Initiation of lifestyle interventions

Refer to structured education programme

Metformin (with active dose titration)
If metformin is contraindicated or patient intolerant refer to algorithm on page 2

Efficacy (↓HbA1c): high, ↓CV events
Hypoglycaemia: low
Weight: neutral/ loss (~0-5kg)
Side effects: GI. See notes re lactic acidosis and renal impairment
Cost (£): low

Insulin (multiple daily doses)**

Efficacy (↓HbA1c): highest
Hypoglycaemia: high
Weight: gain (~4-5kg)
Side effects: hypoglycaemia
Cost (£): variable

Nottinghamshire Health Community Treatment guideline for the Management of Type 2 diabetes. Update Approved by Notts APC Jan 15, Review Feb 17

Nottinghamshire Area Prescribing Committee
Initiation of lifestyle interventions

Refer to structured education programme

Metformin contraindicated or not tolerated?

Yes

Efficacy (↓HbA1c): high
Hypoglycaemia: moderate
Weight: gain (~1.5-2kg)
Side effects: hypoglycaemia
Cost (£): low

No

If not tolerated consider metformin MR

Gliclazide

Ensure that patient is truly intolerant to metformin. Metformin is the only agent with proven effectiveness at reducing CV events

No

Refer to algorithm on page 1

If HbA1c target not achieved after ~3 months at maximum tolerated dose, proceed to dual therapy (order not intended to denote preference-choose according to patient- and disease-specific factors). Consider beginning at this stage if very high HbA1c (e.g. ≥ 75 mmol/mol)

Gliclazide + Metformin (if not tried before)

Efficacy (↓HbA1c): high, ↓CV events
Hypoglycaemia: mod (due to gliclazide)
Weight: neutral/ loss (~0-5kg)
Side effects: GI/ lactic acidosis
Cost (£): low

Gliclazide + DPP-4 inhibitor

Efficacy (↓HbA1c): mid
Hypoglycaemia: mod (due to gliclazide)
Weight: neutral
Side effects*: rare
Cost (£): high

Gliclazide + Pioglitazone

Efficacy (↓HbA1c): high
Hypoglycaemia: mod (due to gliclazide)
Weight: gain (~4.5kg)
Side effects: oedema, HF, fractures
Cost (£): low

Gliclazide + GLP-1 agonist**

Efficacy (↓HbA1c): highest
Hypoglycaemia: high
Weight: gain (~4.5kg)
Side effects*: GI
Cost (£): variable

Gliclazide + Insulin*** (usually basal)

Insulin (multiple daily doses)**

Initial therapy

Dual therapy

Insulin

More complex insulin strategies

If HbA1c target not achieved after ~3 months at maximum tolerated dose, proceed to insulin.

Revert to algorithm on page 1

Gliclazide or DPP-4 inhibitor

+ insulin***

Gliclazide or Pioglitazone

+ insulin***

Gliclazide or GLP-1 agonist

+ insulin***

Insulin

+ DPP4 inhibitor or SGLT2 inhibitor**

* ▼ Side effect profile still being established
**GLP-1 agonists & SGLT2 inhibitors should be initiated in line with NICE TAs- see medicine notes
***Consider referral to structured education programme for patients initiated on insulin
Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes

The following information is to support prescribers regarding the medicines aspects of the Type 2 Diabetes Algorithm, please refer to the BNF or Summary of Product Characteristics for further information on contraindications, precautions, adverse effects and interactions.

Treatment of Hyperglycaemia

- Only prescribe one agent from each class.
- Substituting agents is unlikely to improve glucose control – swapping metformin plus gliclazide for metformin plus pioglitazone is more likely to cause deterioration in glycaemic control.
- The addition of a third agent to a combination of two oral hypoglycaemic drugs taken at maximally tolerated doses may only lower HbA1c by 5.5mmol/mol*.
- For a person on dual therapy who is markedly hyperglycaemic, NICE guidance states to consider starting insulin therapy in preference to adding other drugs to control blood glucose unless there is strong justification not to.

Glycaemic Target

- An individualised target should be discussed and agreed with each patient and reviewed every 2-6 months. This goal may not be appropriate or practical for some patients and clinical judgement needs to be applied.
- Lifestyle should be reviewed before every treatment escalation.

NICE CKS (Diabetes – type 2, June 2010)

- Agree and set a target HbA1c value with the person.
  - For people treated with lifestyle measures alone or who are taking one antidiabetic drug, the usual target HbA1c value is 48 mmol/mol (6.5%). However, an individual's target may be set above this level.
  - For people taking two or more antidiabetic drugs (including insulin), the usual target HbA1c is less than 59 mmol/mol (7.5%). However, an individual's target may be set above this level.
    - In certain circumstances it may be appropriate to maintain a lower target (for example 48 mmol/mol [6.5%]) in people taking two or more antidiabetic drugs. This should be decided on an individual basis.

- When setting a target HbA1c value, take into account:
  - The person's preference.
  - The balance of likely benefits and harms of treatment.
  - The risk of microvascular and macrovascular complications.
  - The risk and consequences of hypoglycaemia.
  - Whether the person will benefit from self monitoring.
  - The intensity of treatment.

- Avoid the use of highly intensive management strategies to achieve an HbA1c level less than 48 mmol/mol (6.5%).

*Reporting Units for HbA1c
Glycated haemoglobin (HbA1c) is the recommended method of measuring long term control of blood glucose in people with both type 1 and type 2 diabetes. Previously the results were reported as a percentage (%). This has changed to millimoles/mole (mmol/mol) where people with diabetes will receive their HbA1c measurement in mmol/mol only. See conversion table for more detail.

