GLP-1 Receptor Agonists in Type 2 Diabetes


Quick Reference Guide

For detailed information on how and when to initiate, please refer to guideline.

GLP-1 receptor agonist treatment is indicated in person with type 2 diabetes (see guideline)

Does patient require once weekly administration (e.g. district nurse administration)?

Prescribe Lixisenatide (REGIME 1)

Can patient tolerate lixisenatide? Does patient meet NICE criteria for continuation (see guideline)?

Yes

continue

No

Switch to liraglutide (REGIME 2)

Can patient tolerate liraglutide? Does patient meet NICE criteria for continuation (see guideline)?

Yes

continue

No

Refer to specialist team

Can patient tolerate dulaglutide? Does patient meet NICE criteria for continuation (see guideline)?

Yes

Prescribe dulaglutide once weekly

No

REMEMBER AT EVERY STAGE:

- Reinforce importance of diet and lifestyle choices
- Check adherence and reinforce the importance of taking medication
- Assess hypoglycaemia risk
- Optimise BP and cholesterol management
- Refer to patient structured education

Consider other treatment including insulin. Refer to specialist team if unsure.
Which GLP-1 receptor agonist should I use?

- Prescribe Lixisenatide (Lyxumia) as first line glucagon-like peptide (GLP-1) receptor agonist treatment due to cost. Prescribe Liraglutide (Victoza) as second line.
- Liraglutide 1.8mg may be used on specialist's advice if the patient has failed to meet the NICE criteria on lixisenatide and liraglutide 1.2mg.
- Trulicity (once weekly dulaglutide) is the first line weekly GLP-1 receptor agonist. Trulicity should only be used when there is a significant benefit to once weekly administration (e.g. when the medication is administered by a carer or practice nurse). Patients already on Bydureon (once weekly exenatide) do not need to switch if they are responsive to treatment.
- The Community Diabetes Service DSNs are available to provide support and advice for GLP-1 initiation.

What are the key differences between lixisenatide and liraglutide?

- Lixisenatide was licensed for use in the UK in 2013; liraglutide in 2009.
- Lixisenatide costs £54.14 per month (top dose); liraglutide costs £78.48 per month (1.2 mg dose) or £117.72 per month (1.8mg dose).
- Lixisenatide and Liraglutide are both administered once a day
- Lixisenatide must be administered 30-60 mins before food, liraglutide can be given independent of food.
- Lixisenatide comes in a one dose pen, whereas liraglutide has 3 dose options
- Lixisenatide should not be used in eGFR less than 30ml/min. Liraglutide must be avoided in end stage renal disease (defined by NICE CG182 as eGFR less than 15ml/min).
- Although liraglutide use is associated with fewer side effects and better clinical outcomes, it is significantly more expensive than lixisenatide. As such, we recommend lixisenatide as first line treatment for appropriate patients.

What about the other GLP-1 receptor agonists?

- Exenatide (Byetta) is more expensive than the first line lixisenatide, and does not have the clinical benefits of liraglutide so has not been included in this guideline. Patients currently treated with exenatide do not need to switch if they are responsive to treatment.
- Exenatide (Bydureon) once weekly is no longer the first line once weekly GLP-1 Receptor Agonist, however patients currently treated with Bydureon do not need to switch.
- Xultophy (degludec 100 units/mL/liraglutide 3.6mg/mL fixed combination) can be used if initiated by a consultant. See requirements on the last page.
- Albiglutide is not recommended for use in Oxfordshire.

Are these drugs safe and effective?

- There are currently no long term safety data for any GLP-1 receptor agonist and there have been no studies showing outcomes on diabetes related mortality and morbidity (other than the LEADER trial that showed liraglutide 1.8mg reduced risk of major cardiovascular events and death in patients at high risk of cardiovascular events. The ELIXA trial on lixisenatide found the CV effect to be neutral), only data showing its effect on HbA1c and weight. Any GLP-1 receptor agonist carrying a black triangle should have all adverse effects reported via the yellow card system.
- Responses to GLP-1 receptor agonists can be very variable.

Can I use these drugs in combination with insulin?

