

# **Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus**

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## **ABSTRACT**

Diabetes mellitus (DM) is a chronic disease which caused around 1.5 million deaths in 2012. Type 2 diabetes mellitus (T2DM) accounts for 90% of DM worldwide. The prevalence of T2DM is increasing due to obesity. Clinical guidelines recommend the use of metformin as the first-line treatment, followed by the addition of 1 or 2 oral antidiabetic drugs (OADs), such as sulphonylurea (SU), an alpha-glucosidase inhibitor, or thiazolidinediones (TZDs). Recently, newer agents such as dipeptidyl peptidase 4 (DPP-4) inhibitors have been added to those treatment algorithms. The DPP-4 inhibitor is a class of OAD that inhibits the DPP-4 enzyme. Sitagliptin, saxagliptin, vildagliptin and linagliptin are DPP-4 inhibitors available for the treatment of T2DM in Indonesia and many other countries. The DPP-4 inhibitors have similar glycemic efficacy. However, they produce a moderate improvement in glycated hemoglobin (A1C). There are limited numbers of head-to-head trials of DPP-4 inhibitors. In addition, there are no data on the long-term DPP-4 inhibitors use safety (more than two years), mortality, diabetic complications, or health-related quality of life. Although DPP-inhibitors are not used as initial treatment for a majority of patients with T2DM, DPP-4 inhibitors can be used as add-on therapy in T2DM patients who are intolerant to, have contraindications for, or uncontrolled with the use of metformin, SU, or TZDs. The exact role of DPP-4 inhibitors among several other agents to manage T2DM is not clear. There are only a small number of long-term studies on DPP-4 inhibitors assessing the glycemic decrease efficacy, important clinical outcomes (cardiovascular events, mortality), or safety. In patients with chronic renal failure considered to use DPP-4 inhibitors, linagliptin can be recommended. There are inadequate data to assess the effect of DPP-4 inhibitors on the occurrence of acute pancreatitis. Overall, DPP-4 inhibitors are well-tolerated.

## **ABSTRAK**

Diabetes melitus (DM) merupakan penyakit kronis yang menyebabkan sekitar 1,5 juta kematian pada tahun 2012. Prevalensi DM tipe 2 (DMT2) menapai 90% dari keseluruhan DM di seluruh dunia. Prevalensi DMT2 ini meningkat karena faktor obesitas. Pedoman pengobatan merekomendasikan penggunaan metformin sebagai obat lini pertama, bisa diikuti dengan penambahan 1 atau 2 oral antidiabetes oral (OAD), seperti sulfonilurea (SU), inhibitor alpha-glucosidase, atau thiazolidinediones (TZD). Obat baru golongan penghambat dipeptidil peptidase-4 (DPP-4) telah ditambahkan ke algoritma pengobatan DM. Penghambat DPP-4 inhibitor adalah golongan OAD yang bekerja menghambat enzim

DPP-4. Sitagliptin, saxagliptin, vildagliptin dan linagliptin termasuk golongan penghambat DPP-4 yang beredar di Indonesia dan beberapa negara lain. Penghambat DPP-4 memiliki efek hipoglikemik yang setara OAD lain, namun obat ini dapat meningkatkan hemoglobin terglikasi (A1C) secara moderat. Uji klinik penghambat DPP-4 sebagai antidiabetes jumlahnya terbatas. Selain itu tidak ada data tentang keamanan penggunaan obat ini dalam jangka panjang (lebih dari dua tahun), kematian, komplikasi diabetes, atau kualitas-hidup pasien. Meskipun penghambat DPP-4 tidak digunakan sebagai terapi awal untuk pasien DMT2, obat ini dapat digunakan sebagai terapi tambahan pada pasien yang tidak toleran, ada kontraindikasi, atau tidak terkontrol pada penggunaan metformin, SU, atau TZD. Peran sebenarnya dari penghambat DPP-4 di antara obat antidiabetes lainnya dalam pengelolaan DMT2 belum begitu jelas. Belum banyak penelitian jangka panjang untuk mengkaji efek hipoglikemik, luaran klinik penting seperti efek samping terhadap kardiovaskular dan kematian yang ditimbulkan, atau keamanan dari penghambat DPP-4. Pada pasien gagal ginjal kronis dapat menggunakan penghambat DPP-4 linagliptin sebagai obat pilihan. Data untuk mengkaji efek penggunaan penghambat DPP-4 terhadap kejadian pankreatitis akut tidak cukup tersedia. Secara keseluruhan, penggunaan penghambat DPP-4 dapat ditoleransi oleh pasien.