### HbA1c conversion table

<table>
<thead>
<tr>
<th>HbA1c (new units) (mmol/mol)</th>
<th>HbA1c (old units) %</th>
<th>A 0.5% difference in HbA1c is equivalent to a difference of about 5.5mmol/mol, and a 1% difference is equivalent to a difference of about 11mmol/mol. Note that these are rounded equivalents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>6.5</td>
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<tr>
<td>53</td>
<td>7.0</td>
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<tr>
<td>59</td>
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<tr>
<td>64</td>
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<tr>
<td>75</td>
<td>9.0</td>
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</tr>
<tr>
<td>86</td>
<td>10.0</td>
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</tr>
</tbody>
</table>

### Patient education

All people newly diagnosed with type 2 diabetes (and/or their carer) should be offered referral to a structured education programme (e.g. JUGGLE). Inform people and their carers that structured education is an integral part of diabetes care. If patients are unable or unwilling to attend the group education sessions they should be referred to a dietitian and early initiation of metformin should be considered.
**BIGUANIDES - METFORMIN**  
(Metformin is the only available biguanide)  
Decreases gluconeogenesis and increases peripheral utilisation of glucose.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>NOTES</th>
<th>FORMULARY CHOICE</th>
<th>PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Must be started in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group) and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone. Consider metformin as an option for first-line glucose-lowering therapy for a person who is not overweight. Continue with metformin if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added. <strong>NICE guidance (CG87):</strong> Use clinical judgement on whether (and when) to offer standard-release metformin to support lifestyle change for people whose HbA1c or fasting plasma glucose blood test results have deteriorated if: this has happened despite their participation in an intensive lifestyle-change programme, or they are unable to participate in an intensive lifestyle-change programme. For patients unable to swallow tablets consider crushing the standard tablet. The oral powder was discontinued in April 2014. A liquid is on the market but is not cost-effective (£320 per month!)</td>
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<tr>
<td></td>
<td>First choice</td>
<td>Actively titrate the dose of metformin (i.e. increase to the maximum tolerated dose). This must be done over several weeks to minimise risk of gastrointestinal (GI) side effects. (NICE CG87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>If adding metformin to gliclazide, it may be appropriate to decrease the gliclazide dose in order to titrate the metformin. HbA1c target for patients on metformin plus gliclazide should not be lower than 59mmol/ml.</td>
<td></td>
</tr>
<tr>
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<td></td>
<td><strong>RENA IMPAIRMENT (NICE CG87):</strong> Review the dose of metformin if the serum creatinine exceeds 130 micromol/litre or the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73-m².</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stop the metformin if the serum creatinine exceeds 150 micromol/litre or the eGFR is below 30 ml/minute/1.73-m².</td>
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<tr>
<td></td>
<td></td>
<td>• Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73-m².</td>
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<td><strong>LIVER OR CARDIAC IMPAIRMENT (NICE CG87):</strong> The benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that: due consideration can be given to the</td>
<td></td>
</tr>
<tr>
<td>Metformin MR</td>
<td>Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy. (NICE CG87)</td>
<td>Second choice (for patients with proven GI intolerance)</td>
<td>cardiovascular-protective effects of the drug • an informed decision can be made on whether to continue or stop the metformin.</td>
</tr>
</tbody>
</table>
**SULFONYLUREAS - Gliclazide**
Augments insulin secretion and consequently is only effective when some residual pancreatic beta-cell activity is present.

<table>
<thead>
<tr>
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</table>
| Gliclazide | **Prescribe gliclazide when a sulfonylurea is indicated.**<br><br>NICE guidance (CG87): Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:<br>• the person is not overweight<br>• the person does not tolerate metformin (or it is contraindicated)<br>or<br>• a rapid response to therapy is required because of hyperglycaemic symptoms.<br>Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate with metformin. | First choice | Educate the person about the risk of hypoglycaemia, particularly if they have renal impairment.<br>Increase dose every 4-6 weeks to achieve glycaemic target (do not exceed maximum dose). Check blood glucose (finger prick) before each titration to reduce risk of causing hypoglycaemia.<br>HbA1c results of less than 48mmol/ml in patients on gliclazide should prompt a review of therapy due to a risk of symptomatic hypoglycaemia.<br>If adding metformin to gliclazide, it may be appropriate to decrease the gliclazide dose in order to titrate the metformin.<br>HbA1c target for patients on gliclazide plus metformin should not be lower than 59mmol/ml.<br>Gliclazide can cause weight gain (a few kilograms).<br>Advice for drivers:<br>For Group 1 drivers (car/motorcycle) it may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia. Group 2 drivers (bus/lorry) on sulfonylureas are required by law to monitor glucose level at least twice daily and at times relevant to driving.<br>For more information about driving with diabetes see the [Government guidance for drivers with diabetes](https://www.gov.uk/guidance/diabetes-and-driving) and advice for drivers on the [Diabetes UK website](https://www.diabetes.org.uk/information-for-healthcare-professionals/diabetes-and-driving). DVLA also has info- see [guidance for professionals](https://www.gov.uk/guidance/diabetes-and-driving).