- Not all GLP-1 receptor agonists are licensed with all insulin combinations – seek advice if unsure.
  1) Adding a GLP-1 to insulin
      It is recommended that patients on insulin who are starting a GLP-1 receptor agonist are referred to the Community Diabetes Specialist nurse team for initiation. This is important because an insulin dose reduction is required to reduce hypoglycaemia risk.
  2) Adding insulin to a GLP-1
      A background insulin can be initiated in primary care, within the licensed guidelines, by those who are competent in insulin initiation.

When should I stop these drugs?

Consider stopping these drugs if there is no response within 6 months of initiating treatment. Non-responders would be defined by NICE criteria as patients who fail to decrease their HbA1c by 1% point (11 mmol/mol if measured in IFCC units) and lose 3% of their body weight. The Patient Agreement Form Checklist will assist with this.
Glycaemic control in type 2 diabetes: Regime 1: Use of lixisenatide

**DO NOT USE IN:**
- Type 1 diabetes
- eGFR less than 30 ml/min
- Patients under 18 years old
- Gastrointestinal disease (e.g. gastroparesis)
- Pregnancy or breastfeeding

**CAUTION IN:**
- Patients over 75 years old
- Patients with a history of pancreatitis (seek expert advice)

**ADMINISTRATION**
- Give up to 30 - 60 minutes before eating
- Do not give AFTER a meal.
- If a dose is missed, just give the dose before next meal.
- Consider reducing sulphonylurea dose by 50%

**INTERACTIONS:**
- Lixisenatide can affect absorption of drugs e.g. proton pump inhibitors, contraceptives (no dose adjustment required), antibiotics.
- Care when using with drugs with a narrow therapeutic window (e.g. warfarin - monitor INR on lixisenatide initiation / dose change).

**PATIENT INFORMATION:**
- Nausea is likely to be temporary
- Stop eating before full to minimise nausea

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**Type 2 diabetes with HbA1c 58 mmol/mol (7.5%) or greater, or above personalised agreed target**

Refer to specialist diabetes services for consideration of combination therapy with insulin

**Is patient on insulin?**
- Yes
- No

**Optimise all blood glucose lowering medication**

**HbA1c?**
- Less than 58 mmol/mol (7.5%)
- 58 mmol/mol (7.5%) or greater

**BMI?**
- Less than 35 kg/m² (see notes)
- 35 kg/m² or greater (see notes)

Consider lixisenatide.
Check for exclusions, contraindications and cautions

Start lixisenatide 10 micrograms once daily s/c.
Administer 30-60 minutes before specified meal.

**Review at 2 weeks**

**Adverse reaction or persistent nausea or vomiting?**
- Yes
- No

Increase dose to 20 micrograms daily

**Adverse reaction or persistent nausea or vomiting?**
- Yes
- No

Reduce dose back to 10 micrograms once daily

If fall in HbA1c less than 11 mmol/mol (1% point in DCCT units) and weight loss less than 3% from baseline, consider stopping lixisenatide and starting liraglutide (regime 2)
What is lixisenatide?

- It’s a glucagon-like peptide (GLP-1) analogue indicated for use in type 2 diabetes. It affects the incretin system. When administered subcutaneously, it lowers blood glucose.
- It is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control 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.
- It is recommended that patients on insulin who are starting a GLP-1 receptor agonist are referred to the Community Diabetes Specialist nurse team for initiation. This is important because an insulin dose reduction is required to reduce hypoglycaemia risk.

What benefits does it have?

- Randomised controlled trials have shown benefit in terms of lowering HbA1c by about 10.1 mmol/mol (0.92%) and weight loss (about 2.3kg compared with placebo; weight loss continues beyond 12 months).
- Lixisenatide represents a treatment option for type 2 diabetes, particularly in those with obesity who have inadequate glycaemic control on maximally tolerated oral agents or on insulin.
- ELIXA study showed lixisenatide is safe and reduces HbA1c. Lixisenatide was shown to have a neutral effect on CV outcomes.

When should I use it?

