

## Prescribing vildagliptin for type 2 diabetes

With two new medicines, empagliflozin and dulaglutide, available in New Zealand\* for the management of type 2 diabetes, the place of vildagliptin in treatment has been revised. Vildagliptin is an option for patients who have not achieved sufficient lowering of HbA<sub>1c</sub> levels with metformin and are not eligible for funded treatment with empagliflozin or dulaglutide; other options include a sulfonylurea or pioglitazone.

\* Special authority criteria apply; dulaglutide is funded from 1 September, 2021

### 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, empagliflozin or dulaglutide are preferred for eligible patients, i.e. those who are at high risk of cardiovascular disease or have renal complications; vildagliptin is preferred for patients who are not eligible for funded treatment
- Vildagliptin is taken once or twice daily, and is available alone or in combination with metformin
- Vildagliptin results in reductions in HbA<sub>1c</sub> levels of 6 – 12 mmol/mol
- Vildagliptin does not cause weight gain and has less risk of hypoglycaemia than sulfonylurea medicines but is slightly less effective at reducing HbA<sub>1c</sub> levels
- Nasopharyngitis, headache and dizziness are the most common adverse effects associated with vildagliptin, occurring in 6 – 9% of patients

This is a revision of a previously published article. What's new for this update:

- Vildagliptin has been funded without restriction since October, 2018. It continues to have a place in the treatment of type 2 diabetes, even though new treatments are available.
- Vildagliptin is recommended for patients who require a step up in treatment but are not eligible for funded empagliflozin or dulaglutide treatment

## Vildagliptin is a DPP-4 inhibitor approved for the treatment of type 2 diabetes

Glucagon-like peptide-1 (GLP-1) is a hormone that is rapidly released from the intestine after eating.<sup>1</sup> 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).<sup>1</sup>

Several anti-diabetic medicines have been developed which aim to amplify the effects of GLP-1. These include oral DPP-4 inhibitors (e.g. vildagliptin), 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 (e.g. dulaglutide).

Vildagliptin is typically used in combination with metformin, but can also be used concurrently with empagliflozin, a sulfonylurea, pioglitazone or basal insulin.<sup>2</sup> It cannot be used concurrently with GLP-1 receptor agonists, e.g. dulaglutide, due to a similar mechanism of action. In people with type 2 diabetes who are already taking metformin, adding vildagliptin once or twice daily to their treatment regimen reduces HbA<sub>1c</sub> levels by a further 7 – 12 mmol/mol after 12 weeks of treatment.<sup>3,4</sup> When vildagliptin is used alone in people who do not tolerate metformin, it reduces HbA<sub>1c</sub> levels by an average of 6 – 9 mmol/mol.<sup>5</sup>

## Guidelines recommend lifestyle measures and metformin as first-line approaches

Lifestyle interventions and metformin are the cornerstone of treatment for people with type 2 diabetes (Step 1).<sup>2</sup> If a sufficient reduction in HbA<sub>1c</sub> levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise, and adding a second pharmacological treatment. Funded options at Step 2 include:

- Empagliflozin\*\*
- Dulaglutide†
- Vildagliptin\*
- A sulfonylurea, such as gliclazide or glipizide
- Pioglitazone
- Arcabose

\* Available in a single formulation and in combination with metformin

† Special Authority criteria apply for funded treatment. For further information, see: Page 22

For patients with higher HbA<sub>1c</sub> levels at diagnosis, e.g. > 64 mmol/mol, starting at Step 2 is recommended, i.e. initiating two oral medicines simultaneously (e.g. metformin and

vildagliptin)\*.<sup>2</sup> The use of insulin (Step 3) in addition to metformin is recommended for patients with marked hyperglycaemia at diagnosis (e.g. > 80 – 90 mmol/mol) to reduce HbA<sub>1c</sub> levels rapidly.<sup>2</sup>

People who have contraindications to, or cannot tolerate, metformin can initiate one of these other medicines alone.

\* Other combinations may be preferable depending on the patient's risk factors, however, the Special Authority criteria for funded empagliflozin or dulaglutide treatment specify that the patient must have been taking another glucose-lowering medicine for at least three months to be eligible


## Vildagliptin is the preferred next step for people who are not eligible for funded empagliflozin or dulaglutide

Vildagliptin is recommended for patients who require a step up in pharmacological treatment but are not eligible for funded empagliflozin or dulaglutide treatment (or are unable to self-fund treatment as some patients may choose to do this).<sup>2</sup>

Vildagliptin is generally well tolerated, weight neutral, i.e. does not cause weight gain or weight loss, does not cause hypoglycaemia, and can be used safely in people with renal impairment.<sup>2</sup> N.B. Dose adjustment is required for patients with moderate or severe renal impairment (see: "Prescribing in patients with renal impairment", Page 31).

