The GLP-1 analogues are injected, non-insulin drugs. They cause modest weight loss as well as HbA1c reduction, but are more expensive than other treatments (except high-dose insulin).

Three are daily injection: exenatide (Byetta), liraglutide (Victoza) and lixisenatide (Lyxumia). Two are for weekly injection: exenatide (Bydureon) and dulaglutide (Trulicity).

**Which is best?**

No clear winner. Your decision may depend on frequency of injection, and cost.

The once-weekly versions are a little more effective, and may have lower incidence of side effects. The drug costs are higher, but partially offset by fewer needles used.

At time of writing, liraglutide has published evidence of cardiovascular benefit. A large study of lixisenatide failed to show benefit over older diabetes drugs, so although it is cheaper and on Formulary, we do not recommend lixisenatide (Lyxumia).

**When to start GLP-1 analogues (NICE):**

- Add to metformin and sulphonylurea, as alternative to insulin;
- When HbA1c $\geq 58$ mmol/mol or higher as agreed with individual;
- And BMI $\geq 35$ (adjust for ethnicity) and psychological/medical problems associated with obesity; or BMI<35, and insulin would have occupational implications, or weight loss would help other obesity-related comorbidities.

**Review efficacy at 6 months, and stop if these criteria not met (NICE):**

- HbA1c reduction at least 11 mmol/mol;
- weight reduction at least 3% of initial weight;
- usually will require conversion to insulin if GLP-1 treatment is stopped.

**Use in non-NICE and non-Formulary combinations**

Although NICE only recommend using GLP-1 agonists with MF & SU (in guideline NG28), the reality is that other combinations are quite widely used.

Each GLP-1 agonist has a slightly different list of licenced uses (e.g. as monotherapy, or in combination with insulin and/or oral drugs). The different licences cannot be summarised succinctly, and don’t have clear justification. Prescribing according to licence is of course the default recommendation. See BNF or [www.medicines.org.uk](http://www.medicines.org.uk) for each drug.
We cannot advocate off-licence use, but in terms of what seems clinically reasonable, we make the following broad points:

- The GLP-1 agonists are licensed with most combinations of MF, SU or pioglitazone. Any GLP-1 with any combination of these seems reasonable.
- We do not routinely combine GLP-1 agonists with SGLT-2 inhibitors due to high cost.
- It is not sensible to combine GLP-1 agonists with DPP-4 inhibitors.
- All GLP-1 except Byetta are licensed with insulin. They are also licensed with insulin plus oral agents, though the exact combinations vary. To us, any GLP-1 plus insulin plus any oral agent except a DPP-4 inhibitor seems reasonable.

Effects:
- Average HbA1c fall is about 10 mmol/mol. Average weight reduction is around 2kg.
- In our experience, GLP-1 agonists are “jackpot” drugs – some patients do very well and some see little benefit.

When to avoid:
- Pregnancy or breastfeeding.
- Inflammatory bowel disease, gastroparesis, bowel stoma.
- Symptoms of, or active risk factors for, pancreatitis.

Hypoglycaemia:
- Alone, GLP-1 analogues should not cause hypoglycaemia;
- but will increase hypo risk in patients also taking sulphonylurea or insulin.

Other side effects:
- Predominantly nausea, abdominal discomfort, bloating, diarrhoea or constipation.

Renal impairment:
- Exenatide standard (Byetta), liraglutide, lixisenatide – avoid if eGFR<30.
- Exenatide prolonged-release (Bydureon) – avoid if eGFR<50.
- Dulaglutide – avoid in “severe impairment and end-stage renal disease” – we interpret to mean eGFR<30.

Cost: (prices for standard dose, 30 days, Nov 2016)
- Dulaglutide £78. Exenatide £68 (Byetta), £77 (Bydureon). Liraglutide £78 at 1.2mg. Lixisenatide £58.

Driving:
- Group 1 (normal) licence: no need to notify unless disabling hypos (very unlikely).
- Group 2 licence: notify DVLA, but should not affect licence, and can continue driving while waiting DVLA assessment. No obligation from DVLA to monitor blood glucose, but they advise monitoring regularly and at times relevant to driving.
Dulaglutide (Trulicity)
How to start dulaglutide
- If used as monotherapy, prescribe the 0.75mg pen. The dose is 0.75mg (one pen) once per week. There is no dose increase.
- If used with other diabetes drugs, prescribe the 1.5mg pen. The dose is 1.5mg (one pen) once per week. There is no dose increase.

Exenatide (Byetta)
How to start exenatide
- 5mcg pen for first month. Initial dose is 5mcg bd, within an hour before meals.
- If 5mcg is tolerated, change to 10mcg pen for subsequent months – dose is 10mcg bd. The dose increase can be delayed if there are side effects.

Prolonged-release exenatide (Bydureon)
Role
- Lowers HbA1c (and possibly weight) slightly more than standard exenatide.
- It is very slightly more complicated to administer, but the second generation pen is much easier than the original mixing kit.
How to start prolonged-release exenatide
- Dose is 2mg once weekly. There is no dose increase.

Liraglutide (Victoza)
How to start liraglutide
- Same pen for all doses. Initial dose is 0.6mg (one click) once daily, increased to 1.2mg (two clicks) after a month. The dose increase can be delayed if there are side effects.
- A 1.8mg dose is licensed, but not approved by NICE.

Lixisenatide (Lyxumia)
Role
- We do not recommend lixisenatide, as published evidence does not show a benefit over older diabetes drugs for cardiovascular disease.
How to start lixisenatide
- 10mcg pen is prescribed for first 14 days. Initial dose 10mcg once daily, within an hour before breakfast or evening meal.
- After 14 days, change to 20mcg pen. Dose 20mcg once daily. The dose increase can be delayed if there are side effects.