**Keywords :** type 2 diabetes mellitus - dipeptidyl peptidase 4 (DPP-4) inhibitors - sitagliptin, saxagliptin - vildagliptin - linagliptin

## **INTRODUCTION**

Diabetes mellitus (DM) is a chronic disease which caused around 1.5 million deaths in 2012 according to the World Health Organization. It is estimated that DM will be the seventh leading cause of mortality in 2030. Type 2 diabetes mellitus (T2DM) accounts for 90% of DM worldwide. The prevalence of T2DM is increasing due to obesity.<sup>1</sup> The goals in management of T2DM are directed to eliminate symptoms and to prevent or reduce the progress to micro- and macrovascular complications. The management includes diet, exercise, medications and blood glucose and T2DM complications monitoring. A wide range of oral anti-diabetic drugs (OADs) is effective in decreasing blood glucose level. however, they are also associated with side effects that may have an impact on healthcare resource use and quality of life.<sup>2</sup>

Clinical guidelines recommend the use of metformin as the first-line treatment unless contraindicated, followed by the addition of 1

or 2 OADs, such as sulphonylurea (SU), alpha-glucosidase inhibitor, or thiazolidinediones (TZDs).<sup>2</sup> Recently, newer agents such as dipeptidyl-peptidase 4 (DPP-4) inhibitors have been added to those treatment algorithms. The approach is to use OADs with complementary mechanisms of action in combination. Pharmacological treatment for type 2 diabetes is aimed to increase insulin availability, to rise the sensitivity to insulin, to prolong insulin absorption from gastrointestinal tract, or to rise glucose excretion via urine. Treatment with DPP-4 inhibitors affect the glycemic control through several mechanisms i.e. by increasing glucose-dependent insulin secretion, delaying gastric emptying, and decreasing postprandial glucose and food intake. Dipeptidyl peptidase-4 inhibitor usually does not cause hypoglycemia, except when it is combined with a treatment that may lead to hypoglycemia.<sup>3,4</sup>

Dipeptidyl peptidase-4 inhibitor is a class of oral antidiabetic drug that inhibits the DPP-4 enzyme. Dipeptidyl peptidase-4

is an enzyme expressed on the surface of most cell types that inactivates various other bioactive peptides. Therefore, the inhibition potentially affects glucose regulation through several mechanisms. Sitagliptin, saxagliptin, vildagliptin and linagliptin are DPP-4 inhibitors available for the treatment for T2DM in Indonesia and many other countries. Vildagliptin is available in several countries, but not in the United State of America. If a DPP-4 inhibitor will be used on patients with chronic renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min), linagliptin is the treatment of choice because its elimination is mainly through enterohepatic system.<sup>3-6</sup>