## 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<sub>1c</sub> levels, without an increase in episodes of hypoglycaemia.<sup>6</sup> If patients initiate more complex insulin regimens, e.g. by adding rapid-acting insulin at meal-times, continuing the use of vildagliptin is possible.<sup>7</sup> However, in clinical practice, oral glucose-lowering medicines are often withdrawn if patients initiate complex insulin regimens in order to simplify their treatment.<sup>8</sup>

 For further information on lifestyle management, escalating treatment and initiating insulin, see: "Type 2 diabetes management toolbox: from lifestyle to insulin", Page 6

## Prescribing vildagliptin

Vildagliptin is available in three formulations, all taken either once or twice daily:<sup>9</sup>

- 50 mg vildagliptin tablet
- 50 mg vildagliptin + 850 mg metformin tablet
- 50 mg vildagliptin + 1000 mg metformin tablet

Vildagliptin is prescribed as one 50 mg tablet (with or without metformin), either once or twice daily, depending on the extent of HbA<sub>1c</sub> reduction required and whether patients have renal impairment (Table 1).

If vildagliptin is prescribed concurrently with a sulfonylurea, 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.<sup>10</sup>

### 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<sub>1c</sub> level if vildagliptin and metformin are prescribed as a single tablet, which may be due to increased adherence with a simpler regimen.<sup>11</sup>

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.<sup>12</sup>

### Contraindications and cautions

Vildagliptin should not be taken by people who are in a state of ketoacidosis.<sup>9</sup> Prescribing vildagliptin to people aged < 18 years or to women who are pregnant or breastfeeding is not recommended due to a lack of clinical trials or data in these patient populations (Table 1).<sup>9</sup> Vildagliptin has been studied in people with heart failure, however, those with severe heart failure (New York Heart 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.<sup>10</sup>

 Vildagliptin should not be used at the same time as dulaglutide as they have similar mechanisms of action.

**Table 1:** Cautions and associated dosing recommendations for prescribing vildagliptin.<sup>2, 9, 10, 14</sup>

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 <sup>2</sup>	Some vildagliptin is excreted unchanged by the kidneys
Prescribing vildagliptin + metformin	Prescribing not recommended in patients with eGFR < 60 mL/min/1.73m <sup>2</sup>	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 Heart 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	Prescribing not recommended (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

### 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.<sup>13</sup> Assessing liver function tests before initiating treatment and monitoring every three months for the first year is recommended.<sup>2</sup> 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.<sup>2</sup> When prescribing vildagliptin, inform patients 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.<sup>9</sup> If elevations in ALT or AST to greater than two and a half times the upper limit of normal occur during treatment, re-test liver function after considering and addressing other possible causes of hepatic dysfunction. New Zealand guidelines recommended withdrawing vildagliptin if patients persistently have ALT or AST levels greater than two and a half times the upper limit of normal; this is more conservative than the NZF and the manufacturer.<sup>2,9,10</sup>

\* AST is not always routinely measured as part of LFTs in New Zealand, but can be requested

### 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 an eGFR < 50 mL/min/1.73m<sup>2</sup>, dosing should be once daily only.<sup>9</sup>

The manufacturer recommends to avoid prescribing vildagliptin + metformin formulations in patients with an eGFR < 60 mL/min/1.73m<sup>2</sup> due to the risk of metformin accumulation in patients with impaired renal function.<sup>14</sup> 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<sup>2</sup>, 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:<sup>15</sup>

- 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.<sup>16,17</sup>

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%.<sup>18</sup> Bullous pemphigoid is a rare but serious complication of vildagliptin treatment. The median time to onset is 11 months after treatment initiation.<sup>19</sup>

### 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.<sup>20</sup> However, the absolute risk remains small with an incidence rate of 0.5% or lower.<sup>20</sup> Reported cases have often occurred in the first three months of initiating vildagliptin in people already taking an ACE inhibitor.<sup>21</sup> Vildagliptin use alone is not associated with angioedema.<sup>20</sup>

### Switching patients from a sulfonylurea or pioglitazone

Patients who have been taking a sulfonylurea or pioglitazone but are experiencing adverse effects such as hypoglycaemia may wish to switch to vildagliptin. The half-life and duration of effect of sulfonylurea medicines is less than 24 hours, and patients taking these medicines could switch to vildagliptin the next day.<sup>22</sup> 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.<sup>22</sup> 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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