# Type 2 Diabetes – Oral Hypoglycaemic Agents (1)

**Endorsed by CWHHE Diabetes Strategy Group**

## Oral Hypoglycaemic Agents

<table>
<thead>
<tr>
<th><strong>Metformin</strong></th>
<th><strong>Sulphonylureas</strong></th>
<th><strong>Thiazolidinediones (Pioglitazone)</strong></th>
</tr>
</thead>
</table>
| • Reduces hepatic glucose production and appetite.  
  • Start with 500mg daily for 1-2 weeks.  
  • Titrate every 2-4 weeks to achieve glycaemic target.  
  • Usual maximum tolerated dose is 1 gram BD or 850mg TDS  
  • Tables should be taken with or immediately after a meal.  
  • Not associated with weight gain, and associated with reduced cardiovascular disease in overweight or obese patients - hence first line therapy in these patients.  
  • Diarrhoea occurs in up to 10%, but is dose dependent and may resolve with dose reduction.  
  • Metformin MR is an option in patients poorly tolerant of generic Metformin, starting with 500mg with evening meal, and then slowly up-titrating to 1g BD.  
  • Metformin dissolvable powder should be used in preference to Metformin syrup.  
  • Do not initiate in patients with eGFR <45 ml/min, severe heart failure, severe liver disease (because of the increased risk of lactic acidosis) or alcohol dependency.  
  • Stop if there is progressive renal impairment and eGFR <30 ml/min.  
  • Metformin reduces cardiovascular events in overweight and obese patients to a greater extent than predicted by its glucose lowering effects.  
| • Stimulate insulin release from the pancreas.  
  • Gliclazide initially 40-80 mg OD, with titration every 4-6 weeks to achieve glycaemic target or until maximum dose of 160mg B.D is reached.  
| In patients over 70 yrs start at 40mg OD and do not increase dose above 80mg bd due to hypoglycaemia risk.  
| • Pioglitazone should not be started or continued in any individual who has heart failure, is at risk of a bone fracture or bladder cancer.  
  • Reduces insulin resistance and increases glucose uptake into peripheral tissues.  
  • Pioglitazone is the only agent currently available. 30mg OD increasing to 45mg OD after 3 months.  
  • Contra-indicated in patients with heart failure or active liver disease, and women of child-bearing age considering pregnancy and post-menopausal women.  
  • Monitoring of liver function tests prior to commencing therapy, and periodically thereafter is recommended. Discontinue / do not commence glitazone therapy if the ALT is 2.5 times the upper limit of normal.  
  • Pioglitazone use is associated with weight gain but this may be attributable to fluid retention.  
  • Pioglitazone is licensed for use with insulin.  
  • Hypoglycaemia may occur in patients already taking a sulphonylurea, and in such circumstances the sulphonylurea dose needs reducing.  
  • Side effect profile includes fluid retention, increased fractures and a small fall in haemoglobin concentration.  
  • Continue pioglitazone only if there is a reduction in HbA1c of 5mmol/mol (0.5%) in 6 months unless substituting Pioglitizone for another hypoglycaemic agent.  
| • Gliclazide 1mg OD titrate up to 4mg OD  
  • Gliclazide M/R is associated with less hypoglycaemia than generic Gliclazide.  
  • Tablets should be taken before or with meals.  
  • Weight gain averaging 2-4 kg is a recognised consequence of sulphonylurea therapy; in some patients it may exceed 10kg. Always re-assess the patient and emphasise lifestyle issues before prescribing.  
  • ALL patients should be told about recognition and management of hypoglycaemia when prescribed a sulphonylurea.  
  • AVOID long acting sulphonylureas (Glibenclamide and Chlorpropamide) unless recommended by a consultant in either  
  ○ 1) MODY (Maturity onset Diabetes of the young)  
  ○ 2) pregnancy  
  People on sulphonylureas should perform up to 4 tests per week, usually testing once a week before each of the three daily meals and before bedtime.  
  • Note recommendations about driving and the need for self-testing for patients on sulphonylureas.  
  • Continue pioglitazone only if there is a reduction in HbA1c of 5mmol/mol (0.5%) in 6 months unless substituting Pioglitizone for another hypoglycaemic agent.  
| • Glimepiride 1mg OD titrate up to 4mg OD  
  • Gliclazide initially 40-80 mg OD, with titration every 4-6 weeks to achieve glycaemic target or until maximum dose of 160mg B.D is reached.  
  • Tablets should be taken before or with meals.  
  • Weight gain averaging 2-4 kg is a recognised consequence of sulphonylurea therapy; in some patients it may exceed 10kg. Always re-assess the patient and emphasise lifestyle issues before prescribing.  
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  People on sulphonylureas should perform up to 4 tests per week, usually testing once a week before each of the three daily meals and before bedtime.  
  • Note recommendations about driving and the need for self-testing for patients on sulphonylureas.  
  • Continue pioglitazone only if there is a reduction in HbA1c of 5mmol/mol (0.5%) in 6 months unless substituting Pioglitizone for another hypoglycaemic agent.  |
## Type 2 Diabetes – Oral Hypoglycaemic Agents (2)