## **DISCUSSION**

### **Efficacy of DPP-4 inhibitors.**

Dipeptidyl peptidase-4 inhibitors have similar glycemic efficacy. They produce a moderate improvement in glycated hemoglobin (A1C). However, there are limited numbers of head-to-head trials, and there are no data on the use of long-term use (more than two years) safety, mortality, diabetic complications, or health-related quality of life. In a 18-week study of saxagliptin (5 mg) versus sitagliptin (100 mg) in 800 patients who were uncontrolled with stable dose metformin, there was a similar reduction of A1C values (-0.52% vs -0.62%).<sup>4</sup> Furthermore, the results from meta-analysis of the studies comparing sitagliptin and placebo or vildagliptin and placebo showed similar efficacy (mean difference of A1C values -0.74% and -0.73%, 95%CI -0.84 vs -0.63 and -0.94 vs -0.52, respectively, for sitagliptin and vildagliptin compared to placebo).<sup>5</sup> Other meta-analysis on sitagliptin and vildagliptin also reported similar findings.<sup>6</sup> Although DPP-inhibitors are not used as initial treatment for a majority of

patients with T2DM, DPP-4 inhibitors can be used as add-on therapy in T2DM patients who are intolerant to, have contraindications for, or uncontrolled with the use of metformin, SU or TZDs.

### **Safety of DPP-4 inhibitors**

#### ***Cardovascular effect***

There are increasing numbers of trials evaluating the cardiovascular effects of DPP-4 inhibitors. Although the data showed that there was no increase in the risk of cardiovascular adverse effects with short-term use of DPP-4 inhibitors combined with other oral agents, long-term clinical trials are needed to assess the cardiovascular safety of DPP-4 inhibitors use. Until recently, there have been no studies confirming the initial statement on the beneficial effect of DPP-4 inhibitors on the risk of cardiovascular diseases.

#### **Use in chronic renal failure**

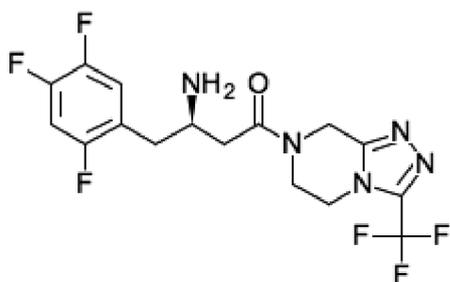
Sitagliptin, saxagliptin, and vildagliptin need a dosage adjustment in patients with chronic renal failure. Linagliptin is mainly eliminated through enterohepatic system, therefore it does not need any dosage adjustment.

### **Pharmacology of DPP-4 inhibitors**

#### ***Sitagliptin***

Sitagliptin (FIGURE 1) is a DPP-4 inhibitor that is approved as a treatment for T2DM (as second-line drug for those who are non-responders to single therapy, such as SU, metformin, or TZDs, and as a third-line drug when dual therapy with metformin and a SU does not give an adequate glycemic control. Usual dose of sitagliptin is 100 mg once daily, with a reduction to 50 mg for patients with moderate-severe renal insufficiency (glomerular filtration rate [GFR]

30-50 mL/min) and to 25 mg for patients with severe renal insufficiency (< 30 mL/min).<sup>7</sup> Sitagliptin is also effective as a combination with metformin,<sup>8-10</sup> a TZD,<sup>11</sup> or a SU,<sup>12</sup> and one study reported that sitagliptin has a similar ability to glipizide in reducing the A1C value.<sup>10</sup> The recommended dose of sitagliptin is 100 mg once daily. Sitagliptin can be taken with or without food. Sitagliptin-metformin is available as a single tablet (50mg/500mg, 50mg/850mg, 50mg/1000mg sitagliptin and metformin respectively) to be taken twice daily along with food.<sup>13</sup>



D08516

FIGURE 1. Chemical structure of sitagliptin

### Saxagliptin

Saxagliptin (FIGURE 2) is approved as initial pharmacological treatment for T2DM or as a second-line agent in those who are non-responders to single agent, such as a SU, metformin, or a TZD. Usual dose of saxagliptin is 2.5 or 5 mg once daily, with the 2.5 mg dose is recommended for patients with moderate-severe chronic renal failure (glomerular filtration rate [GFR]  $\leq$  50 mL/min) and for patients who are using cytochrome P450 3A4/5 strong inhibitors (e.g., ketoconazole).<sup>14</sup> Saxagliptin as monotherapy decreases the A1C.<sup>15,16</sup> As an example, in a 24-weeks randomized trial, saxagliptin (2.5, 5, or 10 mg daily) versus placebo in 401 patients with T2DM without therapy and with average

baseline A1C value of 7.9%, saxagliptin reduced 0.4%, 0.5%, and 0.5% A1C values, respectively for each dose, compared with 0.2% increase in placebo group.<sup>16</sup>



