Guideline for antihyperglycaemic therapy in adults with type 2 diabetes
<table>
<thead>
<tr>
<th>Version Number</th>
<th>Date</th>
<th>Amendments made</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>January 2018</td>
<td></td>
</tr>
<tr>
<td>1.1</td>
<td>February 2018</td>
<td>Amended to reflect updated SPC advice for sitagliptin dosage adjustment in renal impairment.</td>
</tr>
<tr>
<td>1.2</td>
<td>April 2018</td>
<td>Amended to reference appendix B within the algorithm pages and to reflect updated SPC renal impairment advice for dulaglutide. Glimepiride added to appendix B</td>
</tr>
<tr>
<td>1.3</td>
<td>September 2018</td>
<td>Statement added regarding the use of combination GLP-1 mimetics and insulin. Statement relating to continuation of GLP-1 mimetics highlighted in bold red.</td>
</tr>
<tr>
<td>1.4</td>
<td>January 2019</td>
<td>Updated SPC advice relating to renal impairment in dapagliflozin included</td>
</tr>
<tr>
<td>1.5</td>
<td>November 2019</td>
<td>Cardiovascular section added to patient factors. Amendments made to preferred agents for GLP-1 mimetics and SGLT-2 agents.</td>
</tr>
</tbody>
</table>
Care after diagnosis and education

- An individualised approach to diabetes care should be adopted taking into account patient factors including frailty, susceptibility to hypoglycaemia, weight, cardiovascular risk and renal function.
- Upon diagnosis ALL patients should be offered structured education (DESMOND, X-PERT or locally approved courses) within 6-12 months of diagnosis.
- For those patients who are unable or unwilling to attend such courses further education should be offered including signposting to diabetes.org.uk and/or local interventions such as nutrition and dietetic services, local fitness classes/ regimes, mental health services and Local Specialist Obesity Services (for patients with a BMI > 35 kg/m²).
- In order to achieve the best possible care competent patients should be encouraged to take responsibility for the management of their diabetes and receive comprehensive counselling prior to the initiation of any new medicine. A self management contract (see appendix B) may facilitate patients and prescribers to agree care goals and encourage patients to strive for the best possible outcomes from their treatments.

Initiating and optimising treatments

This guideline does not include all antihyperglycaemic medicines for the management of type 2 diabetes. Where appropriate prescribers may prescribe medicines not considered in this guideline (gliptins and acarbose). Medicine preferences stated in the guideline are intended to guide prescribers initiating new treatments. Patients should be able to continue their existing treatments until they and their clinician consider it appropriate to stop.

1. When HbA1c rises above the patients agreed target, lifestyle advice should be reinforced prior to initiating each new treatment. (If a patient is symptomatically hyperglycaemic, clinicians should consider insulin or sulfonylurea rescue therapy and review treatment once blood glucose control is achieved).

2. Before adding/switching treatments, prescribers must be satisfied that:
   - the dose of current treatment has been suitably optimised and
   - the patient is using existing treatment regularly and correctly.

3. Prescribers should ensure that patients are reviewed preferably within 3 months of initiating a new treatment (or no later than 6 months after initiation). In accordance with the NICE quality standard statement 4, adults with type 2 diabetes whose HbA1c level is 58 mmol/mol (7.5%) or above after 6 months with single-drug treatment should be offered dual therapy, as this can delay the need for a second intensification of therapy or commencement of insulin therapy.

4. Where tolerated and not contraindicated, metformin should be offered throughout the treatment pathway (including following insulin initiation).