<table>
<thead>
<tr>
<th>Gliclazide MR</th>
<th><strong>Use gliclazide MR (modified release) if compliance is poor.</strong></th>
<th>Second choice (where there are concerns over compliance to standard release)</th>
<th></th>
</tr>
</thead>
</table>

**Price per month (Nov14):**
80mg daily-160mg twice daily £1.32- £5.28

**Gliclazide MR**
Amb2

**Price per month (Nov14):**
30mg -120mg daily £2.06- £8.56

Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)
Review Date: February 2017
GLIPTINS (also known as DPP-4 inhibitors)
Inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion

<table>
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<tbody>
<tr>
<td>Sitagliptin (Januvia®)</td>
<td>Low risk of hypoglycaemia and are weight neutral.</td>
<td>First choice gliptin</td>
<td>Continue gliptin therapy only if there is a reduction of ≥5.5mmol/mol (0.5%) in HbA1c in 6 months.</td>
</tr>
<tr>
<td><strong>Price per month (Nov14):</strong>&lt;br&gt;25mg -100mg daily £33.26</td>
<td><strong>NICE guidance (CG87):</strong>&lt;br&gt;Consider adding a gliptin instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 48mmol/mol, or other higher level agreed with the individual) if:</td>
<td></td>
<td>No long term safety data available for these agents.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Renal impairment (CrCl, SPC):&lt;br&gt; &gt;50ml/min – no dose adjustment&lt;br&gt;30-50ml/min – 50mg daily&lt;br&gt;&lt;30ml/min – 25mg daily</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>No dose adjustment is necessary based on age. Limited safety data is available in patients ≥ 75 years of age and care should be exercised.</td>
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<td></td>
<td>Applies to all gliptins:&lt;br&gt;Discuss the potential benefits and risks of treatment with a gliptin with the person to enable them to make an informed decision.</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Increased risk of pancreatitis associated with all gliptins. Patients 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. Link to MHRA warning</td>
</tr>
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<tr>
<td>Alogliptin) (Vipidia▼)</td>
<td><strong>Licensed combinations:</strong>&lt;br&gt;Dual therapy with metformin, sulfonylurea or pioglitazone.&lt;br&gt;Triple therapy with metformin &amp; sulfonylurea or pioglitazone.&lt;br&gt;Insulin (with or without metformin)</td>
<td>First choice gliptin</td>
<td>See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.</td>
</tr>
<tr>
<td><strong>Price per month</strong>&lt;br&gt;Combinations approved for use locally:&lt;br&gt;Dual therapy with metformin, sulfonylurea or pioglitazone.&lt;br&gt;Triple therapy with metformin &amp; pioglitazone.&lt;br&gt;Insulin (with or without metformin).</td>
<td></td>
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</tr>
</tbody>
</table>
| (May15): 6.25mg- 25mg daily £26.60 | **Renal impairment (CrCl, SPC):**
| | >50ml/min – no dose adjustment
| | 30-50ml/min – 12.5mg daily
| | <30ml/min – 6.25mg daily
| | No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
| **NB there is currently limited data regarding use of alogliptin when used as triple therapy with metformin and a sulphonylurea**
| **Licensed in combination with:**
| other glucose lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
| **Licensed combinations:**
| • Dual therapy with metformin
| • Triple therapy with metformin & sulfonylurea
| • Insulin (with or without metformin)
| **Second choice gliptin**
| See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.
| Linagliptin (Trajenta ▼)
| | **Renal impairment (SPC):**
| | Does not require dose reduction in renal impairment,
| | No dose adjustment is necessary based on age. However, clinical experience in patients > 80 years of age is limited and caution should be exercised when treating this population.
| Price per month (Nov14): 5mg daily £33.26 |  |
| | **Renal impairment (CrCl, SPC):**
| | >50ml/min – no dose adjustment
| | 30-50ml/min – 12.5mg daily
| | <30ml/min – 6.25mg daily
| | No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
| "Licensed combinations:
| • Dual therapy with metformin
| • Triple therapy with metformin & sulfonylurea
| • Insulin (with or without metformin)
| **Second choice gliptin**
| See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.
| Linagliptin (Trajenta ▼)
| Price per month (Nov14): 5mg daily £33.26 | **Renal impairment (CrCl, SPC):**
| | >50ml/min – no dose adjustment
| | 30-50ml/min – 12.5mg daily
| | <30ml/min – 6.25mg daily
| No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
| **Licensed combinations:**
| • Dual therapy with metformin
| • Triple therapy with metformin & sulfonylurea
| • Insulin (with or without metformin)
| **Second choice gliptin**
| See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.
| Linagliptin (Trajenta ▼)
| Price per month (Nov14): 5mg daily £33.26 | **Renal impairment (CrCl, SPC):**
| | >50ml/min – no dose adjustment
| | 30-50ml/min – 12.5mg daily
| | <30ml/min – 6.25mg daily
| No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
| **Licensed combinations:**
| • Dual therapy with metformin
| • Triple therapy with metformin & sulfonylurea
| • Insulin (with or without metformin)
| **Second choice gliptin**
| See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.
| Linagliptin (Trajenta ▼)
| Price per month (Nov14): 5mg daily £33.26 | **Renal impairment (CrCl, SPC):**
| | >50ml/min – no dose adjustment
| | 30-50ml/min – 12.5mg daily
| | <30ml/min – 6.25mg daily
| No dose adjustment is necessary based on age. However, dosing of alogliptin should be conservative in patients with advanced age due to the potential for decreased renal function.
| **Licensed combinations:**
| • Dual therapy with metformin
| • Triple therapy with metformin & sulfonylurea
| • Insulin (with or without metformin)
| **Second choice gliptin**
| See sitagliptin entry for MHRA warning regarding pancreatitis (applies to all gliptins). No long term safety data available for these agents.
<table>
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<tr>
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</table>
| Pioglitazone (Actos®) | **NICE guidance (CG87):** Consider adding pioglitazone instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate ($HbA_1c \geq 48\text{mmol/mol}$, or other higher level agreed with the individual) if:  
  - the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), or  
  - a person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.  
  Consider adding a pioglitazone as second-line therapy to first-line sulfonylurea monotherapy when control of blood glucose remains or becomes inadequate ($HbA_1c \geq 48\text{mmol/mol}$, or other higher level agreed with the individual) if:  
  - the person does not tolerate metformin or metformin is contraindicated.  
  Consider adding pioglitazone as third-line therapy to first-line metformin and a second-line sulfonylurea when control of blood glucose remains or becomes inadequate ($HbA_1c \geq 59\text{mmol/mol}$, or other higher level agreed with the individual) and insulin is unacceptable or inappropriate.  
  Consider combining pioglitazone with insulin therapy for a person:  
  - who has previously had a marked glucose-lowering response to thiazolidinedione therapy (pioglitazone), or  
  - who is on high-dose insulin therapy and whose blood glucose is inadequately controlled.  
  **Licensed combinations:**  
  - Dual therapy with metformin or sulfonylurea.  
  - Triple therapy with metformin & sulfonylurea.  
  - Insulin (if metformin not appropriate) | Pioglitazone is the only thiazolidinedione available | Continue pioglitazone therapy only if there is a reduction of $\geq 5.5\text{mmol/mol}$ (0.5%) in $HbA1c$ in 6 months  
  Do NOT start or continue pioglitazone in people who:  
  - have heart failure (NYHA class I-IV)  
  - are at a higher risk of fracture  
  - macula oedema  
  - a history of **bladder cancer** or in patients with uninvestigated macroscopic or microscopic haematuria.  
  **Risk of bladder cancer: MHRA safety update**  
  **MHRA guide on patient selection and risk minimisation.**  
  Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin, especially in patients with risk factors for the development of cardiac failure. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain, and oedema.  
  **Risk of cardiac failure when combined with insulin: MHRA safety update**  
  Pioglitazone can cause weight gain.  
  Discuss the potential benefits and risks of treatment with pioglitazone with the person to enable them to make an informed decision.  
  Pioglitazone may be preferable to a gliptin if:  
  - the person has marked insulin insensitivity, or  
  - a gliptin is contraindicated, or  