D08996

FIGURE 2. Chemical structure of saxagliptin

Saxagliptin is also effective when it is combined with metformin,<sup>17,18</sup> a SU,<sup>19</sup> or a TZD.<sup>14</sup> As an example, in a 24-weeks trial in 743 patients who were uncontrolled with metformin monotherapy (1500-2500 mg/day), add-on saxagliptin (2.5-5 mg once daily) versus placebo improved the A1C values (-0.6% and -0.7% vs +0.1% from the baseline value).<sup>17</sup> The recommended dosage of saxagliptin is 2.5 mg or 5 mg once daily taken regardless of meals. Saxagliptin tablets must not be split or cut. Saxagliptin-metformin is available in a combination tablet (5 mg/500 mg, slow-release saxagliptin and metformin combination) to be taken once daily.

### Vildagliptin

Vildagliptin is another dipeptidyl peptidase-4 (DPP-4) inhibitor available in several countries, even though it is not approved by the Food and Drug Administration (FDA) yet. Generally the dose is 50 mg twice daily if it is used as a monotherapy, with a metformin, or with a thiazolidinedione, and 50 mg daily (in the morning) if it is used with a sulphonylurea.<sup>20</sup> There is no need to adjust the

dose in patients with mild renal dysfunction (creatinine  $\geq$  50 mL/min). In patients with moderate or severe renal dysfunction, the dose is 50 mg once daily. Vildagliptin is effective in a combination with metformin,<sup>21,22</sup> a thiazolidinedione,<sup>23</sup> or insulin.<sup>24</sup>

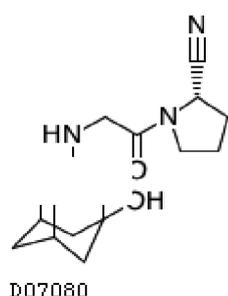


FIGURE 3. Chemical structure of vildagliptin

In a study on patients who were naïve to treatment, vildagliptin decreased the A1C values similarly to rosiglitazone, but less effective than metformin.<sup>25,26</sup> As an example, in a 52-weeks non-inferiority trial on vildagliptin (100 mg daily) versus metformin (titrated to 2000 mg daily) in 780 patients with type 2 diabetes who were naïve to treatment, metformin was better (vildagliptin was not non-inferior) in reducing the A1C values (the difference between groups was 0.4%, 95%CI 0.28-0.65).<sup>26</sup> Target A1C (< 7.0%) was reached by 45% and 35% patients who received metformin and vildagliptin, respectively. When used in combination with metformin, in combination with TZD, in combination with metformin and a SU, or in combination with insulin (with or without metformin), the recommended daily dose of vildagliptin is 100 mg, administered as one dose of 50 mg in the morning and one dose of 50 mg in the evening. When used in dual combination with a SU, the recommended dose of vildagliptin is 50 mg once daily administered in the morning. In this patient population, vildagliptin 100 mg daily was no more effective than

vildagliptin 50 mg once daily. When used in combination with a SU, a lower dose of the SU may be considered to reduce the risk of hypoglycaemia. Doses higher than 100 mg are not recommended. Vildagliptin-metformin is available in a combination tablet (50 mg/500 mg, 50 mg/850 mg, 50 mg/1000 mg of vildagliptin and metformin)

### Linagliptin

Linagliptin (FIGURE 4) is available to be used as an add-on therapy to diet and exercise in adults with type 2 diabetes. Usual dose of linagliptin is 5 mg once daily, with or without food. Linagliptin is mainly eliminated through enterohepatic system. No dosage adjustment is needed in patients with renal or liver dysfunction. Reagents of CYP3A4 or P-glycoprotein (e.g., rifampin) may decrease the effectivity of linagliptin. Therefore, patients who need these drugs should receive an alternative to linagliptin.