5. The benefits/risks of other blood glucose lowering therapies should be reviewed at least 6 monthly.

Cost effective prescribing

- Where more than one treatment is suitable based on patient factors, prescribers should prescribe the treatment with the lowest acquisition cost.
- Review patients on modified release preparations of metformin and gliclazide to ascertain whether they could be managed on immediate release preparations.
- Despite the lower acquisition cost of sulfonylureas, the actual cost of treating patients with sulfonylureas will be higher due to the need for blood glucose monitoring. Review patients taking glibenclamide and tolbutamide to establish whether patients could be switched to gliclazide/glimepiride.
- Only consider GLP-1 mimetics if dual therapy has failed to control HbA1c and only continue if HbA1c reduction of ≥ 1% (11mmol/mol) and weight loss of ≥3% at 6 months.
- Patients may be switched to an alternative drug in the same class on the grounds of efficacy and tolerability if the prescriber feels this is appropriate, however drugs of the same class should not be combined (e.g. 2 gliflozins or 2 gliptins).
- Clinicians should:
   - not use combinations of gliptins and GLP-1 mimetics (increased risk of pancreatic cancer for small benefit in treatment)
   - avoid dapagliflozin with pioglitazone (due to increased risk of bladder cancer)
   - consider titrating the dose of sulfonylureas down and discontinuing in patients who have started bolus insulin therapy or if hypoglycaemia occurs on basal insulin regimens.
- This guideline does not include all antihyperglycaemic medicines for the management of type 2 diabetes. Where appropriate prescribers may prescribe medicines not considered in this guideline (gliptins and acarbose). Medicine preferences stated in the guideline are intended to guide prescribers initiating new treatments. Patients should be able to continue their existing treatments until they and their clinician consider it appropriate to stop.
If confirmed HbA1c ≥ 48mmol/mol (6.5%) following lifestyle interventions.

Metformin

**Monotherapy**

- If the patient is symptomatically hyperglycaemic, consider insulin or a sulfonylurea first line.

**First intensification**

- The ordering of agents in the table does not represent prescribing preference.

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of metformin treatment:

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Continue treatment with metformin and review other blood glucose lowering therapies.</td>
</tr>
</tbody>
</table>

**Second intensification**

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of therapy at first intensification:

- **Insulin based therapy**
  - See insulin algorithm (page 5)
  - Additional annual cost for bolus insulin: £200-400

- **GLP-1 mimetic**
  - If: BMI > 35kg/m² and specific psychological or medical problems associated with obesity
  - OR: BMI < 35kg/m² and insulin would have significant occupational implications
  - OR: weight loss would benefit other obesity-related comorbidities.

- **GLP-1 mimetic in combination**
  - With insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team.

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**N.B.** The triple therapies to be used at second intensification are based on the licensed indications contained in the products SPCs and ADA Standards of care 2017. Some recommendations may vary from NG28 (Type 2 diabetes in adults: management). There are variations in the licensing of drugs in each of the DDP-4 inhibitor and SGLT-2 inhibitor classes of medicines. Please consult individual SPCs for licensed combinations.

**Injection therapy**

- If treatment optimisation and still above target HbA1c. Continue to offer metformin and review other blood glucose lowering therapies.
For patients in whom metformin is contraindicated or not tolerated

**Monotherapy**

The ordering of agents in the table does not represent prescribing preference.

<table>
<thead>
<tr>
<th>Hypoglycaemia Risk</th>
<th>Sulfonylurea</th>
<th>Pioglitazone</th>
<th>Gliptin</th>
<th>Gliflozin</th>
<th>Insulin (basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>£120-£700</td>
</tr>
<tr>
<td>Gain</td>
<td>£&lt;50</td>
<td>£&lt;400</td>
<td>£&lt;450</td>
<td>Gain</td>
<td></td>
</tr>
<tr>
<td>Use in CKD stages 3-5 (GFR &lt; 60 ml/min) #</td>
<td>Stage 5 avoid, Stage 4 use low dose, Stage 3 no dose adjustment necessary</td>
<td>Suitable for all stages (not licensed in dafyn); No dose adjustment necessary for lingfilopine, dose reductions required for other DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in frail/elderly patients</td>
<td>Less suitable in frail patients due to increased risk of hygocagia; if used dose should start low and be increased carefully</td>
<td>Avoid in elderly patients likely to have history of fractures, bladder cancer, cardiac failure</td>
<td>Relatively safe; no dose adjustments necessary based on age (unless due to renal function)</td>
<td>Risk of volume depletion and hyperosmolality in frail/elderly patients and those taking ACE-inhibitors/diuretics</td>
<td></td>
</tr>
</tbody>
</table>

# Use in CKD stages 3-5 section of the table is intended to provide a summary only. For detailed advice please consult appendix A.

