in New Zealand for some time, however, this is the first time a medicine of this class has been subsidised for use in the community. Vildagliptin is an option for a second-line pharmacological treatment, for patients who have not achieved sufficient lowering of HbA_{1c} levels with metformin; other second-line options are a sulphonylurea or pioglitazone.

KEY PRACTICE POINTS:

- Lifestyle interventions and metformin are the first-line treatments for people with type 2 diabetes
- If an additional pharmacological treatment is required, clinicians and patients can choose between adding a sulphonylurea, pioglitazone or vildagliptin to metformin treatment, or using one of these alone if metformin is contraindicated or not tolerated
- Vildagliptin is a newly subsidised oral anti-diabetic medicine, taken once or twice daily, and is available alone or in combination with metformin
- Vildagliptin results in reductions in HbA_{1c} levels of 6–12 mmol/mol
- Vildagliptin does not cause weight gain and has less risk of hypoglycaemia than sulphonylurea medicines but is slightly less effective at reducing HbA_{1c} levels
- Nasopharyngitis, headache and dizziness are the most common adverse effects associated with vildagliptin, occurring in 6–9% of patients

This article focuses on the place of vildagliptin in the treatment of type 2 diabetes in New Zealand. For more extensive information on the management of type 2 diabetes, including advice on lifestyle interventions, managing cardiovascular risk and escalating pharmacological treatment, see:

- "Managing patients with type 2 diabetes: from lifestyle to insulin": **www.bpac.org.nz/BPJ/2015/December/diabetes.aspx**
- "A rising tide of type 2 diabetes in younger people: what can primary care do?": **www.bpac.org.nz/2018/diabetes.aspx**

DPP-4 inhibitors are a newly subsidised class of glucose lowering medicines

Glucagon-like peptide-1 (GLP-1) is a hormone that is rapidly released from the intestine after eating.[1] GLP-1 signals to the pancreas to increase insulin release, and reduce glucagon release, after a meal. In combination, these effects lead to higher insulin levels and a lowering of blood glucose levels. The effects of GLP-1 are usually confined to the period immediately after eating, as it is broken down within minutes by the enzyme dipeptidyl peptidase-4 (DPP-4).[1]

Several anti-diabetic medicines have been developed which aim to amplify the effects of GLP-1. These include oral DPP-4 inhibitors, which inhibit the DPP-4 enzyme and result in increased and prolonged action of GLP-1, and injectable synthetic versions of GLP-1 which are not broken down by DPP-4, known as GLP-1 mimetics or receptor agonists.

Vildagliptin is a DPP-4 inhibitor subsidised from 1 October, 2018

Vildagliptin is an oral DPP-4 inhibitor approved for the treatment of type 2 diabetes. By inhibiting DPP-4 and increasing GLP-1 levels, it results in higher insulin levels and lower glucose levels, particularly after eating.[2] Vildagliptin is typically used in combination with metformin; in people with type 2 diabetes who are already taking metformin, adding vildagliptin once or twice daily to their treatment regimen reduces HbA_{1c} levels by a further 7–12 mmol/mol after 12 weeks of treatment.[3, 4] When vildagliptin is used alone in people who do not tolerate metformin, it reduces HbA_{1c} levels by an average of 6-9 mmol/mol.[5]

Vildagliptin will be fully subsidised without restriction, and available in three formulations, all taken either once or twice daily:[6]

- 50 mg vildagliptin tablet
- 50 mg vildagliptin + 850 mg metformin tablet
- 50 mg vildagliptin + 1 g metformin tablet

Guidelines recommend lifestyle measures and metformin as first-line approaches

Lifestyle interventions are the cornerstone of treatment for people with type 2 diabetes. Metformin is the preferred first-line pharmacological treatment option, particularly for people who are overweight or obese.[7] If a sufficient reduction in HbA_{1c} levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise, and adding a second oral pharmacological treatment.