Price per month (Nov14):  
15mg - 45mg daily  
£1.25- £1.65
- the person has previously had a poor response to, or did not tolerate, a gliptin.

**Renal impairment (SPC):**
No dose adjustment is necessary in patients with impaired renal function (creatinine clearance > 4 ml/min).

**Do not use if hepatically impaired.**
No dose adjustment is necessary for elderly patients. Start with the lowest available dose and increase gradually, particularly when used in combination with insulin.
## GLP-1 (Glucagon-like peptide-1) AGONISTS

*Increase insulin secretion, suppress glucagon secretion, and slow gastric emptying*

<table>
<thead>
<tr>
<th>DRUG</th>
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</tr>
</thead>
</table>
| **Lixisenatide (Lyxumia®▼)** | Once daily subcutaneous injection  
- Lixisenatide is currently the GLP-1 agonist with the lowest acquisition cost.  
Dual / Triple therapy:  
As per exenatide (Byetta®▼)  
Licensed in combination with:  
oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.  
(See exenatide for local patient group comments on use with basal insulin)  
There is no specific NICE guidance for lixisenatide. | Prescriber to decide most appropriate GLP-1 agonist after discussion with patient.  
If all other patient factors are equal prescribe the GLP-1 agonist with the lowest acquisition cost | DUAL THERAPY - continue lixisenatide only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.  
TRIPLE THERAPY - continue lixisenatide only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.  
Renal impairment (CrCl, SPC):  
50-80ml/min – no dose adjustment  
30-50ml/min – use with caution  
<30ml/min – not recommended  
No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs.  
See exenatide for information on hypoglycaemia and pancreatitis risk (applies to all GLP-1 agonists). |
| **Exenatide (Byetta®▼)** | Twice daily subcutaneous injection  
**NICE guidance (CG87):**  
Dual / Triple therapy:  
Can be used in dual or triple therapy regimens when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol or agreed individualised target). Patients should be on maximally tolerated doses of oral hypoglycaemic agents and have a BMI;  
- ≥ 35.0 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or | Prescriber to decide most appropriate GLP-1 agonist after discussion with patient.  
If all other patient factors are equal prescribe the GLP-1 agonist | DUAL THERAPY - continue exenatide only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.  
TRIPLE THERAPY - continue exenatide only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.  
Renal impairment (CrCl, SPC):  
50-80ml/min – no dose adjustment  
30-50ml/min – dose escalation from 5 mcg to 10 mcg  
No long term safety data available.  
See exenatide for information on hypoglycaemia and pancreatitis risk (applies to all GLP-1 agonists). |

**Price per month (Nov14):**  
Lixisenatide:  
20 micrograms daily £54.14  
Exenatide:  
5 or 10mcg daily £68.24

**Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)**

**Review Date:** February 2017
- < 35.0 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

**Licensed indications:**
Dual therapy with metformin, a sulfonylurea or pioglitazone.
Triple therapy with metformin & a sulfonylurea or metformin & pioglitazone.