- Prescribe lixisenatide as first line GLP-1 receptor agonist treatment.
- Combination therapy with DPP-4 inhibitors is not licensed.
- Review whether the patient has responded to the treatment at 6 months. If HbA1c decrease is less than 11 mmol/mol (less than 1.0% point in DCCT units) at 6 months or weight loss is less than 3% at 6 months, then consider stopping treatment.
- Do not use if eGFR is less than 30 ml/min.
- No dose adjustment necessary in liver disease.
- Consider using in patients with a BMI less than 35kg/m² if therapy with insulin would have significant occupational implications or weight loss would benefit other significantly obesity-related comorbidities; BMI may need to be adjusted in non-Caucasian patients.

What are its side effects?

- It causes significant nausea (about 26% of individuals were affected in clinical trials), 4.0% of individuals need to stop lixisenatide because of nausea.
- There are concerns about acute pancreatitis in patients using the drug.
- The DVLA considers that there is an increased risk of hypoglycaemia when lixisenatide and a sulphonylurea or insulin are used in combination and as such this combination is a potentially high risk treatment for drivers holding Group 2 (LCV or PCV) licences. These patients will require individual DVLA assessment.

Remember the following:

- Be alert to the signs and symptoms of acute pancreatitis.
- Instruct patients taking lixisenatide to seek prompt medical care if they experience persistent severe abdominal pain.
- Discontinue lixisenatide if pancreatitis is suspected.
- If pancreatitis in a patient using lixisenatide is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery. Lixisenatide should not be restarted.
Glycaemic Control in Type 2 Diabetes: Regime 2: Use of Liraglutide

**DO NOT USE IN:**
- Type 1 diabetes
- End Stage Renal Disease (defined by NICE CG182 as eGFR less than 15ml/min)
- Patients under 18 years old
- Gastrointestinal disease (e.g. gastroparesis)
- Pregnancy or breastfeeding
- Significant liver impairment
- Inflammatory bowel disease
- Heart failure NYHA class IV

**CAUTION IN:**
- Patients over 75 years old
- Combination with drugs with a narrow therapeutic index
- Patients with a history of pancreatitis (seek expert advice)

**ADMINISTRATION:**
- Can be administered at any time.
- Take liraglutide at the same time every day.
- Consider reducing sulphonylurea dose by 50%
- Monitor INR if on warfarin.

**PATIENT INFORMATION:**
- Nausea is likely to be temporary
- Stop eating before full to minimise nausea

**Type 2 diabetes with HbA1c 58 mmol/mol (7.5%) or greater, or above personalised agreed target, who has failed a trial of lixisenatide**

**Is the patient on insulin?**
- Yes → Refer to specialist diabetes services for consideration of combination therapy with insulin
- No → **Optimise oral hypoglycaemic therapy.** Recheck HbA1c, if HbA1c 58 mmol/mol (7.5%) or greater, continue below.

**BMI less than 35kg/m² (see notes)**
- Yes → Liraglutide is not indicated
- No → Consider trial of liraglutide

**Adverse reaction or persistent nausea or vomiting?**
- Yes → Stop treatment for 1 week and then retry
- No → Increase dose to 1.2 mg once daily

**If fall in HbA1c less than 11 mmol/mol (1% point in DCCT units) and less than 3% weight loss, consider stopping liraglutide and starting other treatment, such as insulin. Alternatively, specialist may recommend increasing liraglutide to 1.8mg.**

What is liraglutide?

- It’s a glucagon-like peptide (GLP-1) analogue indicated for use in type 2 diabetes. It affects the incretin system.
- Indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control as:
  - Monotherapy: When diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance or contraindications.
  - Combination therapy: 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.
- It is recommended that patients on insulin who are starting a GLP-1 receptor agonist are referred to the Community Diabetes Specialist nurse team for initiation. This is important because an insulin dose reduction is required to reduce hypoglycaemia risk.

What benefits does it have?

- Randomised controlled trials have shown benefit in terms of lowering HbA1c of between 10.9-16.4 mmol/mol (1.0-1.5%) and weight loss (1-2kg compared with placebo; weight loss continues beyond 12 months).
- Liraglutide represents a treatment option for type 2 diabetes, particularly in those with obesity who have inadequate glycaemic control on maximally tolerated oral agents.
- LEADER trial showed that liraglutide 1.8mg reduced risk of major cardiovascular events and death in patients at high risk of cardiovascular events.

When should I use it?