For patients with higher HbA_{1c} levels at diagnosis, e.g. >75 mmol/mol, initiating two oral medicines simultaneously or discussing the use of insulin with metformin is recommended to reduce HbA_{1c} levels rapidly.[8, 9]

For further information on lifestyle management of type 2 diabetes and the use of metformin, see: **www.bpac.org.nz/BPJ/2015/December/diabetes.aspx**

Dual therapy: adding a second oral anti-diabetic medicine

The addition of vildagliptin to the pharmaceutical schedule now provides another option for clinicians when deciding on adding a second (or third) oral medicine to metformin treatment. Subsidised options now include:

- Vildagliptin, taken either as separate metformin and vildagliptin tablets, or a combination vildagliptin + metformin formulation
- A sulphonylurea, such as gliclazide or glipizide
- Pioglitazone

Current international guidelines*, including from the United States, United Kingdom, Scotland and Australia, do not favour any one of these subsidised options as the preferred choice; clinicians and patients can jointly decide which of these medicines to use after taking into account any contraindications, medicines interactions or adverse effects (Figure 1).[3, 8, 10, 11] Guidelines refer to DPP-4 inhibitors and sulphonylureas as a class, as existing evidence does not clearly show any differences between individual medicines in terms of efficacy or rates of adverse effects.[10]

In clinical trials where vildagliptin has been compared with placebo medicines, sulphonylureas, pioglitazone or metformin, there has not been any differences between groups in the rates of myocardial infarction, stroke, heart failure or death.[12] Similar results have been found in observational studies in patients taking these medicines.[13]

People who have contraindications to using metformin, or who trial metformin but are unable to continue use due to adverse effects, can initiate vildagliptin, a sulphonylurea or pioglitazone alone.

* A joint consensus statement from the American and European Diabetes Associations was released in October, 2018; it recommends that a DPP-4 inhibitor or pioglitazone be favoured over a sulphonylurea if there is a need to avoid hypoglycaemia or minimise weight gain. We will cover this new statement more comprehensively at a later date. The statement can be found here: **http://diabetologia-journal.org/wp-content/uploads/2018/09/EASD-ADA.pdf**

Triple therapy: insulin is typically initiated if treatment with two oral medicines is insufficient

If further escalation of treatment is required, clinicians can discuss the option of initiating insulin or using three oral medicines in combination. The addition of insulin is the typical course of action and should be considered for patients with a HbA_{1c} level > 65 mmol/mol despite lifestyle interventions and treatment with two oral anti-diabetic medicines.[3, 7, 8]

At diagnosis:

Discuss non-pharmacological treatment:

- Lifestyle changes are the cornerstone of management
- Emphasise the importance of diet and exercise approaches regardless of which medicines are used
- Support and encourage patients to make lifestyle changes throughout follow-up
- Refer patients to support services, e.g. a Green prescription or dietitian, to assist with lifestyle changes

Prescribe an appropriate medicine regimen based on the extent of hyperglycaemia:

- **Initiate metformin at, or soon after, diagnosis** for all patients with type 2 diabetes
  - If patients have contraindications to using metformin, initiate one of the oral anti-diabetic medicines under "Dual therapy"
- Consider prescribing two oral medicines or initiating insulin if patients have high HbA_{1c} levels at diagnosis, e.g. > 75 mmol/mol

Determine an appropriate HbA_{1c} target

Escalating treatment

If patients do not have a sufficient reduction in HbA_{1c} levels

Dual therapy:

Initiate any one of the following medicines **in combination with metformin**:

- Vildagliptin*
- A sulphonylurea
- Pioglitazone

Prescribe one of these medicines instead of metformin if patients have intolerable adverse effects while using metformin or contraindications

Triple therapy:

Discuss initiating insulin for patients with an HbA_{1c} > 65 mmol/mol despite lifestyle and oral pharmacological approaches

Or, a combination of three oral hypoglycaemic medicines may be considered.

For further information on initiating insulin, see:
www.bpac.org.nz/BPJ/2015/December/diabetes.aspx#3

Figure 1: An overview of management for patients with type 2 diabetes.[3, 7, 8, 10] For further information on lifestyle management, escalating treatment and initiating insulin, see: **www.bpac.org.nz/BPJ/2015/December/diabetes.aspx**

* Vildagliptin can be prescribed with metformin either as separate metformin and vildagliptin tablets or in combination metformin + vildagliptin formulations

Vildagliptin can be continued if insulin is initiated; clinical trials have found that adding vildagliptin to insulin treatment results in an additional 6–7 mmol/mol reduction in HbA_{1c} levels, without an increase in episodes of hypoglycaemia.[14] If patients initiate more complex insulin regimens, e.g. by adding rapid-acting insulin at meal-times, continuing the use of vildagliptin is possible.[15] However, in clinical practice, oral antidiabetic medicines are often withdrawn if patients initiate complex insulin regimens in order to simplify their treatment.[8]

For further information on lifestyle management, escalating treatment and initiating insulin, see: **www.bpac.org.nz/BPJ/2015/December/diabetes.aspx**

How does adding vildagliptin to treatment compare with adding a sulphonylurea or pioglitazone?

