Introduction
It is estimated that 6.5% of adults aged 20-79 years have type 2 diabetes in South Africa. An age-adjusted prevalence of up to 13% has been described in urban populations. The effects of urbanisation, lack of exercise and unhealthy eating habits have been found to be important contributors to the rising prevalence of type 2 diabetes, as well as obesity, in our country. Type 2 diabetes is a progressive disease which may require intensification of therapy over time. Management includes a prudent diet, regular exercise and medicines to reduce blood glucose levels. Current pharmacological options in the management of type 2 diabetes include sulphonylureas, insulin, thiazolidinediones, alpha-glucosidase inhibitors and metformin. These treatment options, although highly effective in reducing blood glucose levels, may be associated with an increased risk of hypoglycaemia, as seen with sulphonylureas and insulin; weight gain, as noted with insulin, sulphonylureas and thiazolidinediones; and gastrointestinal intolerance, as observed with metformin. These unwanted adverse effects may act as barriers to optimal glycaemic control.

As a result, newer and safer treatment options for optimal glycaemic control are continuously being investigated and developed. The glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors are examples of such developments.

This article will focus on the DPP-4 inhibitors, also known as the “gliptins”, and their place in therapy in the management of type 2 diabetes.

A closer look at incretin hormones and dipeptidyl peptidase-4 inhibitors
DPP-4 inhibitors are a new class of medicine which work to potentiate the effect of incretin hormones. Incretin hormones are secreted from the gastrointestinal tract (the enteroendocrine cells), into the bloodstream in response to food intake. The two most well-characterised incretin hormones are the GLP-1 and glucose-dependent insulinotropic polypeptide, also known as gastric inhibitory peptide (GIP).

When blood glucose levels are elevated following a meal, incretin hormones are released from the gastrointestinal tract, and they:
• Stimulate insulin secretion from the pancreatic β-cells
• Reduce glucagon secretion from the pancreatic α-cells
• Improve β-cell function
• Slow gastric emptying

Two of the many physiological roles of the incretin hormones as described above are to increase insulin secretion by the pancreatic β-cells and to suppress glucagon secretion by pancreatic α-cells. GLP-1, in particular, appears to be responsible for the majority of the incretin effects on...
pancreatic β-cell function. The net effect is increased peripheral glucose uptake and reduced hepatic glucose output which leads to improved glycaemic control. Figure 1 provides a schematic representation of the effect of incretin hormones on glycaemic control.

Circulating levels of GLP-1 are low in the fasting state, and rise quickly following a meal. In patients with type-2 diabetes, GLP-1 production is reduced. GLP-1 has a very short half-life and is rapidly degraded by the enzyme, dipeptidyl peptidase-4 (DPP-4). In an attempt to harness the beneficial effects of GLP-1, research has focused on interventions along the GLP-1 pathway. The result of this research has been the development of GLP-1 agonists, e.g. exanetide and liraglutide, as well as the DPP-4 inhibitors. The DPP-4 inhibitors prolong the action of endogenous incretins, enhancing the insulin response. GLP-1 agonists have a protein-based structure, and although they have longer half-lives than endogenous GLP-1, they require parenteral administration as is the case with exenatide (Byetta®) and liraglutide (Victoza®). Both of these are available as pen devices.

In contrast, DPP-4 inhibitors are smaller molecules that can be absorbed intact from the gastrointestinal tract, making oral administration possible. Despite their common mechanism of action, the DPP-4 inhibitors show marked differences in their chemical structure. This may explain some of the variance in the pharmacokinetic profiles of these products.

Drug interaction profile
In general, DPP-4 inhibitors do not interfere with cytochrome P450 (CYP450) enzymes. They are neither inhibitors nor inducers. The exception is saxagliptin (Onglyza®), which is metabolised by the CYP3A4/5 isoform into a primary active metabolite. As a result, saxagliptin may require dosage adjustment if taken concurrently with CYP3A4/5 inhibitors, such as ketoconazole, itraconazole, indinavir, nelfinavir, ritonavir and saquinavir.

The absence of significant drug-drug interactions with this class of medicine can be explained by their favourable pharmacokinetic characteristics and their low plasma-protein binding.

Safety profile
DPP-4 inhibitors have been generally well-tolerated in short-term studies. Commonly reported adverse effects include nasopharyngitis (inflammation of the nasal passages and upper part of the pharynx), urinary tract infections, pancreatitis and headaches. Serious allergic reactions have been reported, including anaphylactic reactions, angioedema and exfoliative dermatological reactions. The incidence of hypoglycaemia is low, but may be increased when DPP-4 inhibitors are used in combination with other antidiabetic agents such as insulin or sulphonylureas. The DPP-4 inhibitors also appear to be less likely to be associated with weight gain. DPP-4 inhibitors should be used with caution in patients who have a history of pancreatitis. DPP-4 inhibitors should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.

Since these products are fairly new on the market, long-term, real-life experience with their use is needed to further confirm their safety profile.

Available dipeptidyl peptidase-4 inhibitors
Various DPP-4 inhibitors are at different stages of development and registration across the globe.
Review: Dipeptidyl peptidase-4 inhibitors: their role in the management of type 2 diabetes

Dipeptidyl peptidase-4 (DPP-4) inhibitors include sitagliptin, vildagliptin, alogliptin, saxagliptin and linagliptin.