### SGLT-2 Inhibitors: Sodium Glucose Co-Transporter 2 Agents

**SGLT-2 inhibitors** are a new class of oral drugs for the treatment of Type 2 Diabetes. They inhibit glucose re-absorption in proximal renal tubules providing an insulin dependent mechanism to lower blood glucose. Their use in clinical practice is associated with improved glycaemic control, weight loss and a low risk of hypoglycaemia. SGLT-2 inhibitors prevent the reabsorption of glucose from the kidneys back into the blood, leading to increased glucose in the urine and reduced glucose levels in the blood.

#### Dapagliflozin
- The starting dose for Dapagliflozin is 10 mgs once daily unless there is severe liver failure when a 5 mgs dose should be used and tolerance reviewed before dose titration.
- This preparation can only be used as monotherapy if Metformin is not tolerated or in combination with insulin or Metformin (dual therapy).
- If using Dapagliflozin in combination with insulin then the insulin dose /doses may need to be reduced to reduce the risk of hypoglycaemia.
- Dapagliflozin cannot be used in combination with a loop diuretic or in combination with Pioglitazone. It should not be used if eGFR is less than 60mls/ Min.

#### Canagliflozin
- Canagliflozin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control. Doses are 100mg (starting dose) and 300mg. Intensification to 300mg dose can be considered as alternative to adding further therapy or changing to injectable therapy (e.g. GLP-1).
- Canagliflozin can be used down to an eGFR of 45ml/min/1.73m²

### DPP-4 Inhibitors (Include Sitagliptin*, Saxagliptin*, Linagliptin, Vildagliptin)

**DPP-4 Inhibitors** stimulate insulin response to glucose and prevent glucagon release after meals.
- All DPP-4s are licensed for use in combination with Metformin.
- They are also licensed for use with Pioglitazone if treatment fails to achieve adequate glycaemic control (triple therapy).
- Sitagliptin and Saxagliptin are also licensed for use with insulin.
- Neutral effect on body weight. Low incidence of hypoglycaemia unless used in combination with sulphonylurea and/or insulin.
- **Dosage:**
  - Sitagliptin 100mg OD
  - Saxagliptin 5mg OD
  - Linagliptin 5mg OD
  - Vildagliptin 50mg BD
- **Side effects:**
  - DPP-4s are contra-indicated in women of child-bearing age considering pregnancy.
  - Sitagliptin, Linagliptin and Vildagliptin are licensed for use in CKD5 patients.
  - Vildagliptin is not recommended for prescribing in CWHHE (due to need for LFT monitoring and no evidence of superiority over other agents).

### Use in CKD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linagliptin</strong></td>
<td>Can be used at all stages of CKD with no dose adjustment. There is limited data on use in dialysis patients.</td>
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<tr>
<td><strong>Saxagliptin</strong></td>
<td>In patients with moderate and severe renal insufficiency reduce dose to 2.5mg. It is not recommended in end stage renal disease (dialysis patients).</td>
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<tr>
<td><strong>Sitagliptin</strong></td>
<td>For moderate renal insufficiency (eGFR &gt;30-&lt;50 ml/min) reduce dose to 50mg OD. For severe renal insufficiency (eGFR &lt;30ml/min) reduce to 25mg OD.</td>
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<tr>
<td><strong>Vildagliptin</strong></td>
<td>In patients with moderate or severe renal impairment and end stage renal disease the recommended dose is 50mg OD. There is limited data on use in dialysis patients - use with caution.</td>
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</tbody>
</table>

Monica monitoring of renal function should be undertaken regularly in patients on Sitagliptin, Saxagliptin and Vildagliptin.

### NICE Guidelines (TAG315) - 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 consequences.

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

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People with Diabetes are often taking numerous tablets and this should be considered when consultations take place. It may be useful to try and elicit their values and beliefs about their medication and their understanding of different tablets as this may influence their behaviour around medication. There may be practical problems which may need to be addressed to ensure concordance. Regular medication reviews should take place either by a doctor, practice nurse or pharmacist.