- Lixisenatide therapy is effective in lowering HbA1c and inducing weight loss in most patients without significant side effects, and is cheaper than liraglutide, so we recommend the use of lixisenatide before using liraglutide in most patients.
- If a patient fails on lixisenatide because of side effects (e.g. nausea) or inadequate response (e.g. weight loss but insufficient reduction in HbA1c), consider liraglutide 1.2mg as a second line option.
- Basal insulin is licensed to be added to Liraglutide in line with SPC.
- Review whether the patient has responded to the treatment at 6 months.
- If HbA1c decrease is less than 11 mmol/mol (1% point in DCCT) at 6 months, or weight loss is less than 3% at 6 months, then stop liraglutide treatment.
- On specialist recommendation only, liraglutide 1.8mg can be used for those who fail to meet the NICE criteria. They should be reviewed at 6 months, and if the criteria is not met then liraglutide should be stopped.
- Do not use in end stage renal disease (defined by NICE CG182 as eGFR less than 15ml/min)
- No dose adjustment necessary in patients with mild to moderate hepatic impairment
- Avoid if significant liver impairment, contact diabetes specialist team if unsure.
- Consider using liraglutide in patients with a BMI less than 35kg/m² if therapy with insulin would have significant occupational implications or weight loss would benefit other significantly obesity-related comorbidities. BMI may need to be adjusted in non-Caucasian patients.

What are its side effects?

- It causes significant nausea, 20.7% experience at least one episode of nausea and about 2.8% of individuals need to stop liraglutide because of nausea. 1.5% of people need to stop because of diarrhoea.
- The DVLA considers that there is an increased risk of hypoglycaemia when liraglutide and a sulphonylurea or insulin are used in combination. As such this combination is a potentially high risk treatment for drivers holding Group 2 (LCV or PCV) licences. These patients will require individual DVLA assessment.
- Patients treated with liraglutide should watch for signs of dehydration, particularly because of the gastrointestinal side effects experienced with the drug.

Remember the following:

- Be alert to the signs and symptoms of acute pancreatitis.
- Instruct patients taking liraglutide to seek prompt medical care if they experience persistent severe abdominal pain.
- Discontinue liraglutide if pancreatitis is suspected.
- If pancreatitis in a patient using liraglutide is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery. Liraglutide should not be restarted.
What is dulaglutide (Trulicity)?
- It’s a glucagon-like peptide (GLP-1) analogue indicated for use in type 2 diabetes. It affects the incretin system.
- The dose of dulaglutide is administered once weekly.
- Dulaglutide is the once weekly GLP-1 receptor agonist of choice, however there is no need to switch those already on Bydureon (once weekly exenatide).
- Dulaglutide is indicated in adults with type 2 diabetes mellitus to improve glycaemic control as:
  - Monotherapy, when diet and exercise alone do not provide adequate glycaemic control in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications.
  - Add-on therapy, in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.
- It is recommended that patients on insulin who are starting a GLP-1 receptor agonist are referred to the Community Diabetes Specialist nurse team for initiation. This is important because an insulin dose reduction is required to reduce hypoglycaemia risk.

What benefits does it have?
- The Trulicity pen device is an auto-injector that is safer and easier to use than the Bydureon device.
- There are no comparative data with other weekly dose GLP-1 receptor agonists.
- NICE Evidence summary considers 3 fully published RCTs (AWARD1, 5 and 6) which used HbA1c as endpoint. The summary concluded that:
  - For reducing HbA1c levels in people with type 2 diabetes, dulaglutide once weekly, when added to metformin, was statistically superior to exenatide twice daily (both in combination with pioglitazone), statistically superior to sitagliptin and statistically non-inferior to liraglutide 1.8 mg daily
  - A weight reduction from baseline of between 0.87 kg and 3.03 kg was seen with dulaglutide 1.5 mg in the 6 RCTs in the AWARD programme.