Clinicians in New Zealand will be familiar with the usual therapeutic and adverse effects of metformin and sulphonylurea medicines, as these have been available subsidised for several years. Pioglitazone has been available for clinicians in primary care to prescribe since 2007; initially with Special Authority criteria, which were removed in December, 2012.[16, 17]

Key prescribing points to help clinicians and patients decide between treatment with vildagliptin and other subsidised medicines include the following:

Vildagliptin may be slightly less potent at lowering HbA_{1c} than other options: Evidence suggests that vildagliptin reduces HbA_{1c} by approximately 2 mmol/mol less than a sulphonylurea when used as monotherapy (Table 1).[3] However, a similar reduction in HbA_{1c} is achieved when adding either a DPP-4 inhibitor or a sulphonylurea to metformin treatment.[3,18] Adding a thiazolidinedione (e.g. pioglitazone) to metformin is slightly more effective in reducing HbA_{1c} than adding a DDP-4.[3,18] There is, however, some evidence that differences in efficacy between vildagliptin and other options may not be significant when vildagliptin is used longer-term, e.g. after two years.[3]

DPP-4 inhibitors are not associated with weight gain: Adding a sulphonylurea or pioglitazone treatment to metformin typically leads to weight gain of approximately 2 kg, whereas DPP-4 inhibitors have a neutral effect on weight and are not associated with gain or loss.[18] Metformin is typically associated with a small degree of weight loss (Table 1).

DPP-4 inhibitors have low risks of hypoglycaemia: Treatment with vildagliptin is associated with a lower risk of hypoglycaemia than treatment with a sulphonylurea due to differences in how these medicines stimulate insulin release. Over one to two years of treatment 24–27% of patients taking sulphonylureas experience hypoglycaemia, compared to 3–4% of patients taking DPP-4 inhibitors.[19]

People newly diagnosed with diabetes who do not tolerate metformin may be more likely to benefit from vildagliptin treatment: People who are younger and who are closer to diagnosis, e.g. who have had diabetes for less than a year, are more likely to achieve HbA_{1c} targets with vildagliptin treatment.[20] This is probably due to people earlier in the disease process having better pancreatic function, which enables them to increase insulin release to a greater extent in response to higher GLP-1 levels than people who have had type 2 diabetes for many years.

Prescribing vildagliptin

Vildagliptin is prescribed as one 50 mg tablet, either once or twice daily, depending on the extent of HbA_{1c} reduction required and whether patients have renal impairment (Table 2). Vildagliptin can be prescribed either alone, or in combination formulations of 50 mg vildagliptin with 850 mg or 1 g of metformin.

If vildagliptin is prescribed in combination with a sulphonylurea, e.g. in patients who are unable to tolerate metformin and require more than one oral glucose lowering medicine, once daily dosing should be used as twice daily dosing does not provide any additional benefit.[23]

Table 1: Effects of oral diabetes medicines on HbA_{1c}, weight and risk of hypoglycaemia. Adapted from Scottish Intercollegiate Guidelines Network (SIGN) and American Diabetes Association (ADA) [3, 8]

Medicine	Efficacy* for lowering HbA_{1c}	Effects on weight	Risk of hypoglycaemia
Metformin	High	Weight loss of approximately 1 kg [21]	Low
Sulphonylureas	High	Weight gain of approximately 2 kg [22]	High
Pioglitazone	High	Weight gain of approximately 2 kg [22]	Low
Vildagliptin	Intermediate	No change	Low

* High = mean HbA_{1c} reduction of >11–22 mmol/mol; Intermediate = mean HbA_{1c} reduction of >5.5–11 mmol/mol [8]

Formulations of vildagliptin in combination with metformin may be simpler for patients and more effective

Observational data suggest patients are more likely to reach their target HbA_{1c} level if vildagliptin and metformin are prescribed as a single tablet, which may be due to increased adherence with a simpler regimen.[20]

When taken alone vildagliptin does not need to be taken with food, however, patients prescribed a combination vildagliptin + metformin tablet should be advised to take their medicine with food as they would if taking metformin alone. Rates of gastrointestinal adverse effects with vildagliptin + metformin treatment are similar to rates when metformin is taken alone.[24]

Contraindications and cautions

Vildagliptin should not be taken by people who are in a state of ketoacidosis.[25] Prescribing vildagliptin to women who are pregnant or breastfeeding is not recommended due to a lack of clinical trials or data in these patient populations (Table 2).[25] Vildagliptin has been studied in people with heart failure, however, those with severe heart failure (New York Association functional class IV) were excluded from trials and therefore prescribing in patients with severe heart failure is not recommended due to a lack of data.[23, 26]

