DPP-4 inhibitors (Gliptins) in Adults with Type 2 Diabetes

- There are currently four dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors (‘gliptins’) licensed in the UK for the management of type 2 diabetes (T2DM).
- No comparative trials between the DPP-4 enzyme inhibitors have been conducted.
- There are a number of differences between the gliptins including costs, licensed indications, monitoring requirements, interactions and the need for dose adjustment in renal and hepatic impairment.
- Robust clinical outcome data for gliptins, particularly around their cardiovascular effects and long-term safety in people with type 2 diabetes is limited.

NICE Clinical Guideline Recommendation (CG)

NICE makes recommendations for when DPP-4 inhibitors can be considered (note that at the time of CG publication only sitagliptin or vildagliptin were considered):

- dual therapy in patients with inadequate glycaemic control (HbA1c ≥ 48 mmol/mol [6.5%] or as agreed with the individual) with either metformin or a sulphonylurea when either of these drugs is not tolerated or is contra-indicated, or in the case of sulphonylureas, there is a significant risk of hypoglycaemia.
- sitagliptin may be considered as third-line therapy added to first-line metformin and a second-line sulphonylurea when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59 mmol/mol [7.5%] or as agreed with the individual) and insulin is unacceptable or inappropriate.
- DPP-4 inhibitor therapy should only be continued if the person has a reduction of at least 5.5 mmol/mol [0.5%] in HbA1c in 6 months.

Hertfordshire Medicines Management Committee Recommendations on DPP-4 enzyme inhibitor choice:

1\textsuperscript{st} choice: sitagliptin
2\textsuperscript{nd} choice: linagliptin

Specialists must give clear rationale for choice if recommending an alternative DPP-4 enzyme inhibitor.

Comparative data on available DPP-4 inhibitors (Gliptins)

<table>
<thead>
<tr>
<th></th>
<th>Cost comparison for std daily doses (28 days)</th>
<th>Mono-therapy</th>
<th>With Insulin (+/− MET)</th>
<th>Dual Therapy With MET</th>
<th>Dual Therapy With SU</th>
<th>Dual Therapy With PIO</th>
<th>Triple therapy + MET &amp; SU or PIO</th>
<th>CV outcome data from large RCT</th>
<th>Hepatic impairment</th>
<th>Renal impairment (CrCl ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>100mg daily £33.26</td>
<td>√**</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√*</td>
<td>X</td>
<td>No dose adjustment, mild to mod. No experience in severe disease</td>
<td>100mg daily 50mg daily (±33.26) 25mg daily (±33.26)</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5mg daily £31.60</td>
<td>√**</td>
<td>√</td>
<td>√*</td>
<td>√</td>
<td>(with MET &amp; SU only)</td>
<td>√ (see overleaf)</td>
<td>No dose adjustment, mild to mod. Caution in mod. Not recommended in severe disease</td>
<td>5mg daily 2.5mg daily (£31.60) 2.5mg daily (use with caution; not recommended in ESRD requiring haemodialysis)</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5mg daily £33.26</td>
<td>√**</td>
<td>√</td>
<td>X</td>
<td>X</td>
<td>(with MET &amp; SU only)</td>
<td>X</td>
<td>No dose adjustment ***</td>
<td>5mg daily (Nose dose adjustment)</td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50mg twice daily £31.76</td>
<td>√**</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>* (Reduce dose to 50mg daily)</td>
<td>X</td>
<td>Should not be used in patients with hepatic impairment, including patients with pre-treatment ALT or AST &gt; 3x the upper limit of normal ****</td>
<td>50mg twice daily 50mg daily (±15.88) 50mg daily (use with caution in ESRD)</td>
<td></td>
</tr>
</tbody>
</table>