**In combination with insulin:**
Exenatide (Byetta®▼) is licensed for addition to patient currently receiving insulin +/- metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.
The local patient group indicated to receive this combination the person must fulfill the following criteria:
- BMI >35 and HbA1c > 75mmol/mol and currently using insulin.

with the lowest acquisition cost
should proceed conservatively <30ml/min – not recommended

Use with caution and dose escalation from 5 mcg to 10 mcg should proceed conservatively in patients >70 years. The clinical experience in patients >75 years is very limited.

**Applies to ALL GLP-1 agonists:**
- Discuss the potential benefits and risks of treatment with a GLP-1 agonist with the person to enable them to make an informed decision.
- Routine monitoring of blood glucose levels is only required if the GLP-1 agonist is given in combination with another agent likely to cause hypoglycaemia e.g. sulfonylurea.
- There have been reports of necrotising and haemorrhagic pancreatitis with GLP-1 agonists, some of which were fatal. If pancreatitis is suspected, treatment with the GLP-1 agonist should be suspended immediately; if pancreatitis is diagnosed, the GLP-1 agonist should be permanently discontinued. (MHRA warning)

<table>
<thead>
<tr>
<th>Exenatide prolonged release (Bydureon®▼)</th>
<th>Once weekly subcutaneous injection</th>
<th>Prescriber to decide most appropriate GLP-1 agonist after discussion with patient.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use as per NICE TA248.</td>
<td>If all other patient factors are equal prescribe the GLP-1 agonist</td>
</tr>
<tr>
<td></td>
<td>Exenatide MR is NOT licensed in combination with insulin.</td>
<td>DUAL THERAPY - continue exenatide MR only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) after 6 months.</td>
</tr>
<tr>
<td></td>
<td><strong>NICE TA248 – Exenatide prolonged release:</strong></td>
<td>TRIPLE THERAPY - continue exenatide MR only if the person has a reduction in HbA1c of ≥11mmol/mol (1%) and a 3% loss of initial bodyweight after 6 months.</td>
</tr>
<tr>
<td></td>
<td><em>Dual therapy: (Met or Glic) + Exenatide MR</em></td>
<td>No long term safety data available.</td>
</tr>
<tr>
<td></td>
<td>Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulfonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in 'Liraglutide for the treatment of type 2 diabetes mellitus' (NICE technology appraisal 203); that is, only if:</td>
<td>Renal impairment (CrCl, SPC): 50-80ml/min – no dose adjustment</td>
</tr>
</tbody>
</table>

**Price per month (Nov14):**
- 2mg weekly: £73.36

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Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)
Review Date: February 2017
- the person is intolerant of either metformin or a sulfonylurea, or a treatment with metformin or a sulfonylurea is contraindicated, and
- the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, or a treatment with thiazolidinediones and DPP-4 inhibitors is contraindicated.

**Triple therapy: Met + (Glic or Pio) + Exenatide MR**
Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in 'Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59 mmol/mol or agreed individualised target), and the person has:
- a body mass index (BMI) ≥ 35 kg/m² in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight or
- a BMI < 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

**Licensed combinations:**
- Dual therapy with metformin, a sulfonylurea or pioglitazone.
- Triple therapy with metformin & sulfonylurea or metformin & pioglitazone.

**Liraglutide (Victoza®)**
- Once daily subcutaneous injection
  - Use as per NICE TA203.
  - Liraglutide 1.8 mg daily is not recommended for the treatment of people with type 2 diabetes. (NICE TA203)

**NICE TA203 – Liraglutide**
**Dual therapy: (Met or Glic) + Liraglutide**

Prescriber to decide most appropriate GLP-1 agonist after discussion with patient.

If all other

**DUAL THERAPY** - continue liraglutide only if the person has a reduction in HbA1c of ≥11mmol/mol² (1%) after 6 months.

**TRIPLE THERAPY** - continue liraglutide only if the person has a reduction in HbA1c of ≥11mmol/mol² (1%) and a 3% loss of initial bodyweight after 6 months.

License combinations:
- Dual therapy with metformin, a sulfonylurea or pioglitazone.
- Triple therapy with metformin & sulfonylurea or metformin & pioglitazone.

with the lowest acquisition cost

<50ml/min – not recommended

No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs.

See exenatide for information on hypoglycaemia risk and warning about pancreatitis risk (applies to all GLP-1 agonists).
Liraglutide 1.2 mg daily in dual therapy regimens (in combination with metformin or a sulfonylurea) is recommended as an option for the treatment of people with type 2 diabetes, only if:

- the person is intolerant of either metformin or a sulfonylurea, or treatment with metformin or a sulfonylurea is contraindicated, and
- the person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, or treatment with thiazolidinediones and DPP-4 inhibitors is contraindicated.

**Triple therapy: Met + (Glic or Pio) + Liraglutide**

Liraglutide 1.2 mg daily in triple therapy regimens (in combination with metformin + sulfonylurea, or metformin + thiazolidinedione) is recommended as an option for the treatment of people with type 2 diabetes, only if used as described for exenatide in NICE CG87; that is, when control of blood glucose remains or becomes inadequate (HbA1c ≥ 59mmol/mol, or agreed individualised target), and the person has BMI:

- ≥ 35 kg/m² in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight, or
- < 35 kg/m², and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

**Licensed in combination with:**

- oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

**Patient factors:** are equal prescribe the GLP-1 agonist with the lowest acquisition cost.

**No long term safety data available.**

**Renal impairment (CrCl, SPC):**

- 30-90ml/min - no dose adjustment
- <30ml/min – not recommended

No dose adjustment required based on age, but limited therapeutic experience in patients > 75yrs.