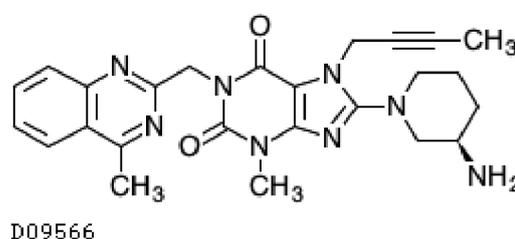


FIGURE 4. Chemical structure of linagliptin

Efficacy of linagliptin in combination with metformin,<sup>27,28</sup> glimepiride,<sup>29</sup> metformin and SU combination,<sup>30</sup> or pioglitazone<sup>31</sup> is illustrated by the following trials: there were several head-to-head trials comparing linagliptin and other agents. In a 2-years non-inferiority trial on glimepiride (1-4 mg, average dose of 3 mg) versus linagliptin (5 mg), both were given once daily, in 1551 patients with type 2 diabetes who were

inadequately controlled with metformin (average baseline value of A1C 7.7%), a significantly better change in A1C values was shown in glimepiride (-0.36% vs -0.16%), although linagliptin was statistically non-inferior to glimepiride.<sup>32</sup> The decrease in A1C values for both drugs in this long-term study was small. This might be related to the adjustment to baseline factors (baseline A1C values, group of therapy, and previous antidiabetic drugs) or high drop-out rate (~40%), and missing data estimation with the last-observation-carried-forward method. The increased dose in glimepiride was associated with a higher risk of hypoglycemia (36% vs 7% patients) and an increase in body weight (+1.3 vs -1.4 kg with linagliptin). There was too small number of cardiovascular events to take any significant conclusion. The recommended dose of linagliptin is 5 mg once daily. Linagliptin tablets can be taken with or without food. Linagliptin-metformin is available in a combination tablet (2.5 mg/500 mg, 2.5 mg/850 mg, 2.5 mg/1000 mg of linagliptin and metformin) taken twice daily with food.

### **Adverse effects**

Dipeptidyl peptidase-4 inhibitors are well tolerated in short-term studies. There were no effects on body weight or hypoglycemic risk (with no concomitant treatment with insulin or SU). Commonly reported adverse effects are headache, nasopharyngitis, and upper respiratory tract infection.<sup>33,34</sup> Several, but not all,<sup>8,22</sup> studies have reported a small increase in the risk of gastrointestinal adverse effects with sitagliptin. Long-term safety with DPP-4 inhibitors has not been determined.

### **Immunological function**

Although DPP-inhibitors are relatively specific for glucagon-like peptide 1 (GLP-1),

long-term consequence of DPP-4 inhibition and its impact on the other DPP-4 substrates are not known. Because of the characteristics of dipeptidyl peptidase substrates and specialized variable DPP-4 inhibitors, each agent in this class is needed to be studied individually for drug adverse effects.<sup>35</sup> There is a possibility that the risk of adverse effect is higher in the less-selective DPP-inhibitors. Residual cross-over with other substrates of DPP-4, particularly related to the immunological function, is still of interest, although it has not been reported yet in the short-term clinical trials. In three head-to-head trials, there were no significant clinical differences in adverse effects between DPP-inhibitors. There are very few data available to develop a conclusion on cardiovascular effects or mortality.

### **Pancreas**

Acute pancreatitis case reported on the use of DPP-4 inhibitors. Nowadays there are inadequate data to establish the causal-effect relationship. Pancreatitis should be considered in patients with persistently severe gastric pain (with or without nausea), and DPP-4 inhibitors should be stopped in these patients. If pancreatitis is confirmed, DPP-4 inhibitors are not to be restarted. DPP-4 inhibitors should also not be used in patients with a history of pancreatitis.