MET= metformin  SU= sulphonylurea  PIO= pioglitazone  ESRD= end-stage renal disease on haemodialysis  * = consider a lower dose of SU/ insulin to prevent hypoglycaemia
** = in patients whom metformin inappropriate  *** = lack of clinical experience  **** = Liver toxicity–rare reports of liver dysfunction –monitor LFTs before Tx and at 3/12ly intervals for 1\textsuperscript{st} yr and periodically after.
Drug Safety Update September 2012

- Patients treated with DPP-4 inhibitors should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain (sometimes radiating to the back) – and encouraged to tell their healthcare provider if they have such symptoms.
- If pancreatitis is suspected, the DPP-4 inhibitor and other potentially suspect medicines should be discontinued
- Report suspected adverse reactions through the Yellow Card Scheme - see www.yellowcard.gov.uk

Drug interactions
To reduce the risk of hypoglycaemia a lower dose of sulphonylurea or insulin may be considered when used in combination with DPP-4 enzyme inhibitors.

Sitagliptin
- It is possible that potent CYP3A4 inhibitors (i.e. ketoconazole, itraconazole, ritonavir, clarithromycin) could alter the pharmacokinetics of sitagliptin in patients with severe renal impairment or ESRD.
- Sitagliptin has a small effect on plasma digoxin concentrations. No dose adjustment of digoxin is recommended. Patients at risk should be monitored for digoxin toxicity.

Saxagliptin
- Using CYP3A4 inducers like carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may reduce the glycaemic lowering effect of saxagliptin.

Linagliptin
- Full efficacy of linagliptin in combination with potent inducers of P-glycoprotein and CYP3A4, such as rifampicin, carbamazepine, phenobarbital and phenytoin might not be achieved, particularly if these are administered long-term.

NB: This list is not exhaustive; please refer to BNF/SPC for further information.

Cardiovascular Outcome Data from Large Randomised Controlled Trials

- All glitnps have cardiovascular outcome RCTs in progress and one for saxagliptin has reported.
- A large RCT comparing the addition of saxagliptin or placebo to other blood-glucose-lowering medication in T2DM has been published. At around 2 years saxagliptin:
  - did not increase or reduce the risk of cardiovascular outcomes
  - increased the risk of hypoglycaemia and may also have increased the risk of admission to hospital because of heart failure

Cost of 28 days supply of metformin with DPP-4 enzyme inhibitors (including combination products)

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin 100mg od</th>
<th>Sitagliptin 50mg / metformin 1g bd (combination tab)</th>
<th>Saxagliptin 5mg od</th>
<th>Saxagliptin 2.5mg / metformin 1g/850mg od (combination tab)</th>
<th>Linagliptin 5mg od</th>
<th>Linagliptin 2.5mg / metformin 1g/850mg od bd (combination tab)</th>
<th>Vildagliptin 50mg bd</th>
<th>Vildagliptin 50mg / metformin 850mg or 1g bd (combination tab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plus metformin 850mg bd (£1.19)</td>
<td>£33.26</td>
<td>£33.26</td>
<td>£31.60</td>
<td>£31.60</td>
<td>£33.26</td>
<td>£33.26</td>
<td>£31.76</td>
<td>£31.72</td>
</tr>
<tr>
<td>Plus metformin 1g bd (£3.44)</td>
<td>£34.45</td>
<td>n/a</td>
<td>£32.79</td>
<td>n/a</td>
<td>£34.45</td>
<td>n/a</td>
<td>£32.95</td>
<td>n/a</td>
</tr>
</tbody>
</table>

References
4. BNF Sept 2013 – Mar 2014
5. NICE MPC KTT12 Type 2 diabetes mellitus http://www.nice.org.uk/mpc/keytherapeutictopics/KTT12.jsp
7. NICE Medicines Evidence Commentary – Type 2 diabetes: study finds no benefit from saxagliptin on cardiovascular outcomes http://arms.evidence.nhs.uk/resources/hub/1029671/attachment

Approved by Hertfordshire Medicines Management Committee Jan 2013 (updated Jan 2014)