Sitagliptin was the first of the DPP-4 inhibitors to be approved by the US Food and Drug Administration in 2006. This was followed by the approval of vildagliptin in February 2007. Saxagliptin (Onglyza®), vildagliptin (Galvus®) and sitagliptin (Januvia®) are currently available on the South African market. Linagliptin is registered in the US as Tradjenta™ and in Europe as Trajenta™. Table 1 lists examples of dipeptidyl peptidase-4 inhibitors.

The place of dipeptidyl peptidase-4 inhibitors in therapy

DPP-4 inhibitors are effective as monotherapy, and also in combination with other oral antidiabetic agents. Plasma DPP-4 inhibition profiles are consistent with once-daily dosing for all members of this class, with the exception of vildagliptin. DPP-4 inhibitors are contraindicated where there is:
- Compelling indication for insulin therapy.
- A history of a serious hypersensitivity reaction to DPP-4 inhibitors.
- Patients with a history of acute pancreatitis, chronic or recurring pancreatitis, and those with pancreatic cancer.

Conclusion

The development of DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme that is

Table 1: A list of dipeptidyl peptidase-4 inhibitors

<table>
<thead>
<tr>
<th>Feature</th>
<th>Saxagliptin (Onglyza®)</th>
<th>Vildagliptin* (Galvus®)</th>
<th>Sitagliptin* (Januvia®)</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended dosage</td>
<td>2.5 mg or 5 mg once daily</td>
<td>50 mg twice daily (once daily when used in combination with sulphonylureas)</td>
<td>100 mg once daily</td>
<td>5 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Indication</td>
<td>Adjunct to diet and exercise in adults with type 2 diabetes, either as monotherapy or in combination with other antidiabetic agents</td>
<td>Adjunct to diet and exercise in adults with type 2 diabetes, either as monotherapy or in combination with other antidiabetic agents</td>
<td>Adjunct to diet and exercise in adults with type 2 diabetes, either as monotherapy or in combination with metformin or a thiazolidinedione</td>
<td>Not registered in South Africa. (Approved by the FDA.)</td>
<td>Not registered in South Africa. (Approved by the FDA.)</td>
</tr>
<tr>
<td>Selectivity for DPP-4</td>
<td>Moderate</td>
<td>Moderate</td>
<td>High</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>HbA1c-lowering effect</td>
<td>Similar efficacy (modest reduction 0.5-1.1%)</td>
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<tr>
<td>Use in renal impairment</td>
<td>eGFR&lt;50ml/min use 2.5 mg once daily</td>
<td>Contraindicated in moderate or severe renal impairment. Maximum dose should be 50 mg in patients with mild renal impairment.</td>
<td>eGFR&lt;50ml/min use 25 mg or 50 mg once daily</td>
<td>No dosage adjustment required</td>
<td>Dosage adjustment is required in patients with moderate to severe renal impairment</td>
</tr>
<tr>
<td>Use in hepatic Impairment</td>
<td>Use with caution in moderate hepatic impairment and not recommended in severe hepatic impairment</td>
<td>Contraindicated in moderate to severe hepatic impairment.</td>
<td>No dosage adjustment is necessary for patients with mild or moderate hepatic insufficiency.</td>
<td>No dosage adjustment required.</td>
<td>No dosage adjustments are required in patients with mild to moderate hepatic impairment.</td>
</tr>
<tr>
<td>Drug-drug interaction potential</td>
<td>Dosage adjustment required if taken concurrently with a strong CYP3A4/5 inhibitor e.g. ketoconazole, itraconazole, saquinavir, ritonavir</td>
<td>Low potential for drug interactions since it is not a CYP450 enzyme substrate and does not inhibit or induce CYP450 enzymes</td>
<td>Low potential for drug interactions</td>
<td>Should not be used if the patients is being treated with a CYP3A4 inducer e.g. rifampicin</td>
<td>Low</td>
</tr>
</tbody>
</table>

* Vildagliptin and sitagliptin are also available in combination with metformin as Galvus Met® and Janumet®, respectively, indicated as an adjunct to diet and exercise in patients with type 2 diabetes who are already stabilised on the combination of the DPP-4 inhibitor and metformin. CYP3A4/5: cytochrome 3A4/5, DDP4: dipeptidyl peptidase-4, FDA: US Food and Drug Administration, HbA1c: haemoglobin A1c.
responsible for their degradation, has recently emerged as an approach that appears to be promising for the treatment of type 2 diabetes.

Although these agents have modest efficacy [they reduce haemoglobin A1c (HbA1c) by 0.5-1.1% compared to placebo], they represent an important class of compounds that provide an alternative to other traditional therapies that are used in the management of type 2 diabetes.1 While they do not appear to lower glucose to a greater extent than existing therapies, when used alone, they offer the potential advantage of a low risk of hypoglycaemia and weight gain. As there is a low risk of hypoglycaemia developing with their use, they may be advantageous in patients who are close to achieving their target HbA1c, but who continually experience elevated glucose levels following a meal.

References

7. MIMS, November 2012.