**If confirmed HbA1c ≥ 48 mmol/mol (6.5%) following lifestyle interventions.**

**If the patient is symptomatically hyperglycaemic, consider insulin or a sulfonylurea first line.**

**First intensification**

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of monotherapy

1. **Preferred drugs included in this guideline are based on cost, safety, inclusion on hospital formularies and current local epc data. Specialists may wish to prescribe alternative agents where they are clinically appropriate.**

- **Sulfonylurea**
  - 1st Line: Gliclazide
  - 2nd Line: Gimepiride

- **Gliptin**
  - 1st Line: Albiglizine (not metformin)
  - 2nd Line: Sitagliptin or linagliptin (in renal impairment)

- **Gliflozin**
  - 1st Line: Canagliride/Dapagliride/Empagliride
  - 2nd Line: Erlotinobin

**N.B. The dual therapy options at first intensification are based on the licensed indications contained in the products SPCs. Some recommendations may vary from NG28 (Type 2 diabetes in adults: management). There are variations in the licensing of some drugs. Please consult individual SPCs for licensed combinations.**

**Second intensification**

If HbA1c rises to 58 mmol/mol (7.5%) despite optimisation of therapy at first intensification

**Insulin based therapy**

See insulin algorithm (page 5)

- Additional annual cost for bolus insulin £200-400

**OR**

**GLP-1 mimetic if:**

- BMI > 35 kg/m² and specific psychological or medical problems associated with obesity
- OR BMI < 35 kg/m² and insulin would have significant occupational implications
- OR weight loss would benefit other obesity-related comorbidities.

- Only continue if 6 month HbA1c reduction of 11 mmol/mol (1.0%) and weight loss ≥ 3%
- Annual cost £700-1400, low risk of hypo, weight loss, avoid in CKD stage 5, and associated cardiovascular benefit for liraglutide, semaglutide, and dulaglutide.

**GLP-1 mimetic in combination with insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team.**
**Insulin-based treatment in type 2 diabetes**

Insulin therapy should be commenced by a healthcare professional who is appropriately trained and experienced in the initiation of insulin.

When starting insulin, use a structured programme and continue metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies.

### Preferred basal treatment

Offer NPH (isophane) insulin once or twice daily

Monitor patients who are on a basal insulin (and pre-mixed insulin) for the need for short-acting insulin before meals

### Preferred biphasic treatment

Offer pre-mixed (biphasic) human insulin if HbA1c > 75mmol/mol (9.0%)*

* If preferred patients may be started on separate NPH and short acting insulin

### Consider pre-mixed preparations that include short-acting analogues (rather than short acting human insulin) if:

- Patient prefers injecting before a meal
- Blood glucose levels rise markedly after meals
- Hypoglycaemia is a problem

### Preferred insulins included in this guideline are based on cost, safety, inclusion on hospital formularies and current local epiact data. Specialists may wish to prescribe alternative agents where they are clinically appropriate

<table>
<thead>
<tr>
<th>Preferred insulins included in this guideline</th>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isophane insulin formulations</td>
<td>Humulin l KwikPen</td>
<td>Insulatard Penfill</td>
<td></td>
</tr>
<tr>
<td>Long-acting insulin analogues formulations</td>
<td>Abasaglar KwikPen</td>
<td>Levemir FlexPen</td>
<td>Tresiba FlexTouch 100 (Specialist initiation)</td>
</tr>
<tr>
<td>High strength long-acting formulations (specialist initiation)</td>
<td>Toujox SoleStar</td>
<td>Tresiba FlexTouch 200</td>
<td></td>
</tr>
<tr>
<td>Biphasic human insulin formulations</td>
<td>Humulin M3 KwikPen</td>
<td>Insman Comb 25 SoleStar</td>
<td></td>
</tr>
<tr>
<td>Biphasic short-acting analogue formulations</td>
<td>NovoMix 30 FlexPen</td>
<td>Humalog Mix KwikPen</td>
<td></td>
</tr>
<tr>
<td>Bolus insulin formulations</td>
<td>Aspida SoleStar</td>
<td>Humalog KwikPen</td>
<td>Novorapid FlexPen or Fiasp FlexTouch</td>
</tr>
</tbody>
</table>