When and how should I use it?
- Dulaglutide should only be used when there is a significant benefit to once weekly administration (e.g. when the medication is administered by a carer, district nurse or practice nurse).
- Trulicity is licenced in patients whose eGFR is greater than 30ml/min.
- In monotherapy, the recommended dose is 0.75 mg once weekly.
- In add-on therapy, the recommended dose is 1.5 mg once weekly.
- For potentially vulnerable populations, such as patients ≥ 75 years, 0.75 mg once weekly can be considered as a starting dose.
- The dose can be administered at any time of day, with or without meals.
- If a dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours) remain before the next scheduled dose, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.
- Review whether the patient has responded to the treatment at 6 months. If HbA1c decrease is less than 11 mmol/mol (less than 1.0% point in DCCT units) at 6 months or weight loss is less than 3% at 6 months, then consider stopping treatment.

What are its side effects?
- When dulaglutide 0.75 mg and 1.5 mg were used as monotherapy or in combination with metformin alone or metformin and pioglitazone, the incidences of documented symptomatic hypoglycaemia were 5.9% to 10.9%. When used in combination with a sulphonylurea and metformin were 39.0% and 40.3% respectively.
- Cumulative reporting of gastrointestinal events up to 104 weeks with dulaglutide 0.75mg and 1.5 mg, respectively, included nausea (12.9% and 21.2 %), diarrhoea (10.7% and 13.7 %) and vomiting (6.9% and 11.5 %). These were typically mild or moderate in severity and were reported to peak during the first 2 weeks of treatment and rapidly declined over the next 4 weeks, after which the rate remained relatively constant.

Remember the following:
- Be alert to the signs and symptoms of acute pancreatitis.
- Instruct patients taking dulaglutide to seek prompt medical care if they experience persistent severe abdominal pain.
- Discontinue dulaglutide if pancreatitis is suspected.
- If pancreatitis in a patient using dulaglutide is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery. Dulaglutide should not be restarted.
What is Xultophy?
• It’s a combination product that contains liraglutide 3.6 mg/mL (a GLP-1 analogue) and degludec 100 units/mL (an ultra long acting insulin).
• It is licensed for the treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with a GLP-1 receptor agonist or basal insulin do not provide adequate glycaemic control.

What benefits does it have?
• Xultophy is given by once-daily subcutaneous injection, which for some people may be preferable to giving basal insulin and GLP-1 receptor agonist injections separately.
• In DUAL I, Xultophy was non-inferior to insulin degludec alone and superior to liraglutide alone for change in HbA1c from baseline.
• In DUAL I, there was more weight loss from baseline with Xultophy compared with insulin degludec alone (−0.5 kg compared with +1.6 kg). However there was less weight loss from baseline with Xultophy compared with liraglutide alone (−0.5 kg compared with −3.0 kg).

When Should I use it?
Initiation by diabetes consultant only for patients who:
• are already using a basal analogue insulin or a GLP1 agonist AND
• have a BMI of 35 kg/m² or greater. Consider using in patients with a BMI less than 35kg/m² if therapy with insulin would have significant occupational implications or weight loss would benefit other significantly obesity-related comorbidities (BMI may need to be adjusted in non-Caucasian patients).
AND in addition one of the following applies
• are already using a basal analogue insulin less than 40 units, have a high hypoglycaemia risk and addition of GLP1 agonist is being considered
• are already on a basal analogue insulin less than 40 units and have not tolerated separate lixisenatide of liraglutide due to gastrointestinal side effects
• are already using a GLP1 agonist, and there is significant concern around further weight gain.
• require a reduced number of injections e.g. 3rd party administration, and flexible timing.

Xultophy should be stopped if:
• The patient is on maximum dose and individual HbA1c target is not reached, or a minimum reduction of 11 mmol/mol (1% point in DCCT units) is not achieved within 6 months
• Problematic hypoglycaemia continues
• Weight gain continues
• Gastrointestinal side-effects continue
When Xultophy is stopped patients should continue on the insulin specified by the initiating consultant.

What are its side effects?
Hypoglycaemia may occur if the Xultophy dose is higher than required. Nausea was reported in 7.8% of patients and was transient in nature for most patients. Diarrhoea and vomiting were reported in 7.5% and 3.9% of patients, respectively.

Remember the following:
• Be alert to the signs and symptoms of acute pancreatitis.
• Instruct patients taking liraglutide to seek prompt medical care if they experience persistent severe abdominal pain.
• Discontinue liraglutide if pancreatitis is suspected.
• If pancreatitis in a patient using liraglutide is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery. Liraglutide should not be restarted.