There are several postmarketing reports on acute pancreatitis cases in the users of sitagliptin, saxagliptin, and alogliptin.<sup>36-38</sup> This finding is similar with the case reports on pancreatitis in the users of GLP-1 receptor agonists. In a retrospective cohort study on a claim database, the incidence of acute pancreatitis was 5.6 cases per 1000 patient-years, which is similar to the incidence in diabetes control group.<sup>39</sup> However, in a

population-based case-control study using insurance database, the treatment with GLP-1 (sitagliptin and exenatide) was associated with an increased risk in hospitalization due to acute pancreatitis (adjusted odds ratio [OR] 2.07, 95%CI 1.36-3.13).<sup>40</sup> In contrast, a meta-analysis of several randomized trials did not find any increased risk of acute pancreatitis.<sup>41,42</sup> Overall incidence of pancreatitis was low (35 cases out of 68,318 patients, 20 in the users of DPP-4 inhibitors and 15 in the control group).<sup>42</sup> In a population-based cohort study, there were no differences in the risk of pancreatitis occurrence in patients who received GLP-1 treatment or sulphonylurea (1.45 and 1.47 per 1000 patient-years, respectively).<sup>43</sup> More carefully planned observational studies are needed to assess the true risk.

There was a report on the increased risk of subclinical pancreatic inflammation, pancreatic cancer, and neuro endocrine tumor in the users of sitagliptin.<sup>36,44-46</sup> Causal-effect relationship could not be determined. After reviewing the available data, the FDA and the European Medicines Agency agreed that there was no adequate evidence to confirm the increased risk in pancreatic cancer in the users of GLP-1 receptor agonists.<sup>47-49</sup> However, because the risk has not been eliminated yet, monitoring and reporting of adverse effects are still continued.<sup>47,49,50</sup>

### **Liver function**

Although it is rare, liver dysfunction cases (the increase in liver enzymes, hepatitis) have been reported in patients who used vildagliptin.<sup>34,51</sup> Consequently, liver function test results should be evaluated before starting vildagliptin, and at 3-months intervals during the first year of treatment.<sup>51</sup> If there is an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) equals to

or more than three times the upper normal value, the drug should be stopped.

### **Skin**

Several DPP-4 inhibitors, including vildagliptin and saxagliptin, have been associated with serious skin reactions during preclinical studies on animals (red discoloration and swelling, blistering and skin sloughing with necrosis with higher doses).<sup>52,53</sup> Skin lesions also occurred in normal volunteers given 4-6 times suggested treatment dose of vildagliptin.<sup>54</sup> In postmarketing reports, sitagliptin, saxagliptin, and linagliptin have been associated with hypersensitivity reactions, including anaphylaxis, angioedema, and blistering skin conditions, including Stevens-Johnson syndrome.<sup>55</sup> DPP-4 inhibitors are contraindicated in patients with a history of hypersensitivity reaction in the previous exposure.<sup>56</sup>

### **CONCLUSION**

Dipeptidyl peptidase-4 (DPP-4) inhibitor is a class of oral antidiabetic drug which inhibits the DPP-4 enzyme. It can be used as add-on therapy in patients who have inadequate control with metformin, TZD, or SU. Dipeptidyl peptidase-4 inhibitors are not considered as initial therapy for most patients with T2DM. The exact role of DPP-4 inhibitors among several other agents to manage T2DM is not clear. There were only a small number of long-term studies on DPP-4 inhibitors assessing the glycemic decrease efficacy, important clinical outcomes (cardiovascular events, mortality), or safety. In patients with chronic renal failure (estimated glomerular filtration rate [eGFR] < 30 mL/min) considered to use DPP-4 inhibitors, linagliptin can be chosen. There are inadequate data to assess the effect of DPP-4 inhibitors on

the occurrence of acute pancreatitis. Overall, DPP-4 inhibitors are well-tolerated.

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