See exenatide for information on hypoglycaemia risk and warning about pancreatitis risk (applies to all GLP-1 agonists).
**SODIUM GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITOR**
Reversibly inhibits sodium-glucose co-transporter-2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>NOTES</th>
<th>FORMULARY CHOICE</th>
<th>PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS</th>
</tr>
</thead>
</table>
| Dapagliflozin (Forxiga®▼) | NICE TA288: *Dual therapy: Met + Dapagliflozin (as per gliptins):* Dapagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if it is used as described for gliptins in Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87).  
*Dapagliflozin + insulin:* Dapagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.  

The NICE TA states that dapagliflozin is not recommended for triple therapy. However, this is considered acceptable practise locally if dapagliflozin is used in combination with metformin and gliclazide.  

Licensed in combination with: other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.  

**Price per 28 days (Nov 14): 5 or 10mg daily £36.59** | Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient.  
If all other patient factors are equal prescribe the SGLT2 inhibitor with the lowest acquisition cost. | No long term safety data available.  
Licensed for initiation in adults between 18 and 75 years only.  
Renal impairment (eGFR or CrCl SPC): >60ml/min – no dose adjustment  
<60ml/min – not recommended  

Due to its mechanism of action, patients taking dapagliflozin are at increased risk of urinary tract infection and will test positive for glucose in their urine.  

Increases diuresis associated with a modest decrease in blood pressure (more pronounced in patients with very high blood glucose concentrations).  

Not recommended for patients receiving loop diuretics or who are volume depleted e.g. due to acute illness (such as gastrointestinal illness).  

While a causal relationship between dapagliflozin and bladder cancer is unlikely, as a precautionary measure, dapagliflozin is not recommended for use in patients concomitantly treated with pioglitazone. |

| Canagliflozin (Invokana®▼) | • For use as per NICE TA315  
Note that although canagliflozin is licensed for monotherapy, the APC have only approved it for use as per NICE TA315.  
NICE TA315: *Dual therapy: Met + Canagliflozin* Canagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:  
• a sulfonylurea is contraindicated or not tolerated or  
• the person is at significant risk of hypoglycaemia or its | Prescriber to decide most appropriate SGLT2 inhibitor after discussion with patient.  
If all other patient factors are equal prescribe the | No long term safety data available.  
Licensed for adults aged over 18 years only. For patients over 65 years renal function and risk of volume depletion should be taken into account.  
Renal impairment (eGFR or CrCl, SPC): 60-89ml/min – no dose adjustment  
<60ml/min – do not initiate canagliflozin. Max dose 100mg daily if eGFR or CrCl persistently falls below 60ml/min whilst on canagliflozin.  
<45 ml/min- discontinue canagliflozin if eGFR or CrCl |

**Price per 28 days (Nov 14): 100mg or 300 mg daily £36.59 or £46.66**
Consequences.

**Triple therapy: Met + (Glic or Pio) + Canagliflozin**
Canagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:
- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

**Canagliflozin + insulin:**
Canagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

**Licensed in combination with:**
Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

<table>
<thead>
<tr>
<th>Empagliflozin (Jardiance®▼)</th>
<th>For use as per NICE TA336:</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICE TA315:</td>
<td>Dual therapy: Met + Empagliflozin</td>
</tr>
<tr>
<td>Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:</td>
<td></td>
</tr>
<tr>
<td>- a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences.</td>
<td></td>
</tr>
</tbody>
</table>

**Triple therapy: Met + (Glic or Pio) + Empagliflozin**
Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:
- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

**Empagliflozin + insulin:**
Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

**Licensed in combination with:**
Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

<table>
<thead>
<tr>
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<th>For use as per NICE TA336:</th>
</tr>
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<tbody>
<tr>
<td>NICE TA315:</td>
<td>Dual therapy: Met + Empagliflozin</td>
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<tr>
<td>Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:</td>
<td></td>
</tr>
<tr>
<td>- a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences.</td>
<td></td>
</tr>
</tbody>
</table>

**Triple therapy: Met + (Glic or Pio) + Empagliflozin**
Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:
- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

**Empagliflozin + insulin:**
Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

**Licensed in combination with:**
Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

<table>
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<tr>
<th>Empagliflozin (Jardiance®▼)</th>
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<tbody>
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<td>NICE TA315:</td>
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</tr>
<tr>
<td>Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if:</td>
<td></td>
</tr>
<tr>
<td>- a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycaemia or its consequences.</td>
<td></td>
</tr>
</tbody>
</table>

**Triple therapy: Met + (Glic or Pio) + Empagliflozin**
Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with:
- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

**Empagliflozin + insulin:**
Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

**Licensed in combination with:**
Other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
## OTHER ANTIDIABETIC AGENTS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>NOTES</th>
<th>FORMULARY CHOICE</th>
<th>PRECAUTIONS / CONTRA-INDICATIONS / LESS DESIRABLE PATIENT GROUPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose (Glucobay®)</td>
<td>Useful in the occasional overweight patient.</td>
<td></td>
<td>Usage by limited by gastrointestinal intolerance.</td>
</tr>
<tr>
<td></td>
<td><strong>NICE guidance (CG87):</strong> Consider acarbose for a person unable to use other oral glucose-lowering medications.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Licensed indication:</strong> Acarbose tablets are recommended for the treatment of non-insulin dependent (NIDDM) diabetes mellitus in patients inadequately controlled on diet alone, or on diet and oral hypoglycaemic agents.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibits intestinal alpha glucosidases (delays digestion and absorption of starch and sucrose)</td>
<td>Price per 28 days (Nov 14): 50mg- 200mg three times daily £9- £30.65</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Insulin Therapy in Type 2 Diabetes

Insulin treatment

- If other measures do not keep HbA1c to <59 mmol/mol (or other agreed target), discuss benefits and risk of insulin treatment.
- **Initiate with a structured programme including patient education and management plan.** Insulin therapy should be initiated from a choice of a number of insulin types and regimens by a practitioner with the appropriate knowledge, competencies and experience to choose the most appropriate starting regimen tailored to each patient.
- Begin with human NPH insulin (Isophane insulin e.g. Insulatard®, Humulin I®, Insuman® Basal) taken at bedtime or twice daily according to need.