### 2nd line alternative basal treatments

Consider insulin glargine/detemir if:

- Patient needs assistance to inject insulin or lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or Patient would otherwise need twice-daily NPH insulin + oral antihyperglycaemic agents

Specialists may exceptionally consider initiating insulin degludec if:

- Patient is experiencing poor glycaemic control or recurrent hypoglycaemic episodes with their existing long-acting insulin analogue or
- Patient is unable to take basal insulin at the same time each day

Specialists may consider high strength formulations (Toujoe or Tresiba 200) if:

Patient experiencing symptomatic nocturnal hypoglycaemia whilst being treated with a first line long-acting insulin analogue

### 2nd line alternative biphasic treatment

### Consider Fiasp (insulin aspart) exceptionally if patient not managed on existing bolus insulin and:

- The prescriber believes a faster onset of action would be beneficial to the patient or
- A patient requires "tight" control of blood glucose levels or
- A patient has rapid post meal increases in blood glucose levels

### Offer a choice of rapid-acting insulin analogues

Patients currently receiving insulin products other than those recommended in this guideline should still continue their treatment unless their clinician considers it appropriate to stop. The insulin table does not imply therapeutic equivalence of drugs or doses.

GLP-1 mimetic in combination with insulin only on advice of specialist with ongoing support from a consultant-led multidisciplinary team
## Appendix A

### Impact of renal function on antihyperglycaemic treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>CKD stage 1 and 2 (GFR &gt; 60 mL/min)</th>
<th>CKD stage 3a (GFR 45–59 mL/min)</th>
<th>CKD stage 3b (GFR 30–44 mL/min)</th>
<th>CKD stage 4 (GFR 15–29 mL/min)</th>
<th>CKD stage 5 (GFR &lt; 15 mL/min) or ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Reduce dose (starting dose ≤ 1/2 maximum dose)</td>
<td></td>
<td>Not recommended at GFR &lt; 25 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not recommended at GFR &lt; 25 mL/min</td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change over to insulin is indicated</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td></td>
<td>Reduce dose to 50 mg if GFR &lt; 45 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alogliptin</td>
<td></td>
<td></td>
<td>Reduce dose to 12.5 mg if GFR &lt; 50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td></td>
<td></td>
<td>Reduce dose to 6.25 mg if GFR &lt; 30 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Reduce dose to 2.5 mg for moderate to severe renal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Reduce dose to 50 mg once daily if GFR &lt; 50 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Not licensed for dialysis patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Do not initiate if GFR &lt; 60 mL/min, if GFR 60–80 mL/min reduce dose by 50%</td>
<td></td>
<td>Discontinue if GFR persistently &lt; 45 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Do not initiate if GFR &lt; 60 mL/min, if GFR 60–80 mL/min reduce dose by 50%</td>
<td></td>
<td>Discontinue if GFR persistently &lt; 45 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Do not initiate if GFR &lt; 60 mL/min, if GFR 60–80 mL/min reduce dose by 50%</td>
<td></td>
<td>Discontinue if GFR persistently &lt; 45 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erugliflozin</td>
<td>Do not initiate if GFR &lt; 60 mL/min, if GFR 60–80 mL/min reduce dose by 50%</td>
<td></td>
<td>Discontinue if GFR persistently &lt; 45 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Not recommended if GFR &lt; 50 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide MR</td>
<td>Use 10 mcg dose, conservatively if GFR 30–50 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Not recommended if GFR &lt; 50 mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lixisenatide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not recommended for use in end-stage renal</td>
</tr>
<tr>
<td>Semaglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>Requirements may reduce in severe renal disease, monitor and adjust dose accordingly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type 2 Diabetes Self-Management Plan**

Effective diabetes care can only be achieved through working closely with your diabetes healthcare team. Taking responsibility for your diabetes will enable you to manage your diabetes more effectively and reduce your risk of complications in the future. At around the time you are diagnosed, your doctor or nurse should provide you with information about Type 2 diabetes. You should be offered a course to help you improve your understanding of Type 2 diabetes and how to manage it in your everyday life.