Testing liver function prior to initiation and monitoring during treatment is recommended

In clinical trials a small proportion of people (0.5% or fewer) have experienced elevations in ALT or AST levels to greater than three times the upper limit of normal.[27] Assessing liver function before initiating treatment and monitoring every three months for the first year is recommended.[25] Initiating vildagliptin is not recommended if patients have ALT or AST levels over two and a half times the upper limit of normal prior to treatment.[23] When prescribing vildagliptin, inform people of symptoms associated with acute liver dysfunction, including nausea, jaundice, vomiting, abdominal pain and fatigue and advise them to seek medical attention if these occur.[25] If elevations in ALT or AST to greater than three times the upper limit of normal occur during treatment, re-test liver function after considering and addressing other possible causes of hepatic dysfunction. Vildagliptin should be withdrawn if patients persistently have ALT or AST levels greater than three times the upper limit of normal.[23]

Prescribing in patients with renal impairment

Approximately one-quarter of a dose of vildagliptin is excreted unchanged by the kidneys, and the remainder metabolised by hydrolysis. In patients with eGFR < 50 mL/min/1.73m^2, dosing should be once daily only.[25]

Table 2: Cautions and associated dosing recommendations for prescribing vildagliptin [23, 25, 28]

Patient population	Prescribing or dosing recommendation	Explanations
Women who are pregnant or breastfeeding	Prescribing not recommended	There is a lack of safety data in women who are pregnant or breastfeeding
Patients with renal impairment:		
Prescribing vildagliptin	Maximum once daily dosing of vildagliptin recommended in patients with eGFR < 50 mL/min/1.73m^2	Some vildagliptin is excreted unchanged by the kidneys
Prescribing vildagliptin + metformin	Prescribing not recommended in patients with eGFR < 60 mL/min/1.73m^2	Prescribing metformin and vildagliptin in separate tablets may be preferable to allow for an appropriate reduced dose of metformin
Patients with severe heart failure (New York Association functional class IV)	Prescribing not recommended	There is a lack of safety data in this patient population
Patients with elevations of ALT or AST to over 2.5 times the upper limit of normal prior to initiation	Prescribe with caution and monitor liver function (see: "Contraindications and cautions")	A minority of patients (0.5%) have shown increases in ALT and AST levels to over three times the upper of normal in clinical trials

The manufacturer recommends to avoid prescribing vildagliptin + metformin formulations in patients with an eGFR < 60 mL/min/1.73m^2 due to the risk of metformin accumulation in patients with impaired renal function.[28] However, in clinical practice metformin can be prescribed to patients with impaired renal function provided appropriate dose reductions are used and renal function is monitored. For patients with an eGFR < 60 mL/min/1.73m^2, prescribing vildagliptin and metformin in separate tablets may be easier to allow an appropriate dose of metformin to be used in combination with vildagliptin.

Adverse effects of vildagliptin

A minority of people taking vildagliptin experience adverse effects, including:[29]

- Nasopharyngitis: 9%
- Headache: 7%
- Dizziness: 6%
- Back pain: 6%
- Diarrhoea: 6%

These adverse effects are typically mild; approximately 2–5% of people choose to discontinue vildagliptin due to adverse effects.[30, 31]