**There is no evidence of a clinical benefit of analogue insulins over human insulins in type 2 diabetes.**

- Consider twice-daily biphasic human insulin (pre-mix) regimens in particular where HbA1c >75 mmol/mol. A once-daily regimen may be an option when initiating this therapy.
- Insulin analogues rather than pre-mixed human insulin preparations should only be considered when:
  - immediate injection before a meal is needed, or
  - hypoglycaemia is a problem, or
  - there are marked postprandial blood glucose excursions.
- Recurrent symptomatic hypoglycaemia should prompt a re-examination of the current insulin regimen, injection sites, a search for other co-morbidities (such as liver or renal disease) and a review of the agreed HbA1c target. If tight control is still required, then consider a trial of analogue insulin.
- If a patient requires once a day insulin administration because a carer or healthcare professional is needed to administer the insulin injection, and once daily NPH insulin does not provide sufficient control, then consider a trial of basal analogue insulin.
- Note that insulin degludec may only be initiated by consultant diabetologist/endocrinologist for type 1 diabetes (see formulary for more detail).
- Monitor a person using a basal insulin regimen (NPH or a long-acting insulin analogue [insulin glargine/detemir]) for the need for mealtime insulin (or a pre-mixed insulin preparation). If blood glucose control remains inadequate (not to agreed target levels without problematic hypoglycaemia), move to a more intensive, twice/three times daily mixed insulin or mealtime plus basal insulin regimen.
- Human insulins (such as Humulin S®, Actrapid®, Insuman Rapid®, Isophane insulin, biphasic isophane insulin) should be considered as first line therapy before moving to analogue or analogue mixtures. Insulin analogues should only be considered if one of the criteria described above is met.
- Monitor a person using pre-mixed insulin once or twice daily for the need for a further pre-prandial injection or for an eventual change to a mealtime plus basal insulin regimen, based on human or analogue insulins, if blood glucose control remains inadequate.

Oral agent combination therapy with insulin

- When starting basal insulin therapy:
  - Continue with metformin and gliclazide (and acarbose, if used)
  - Review the use of gliclazide if hypoglycaemia occurs.
  - When prandial quick or rapid acting insulin injections or mixed insulins are started, gliclazide should be discontinued, or tapered and then discontinued, since it is not considered synergistic when with administered insulin.
When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens):
  - Continue with metformin
  - Consider combining an SGLT2 inhibitor with insulin therapy if:
    - An SGLT2 inhibitor has previously had a marked glucose lowering effect, or
    - Blood glucose control is inadequate with high dose insulin.

Use of GLP1 analogues in combination with insulin

- Exenatide (Byetta®), lixisenatide and liraglutide are licensed for addition to patients currently receiving insulin.
- The patient group indicated to receive this combination must fulfil the following criteria; morbidly obese (BMI >35) **and** HbA1c >75mmol/mol **and** currently using insulin.
- This regimen must be initiated by a specialist.
- Continue the GLP1 in combination with insulin only if the person has a reduction in HbA1c of ≥11mmol/mol and a 3% loss of initial bodyweight in 6 months.

Intensifying the insulin regimen

- Monitor those using basal insulin regimens for the need for short acting insulin before meals or pre-mixed insulin.
- Monitor those using premixed insulin once or twice daily for need for further injections of short acting insulin before meals or change to mealtime plus basal regimen.

Insulin delivery devices

- Offer education to a person who requires insulin on using an injection device (usually a pen injector and cartridge or a disposable pen) to ensure that they and/or their carer find it easy to use.
- Appropriate local arrangements should be in place for the disposal of sharps.
- Only insulin detemir (Levemir®) and Insulatard® can be used with the Innolet® device.
- If a person has a manual or visual disability and requires insulin, offer a device or adaptation that:
  - takes into account his or her individual needs
  - he or she can use successfully.
Worsening renal function (GFR range in ml/min)