**Patient commitment**

To get the most from my treatment for my diabetes, I agree to:

- Aim to keep my HbA1c below ........ as agreed with my diabetes healthcare team.
- Exercise at least 5 days of the week:
  - You should try to do 150 minutes of moderate-intensity exercise (walking fast or hiking, pushing a lawn mower, cycling on level ground) OR
  - try to do 75 minutes of vigorous activity (biking, team sports, swimming, cycling fast or on hilly terrain) OR
  - a mixture of moderate and vigorous activity where 1 minute of vigorous activity gives the same health benefits as 2 minutes of moderate exercise.
- Try to eat a lower sugar and lower fat diet to help control my blood sugar and cholesterol:
  - Total energy intake is less than energy expenditure where high sugar/saturated fat foods are eaten occasionally and in small portions.
  - Choose foods lower in fat, salt and sugar including 5 daily portions of fruit and vegetables, wholegrains or higher fibre starchy carbohydrates, beans, pulses and oily fish twice weekly.
- I will try to obtain my ideal body weight/target body weight of ........ and maintain my weight loss.
- Stop smoking.
- Attend an eye examination at least yearly following my initial eye screening examination.

- Check my feet every day to look for signs of redness, pain, breakdown of the skin or changes in the shape of my feet and attend a quality foot check by an appropriately trained person at least once per year.
- Take my medication regularly and as directed by my diabetes healthcare team and report any issues or side effects with my medication to the diabetes healthcare team.
- If requested by the diabetes care team, I will test my blood sugar at the frequencies agreed and:
  - Know my target range.
  - Contact my GP/nurse if my readings are consistently outside my target range.

**Patient agreement**

I have discussed the above information with a member of the diabetes healthcare team and I understand that I need to follow the commitments above to improve control of my diabetes and minimise the risk of long-term complications.

**Patient name:**

**Patient signature:**

**Clinician name:**

**Clinician signature:**

**Date:**
Appendix B continued – GLP-1 patient plan

(word version of this document available at http://www.lancsmmg.nhs.uk/prescribing-guidance/information-leaflets/).

Giuregoun-like-Peployde-1 (GLP-1) mimetic treatment

To help you lose weight and control your blood glucose levels, your diabetes health care team have started you on a glagule-like peptide-1 mimetic (GLP-1) medicine called sitagliptin (Victoza), exenatide (Byetta or Bydureon), or liraglutide (Lyspro) or semaglutide (Ozempic). You will need to follow a low sugar and low-fat diet and undertake regular exercise in combination with these medicines.

The GLP-1 medicines only benefit some patients therefore the National Institute for Health and Care Excellence (NICE) advise that these treatments should only be continued in those patients who have had a 11 mmol/mol or 13% reduction in their HbA1c (the blood test that measures your average blood glucose levels over 2-3 months) and a reduction in weight of 3% following 6 months of treatment.

Over the next 6 months your diabetes health care team will monitor your HbA1c and weight to assess if you are a patient who benefits from GLP-1 treatment. After 6 months, your HbA1c and weight have not reduced by the above levels, your GLP-1 treatment will be stopped.

If you are a patient who has had the above reduction in HbA1c and weight, treatment will continue beyond 6 months and your diabetes health care team will review your treatment every 6 months to ensure that you are still benefiting from your treatment.

Your most recent HbA1c is ______ mmol/mol
After 6 months, your target HbA1c is ______ mmol/mol
Your current weight is ______ kg
After 6 months, your target weight is ______ kg

Patient agreement

I have discussed the above information with a member of the diabetes health care team and understand that treatment with a GLP-1 mimetic will only continue after 6 months if my HbA1c and weight measurements at 6 months demonstrate a beneficial effect as outlined above.

Patient name: ____________________________
Patient signature: ________________________
Clinician name: __________________________
Clinician signature: ______________________
Date: _________________________
References


The Summary of Product Characteristics for all medicines included in the guideline have been consulted when including product specific information.