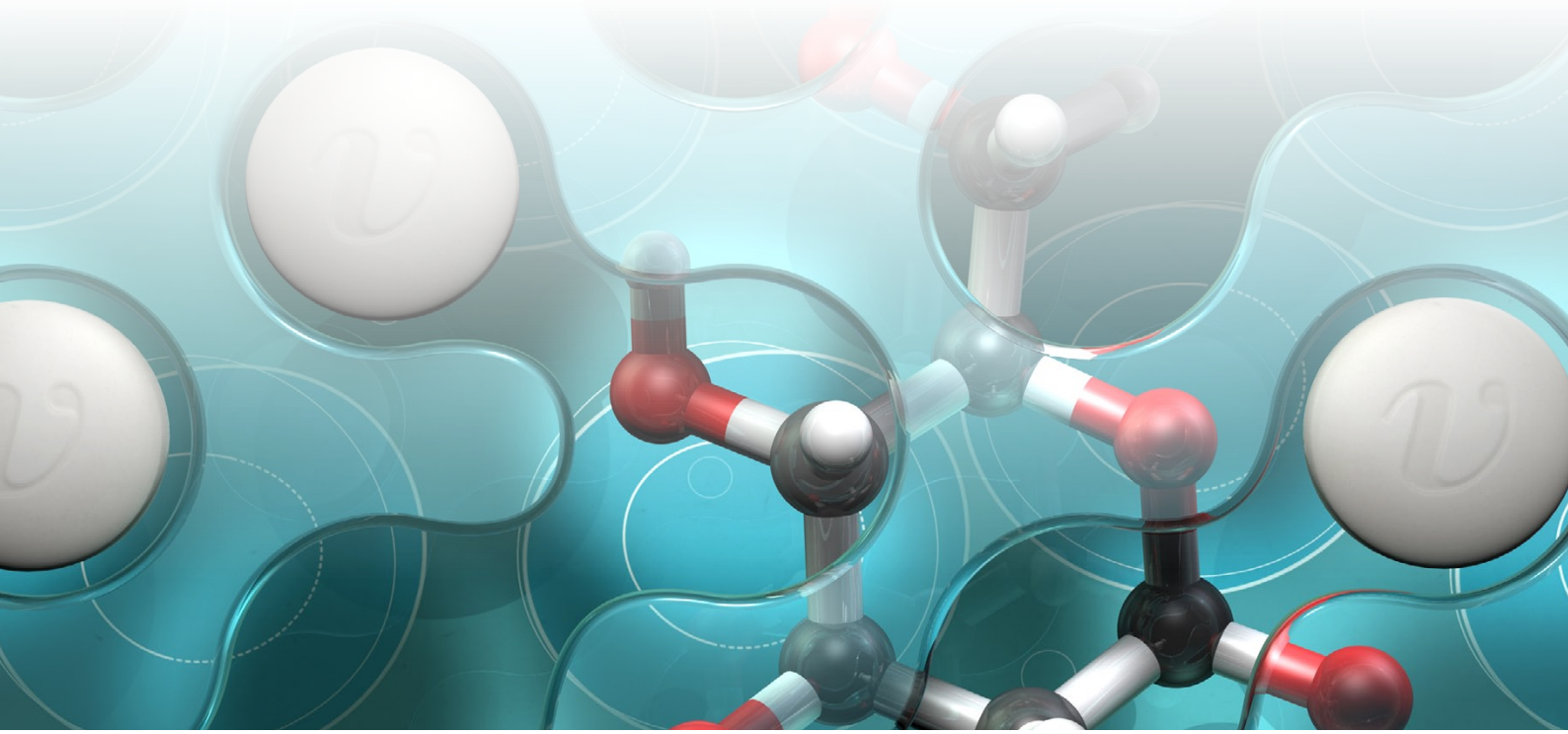
The use of DPP-4 inhibitors is associated with an increased risk of pancreatitis, however, there is still considerable uncertainty regarding the strength of this association. A meta-analysis of three randomised controlled trials reported a statistically significant increased odds of acute pancreatitis in participants taking DPP-4 inhibitors, however, the difference in absolute risk was low, at 0.13%.[32]

Patients taking ACE inhibitors have a higher risk of angioedema, but the absolute rate is still low

Patients with type 2 diabetes are often prescribed ACE inhibitors to treat hypertension or to reduce the risk or progression of diabetic nephropathy. Evidence suggests there may be an interaction between vildagliptin and ACE inhibitors which leads to an increased risk of angioedema, with a meta-analysis reporting an increased odds of angioedema of 4.57 (95% CI: 1.57–13.28) in people taking an ACE inhibitor who were also taking vildagliptin, compared to ACE inhibitor use alone.[33] However, the absolute risk remains small with an incidence rate of 0.5% or lower.[33] Reported cases have often occurred in the first three months of initiating vildagliptin in people already taking an ACE inhibitor.[34] Vildagliptin use alone is not associated with angioedema.[33]

Switching patients from a sulphonylurea or pioglitazone

Patients who have been using a sulphonylurea or pioglitazone but are experiencing adverse effects such as hypoglycaemia may wish to switch to vildagliptin. The half-life and duration of effect of sulphonylurea medicines is less than 24 hours, and patients taking these medicines could switch to vildagliptin the next day.[35] Pioglitazone has a half-life of seven hours or less, however, it is expected to have a prolonged duration of effect as a result of increasing insulin sensitivity.[35] Patients taking pioglitazone could initiate vildagliptin the next day with a more cautious approach to avoid hypoglycaemia, e.g. initially only taking vildagliptin once daily, before increasing to twice daily use.



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