<table>
<thead>
<tr>
<th>Drug</th>
<th>CKD stage 1 (GFR&gt;90)</th>
<th>2 (60-90)</th>
<th>3a (50-45)</th>
<th>3b (44-30)</th>
<th>4 (29-15)</th>
<th>5 (&lt;15 or RRT)</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild / Moderate</td>
</tr>
<tr>
<td>Acarbose</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓ (GFR &lt;25ml/min)</td>
<td>Severe</td>
</tr>
<tr>
<td>Metformin / Metformin MR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (review regularly)</td>
<td>Contraindicated in hepatic insufficiency</td>
</tr>
<tr>
<td>Gliclazide / Gliclazide MR</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Use lowest effective dose)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100mg</td>
<td>50mg (GFR&lt;50ml/min)</td>
<td></td>
<td></td>
<td>25mg</td>
<td></td>
<td>No dose adjustment required, but clinical experience is lacking in hepatic impairment</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>Not studied in severe hepatic impairment</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>25mg</td>
<td>12.5mg (GFR&lt;50ml/min)</td>
<td></td>
<td></td>
<td>6.25mg</td>
<td></td>
<td>Not studied in severe hepatic impairment</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (not if dialysis)</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Caution if GFR &lt;50ml/min)</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Exenatide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ (conservative dose escalation)</td>
<td></td>
</tr>
<tr>
<td>Exenatide MR</td>
<td>✓</td>
<td>✓</td>
<td>✓ (not if GFR&lt;50ml/min)</td>
<td></td>
<td>✓</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Start at 5mg, increase to 10mg if well tolerated</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Do not initiate if GFR &lt;60ml/min, max dose 100mg od if GFR persistently falls below 60ml/min after initiation)</td>
<td></td>
<td>✓</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>✓</td>
<td>✓</td>
<td>✓ (Do not initiate if GFR &lt;60ml/min, max dose 10mg od if GFR persistently falls below 60ml/min after initiation)</td>
<td></td>
<td>✓</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Insulin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓ Requirements may be reduced in severe renal impairment – monitor and adjust dose accordingly</td>
<td>Requirements may be altered in hepatic impairment – monitor and adjust dose accordingly</td>
</tr>
</tbody>
</table>

N.B. In patients at extremes of weight (BMI <18.5 kg/m² or >30 kg/m²) or age (>70yr), calculate renal function using Cockcroft and Gault equation (see calculator available here). Source of data is NICE guidance and manufacturers’ recommendations. The Renal Drug Database

Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)

Review Date: February 2017
## Type 2 diabetes mellitus treatments – Dual therapy combination table

### Alphabetical

<table>
<thead>
<tr>
<th>Drug</th>
<th>Alogliptin</th>
<th>Albiglutin</th>
<th>Canagliflozin</th>
<th>Dasagliflozin</th>
<th>Empagliflozin</th>
<th>Exenatide</th>
<th>Exenatide MR</th>
<th>Gliclizide</th>
<th>Glicazide</th>
<th>Insulin</th>
<th>Linagliptin</th>
<th>Liraglutide</th>
<th>Lixisenatide</th>
<th>Metformin</th>
<th>Metformin MR</th>
<th>Pioglitazone</th>
<th>Sitagliptin</th>
<th>Steagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>L</td>
<td>L</td>
<td>NICE</td>
<td>L--------------</td>
<td>L--------------</td>
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### Key

- **L**: Not licensed
- **NICE**: Licensed, but not NICE approved
- **LOCAL**: Licensed, but not approved for use locally
- **Y**: Combination can be used as per guideline
- **NICE**: Combination can be used as per guideline, but outside of NICE
- **Combination not recommended**

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**Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)**

**Review Date**: February 2017
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This partial update (November 2014) written by: Jill Theobald and Lynne Kennell, Specialist Interface & Formulary Pharmacists, Nottinghamshire APC. Updated July 2015 to include alogliptin and empagliflozin.

Written in consultation with:
Dr Devaka Fernando, Diabetes Consultant, SFHT
Dr Manjusha Rathi, Diabetes Consultant, SFHT
Dr Sarbpreet Sihota, Diabetes Consultant, SFHT
Dr Renee Page, Diabetes & Endocrinology Consultant, NUH
Dr Kamal Chokkalingham (Nottingham University NHS Hospitals Trust)
Diabetes Specialist Nurses, SFHT
CityCare Diabetes Specialist Nurses via Panchmatia Shailesh - Head of Medicines Management
Michelle Haigh, Practice Pharmacist / Independent Prescriber for Diabetes, Nottingham City CCG
Aynge Jeremy, Practice Pharmacist / Independent Prescriber for Diabetes, Nottingham City CCG

Additional comments received from:
Dr Peter Mansell (Nottingham University NHS Hospitals Trust)
Diabetes Specialist Nurses, City Campus NUH
Diabetes Specialist Nurses in County CCGs

Original Authors:
Nicky Bird, Senior Prescribing Advisor and APC Manager, NHS Nottinghamshire County
James Sutton, Specialist Interface & Formulary Pharmacist, Nottinghamshire APC.

In consultation with
Dr Iskandar Idris (Sherwood Forest NHS Foundation Trust)
Dr Kamal Chokkalingham (Nottingham University NHS Hospitals Trust)

Comments received from
Dr Renee Page (Nottingham University NHS Hospitals Trust)
Dr Simon Page (Diabetes and Endocrinology Clinical Lead, Nottingham NHS Treatment Centre)
Nottinghamshire County Clinical Commissioning Groups & Medicines Management teams
Nottingham City Clinical Commissioning Group & Medicines Management team

References
Derbyshire JAPC Guideline – Glucose control in type 2 diabetes May 2011
MHRA Drug Safety Update March 2009
NICE Clinical Guideline 87 Type 2 Diabetes May 2009
NICE Technology Appraisal – Liraglutide for the treatment of Type 2 Diabetes Mellitus October 2010
NICE Technology Appraisal – Dapagliflozin combination therapy June 2013
NICE Technology Appraisal – Canagliflozin combination therapy June 2014

Nottinghamshire Health Community Treatment Guideline for the Management of Type 2 Diabetes. APC approved February 2014 (Partial update approved January 2015)
Review Date: February 2017
Type 2 Diabetes mellitus and renal impairment – dosing guidelines. Author: Dr Simon Page (Diabetes and Endocrinology Clinical Lead, Nottingham NHS Treatment Centre)