

# Macleod Diabetes & Endocrine Centre Royal Devon & Exeter Hospital

## GLP-1 agonists

The GLP-1 analogues are injected, non-insulin drugs. They cause modest weight loss as well as HbA1c reduction, and some have good evidence for cardiovascular disease prevention, but are more expensive than other treatments (except high-dose insulin).

Three are given weekly: exenatide M/R (Bydureon), dulaglutide and semaglutide.  
Three are given once or twice daily: exenatide (Byetta), liraglutide and lixisenatide.

### Which is best?

Semaglutide is now first-line in the Formulary. Please note, we recommend using the highest dose (1mg) unless side effects limit the dose to 0.25 or 0.5mg – this is because the impressive benefits in clinical trials were with the 1mg dose.

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

Lixisenatide is cheapest, but has least evidence and we do not recommend it.

### When to start GLP-1 analogues (NICE)

- Add to metformin and sulphonylurea, as alternative to insulin;
- if HbA1c  $\geq 58$  mmol/mol or higher target if agreed for 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;
- and weight reduction at least 3% of initial weight.

### GLP-1 analogues with other drug combinations

NICE and Formulary only recommend GLP-1 agonists with metformin & sulphonylurea. However, other combinations are licensed and quite widely used.

Different GLP-1 agonists have slightly different licences (e.g. monotherapy, or combination with insulin and/or oral drugs). Prescribing according to licence is the default recommendation. See BNF or [www.medicines.org.uk](http://www.medicines.org.uk) for each drug.

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We cannot advocate off-licence use, but in terms of what seems clinically reasonable, we make the following 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.
- It is not sensible to combine GLP-1 agonists with DPP-4 inhibitors.
- We do not routinely combine GLP-1 agonists with SGLT-2 inhibitors due to high cost.
- If wishing to add a weight-losing drug to insulin, consider metformin or SGLT-2 inhibitor first as they are cheaper and taken orally.
- If adding to insulin or SU, consider reducing the dose of insulin or SU if tighter control may cause problematic hypos.
- All GLP-1 are licensed with insulin. In some cases, the licence restricts to basal insulin, but we see no justification for this and are happy with any insulin.

### **Effects:**

- Average HbA1c fall is about 10 mmol/mol. Average weight reduction is around 2kg. This means NICE have set a very high bar for continuation.
- In our experience, GLP-1 agonists are “jackpot” drugs – some patients do very well and some see little benefit.

### **General contraindications (see BNF for each drug):**

- Pregnancy or breastfeeding.
- Caution in inflammatory bowel disease, gastroparesis, bowel stoma.
- Active or history of significant gallstone problems.
- Active or high risk of 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), lixisenatide – not recommended if eGFR<30.
- Exenatide prolonged-release (Bydureon) – not recommended if eGFR<50.
- Dulaglutide – not recommended if eGFR<15.
- Liraglutide – not recommended in “end stage” – we interpret as eGFR<15.
- Lixisenatide – not recommended if eGFR<30.
- Semaglutide – not recommended in “end-stage” – we interpret as eGFR<15.

### **Cost: (per 30 days, as of June 2019)**

- Dulaglutide £78. Exenatide £81 (Byetta), £79 (Bydureon). Liraglutide £78 at 1.2mg, £117 at 1.8mg. Lixisenatide £58. Semaglutide £78.

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## **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.

## **Prescribing for each GLP-1 agonist**

### **Dulaglutide (Trulicity)**

- 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. (A starting dose of 0.75mg can be considered if high risk of side effects).

### **Exenatide (Byetta)**

- 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.

### **Exenatide modified release (Bydureon)**

- Dose is 2mg once weekly. There is no dose increase.

### **Liraglutide (Victoza)**

- 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.

### **Lixisenatide (Lyxumia)**

- We do not recommend lixisenatide, as published evidence does not show a benefit over older diabetes drugs for cardiovascular disease.
- 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.

### **Semaglutide (Ozempic)**

- Start at 0.25mg once per week. Prescribe 0.25mg/dose pen for first four weeks.
- After four weeks, increase to 0.5mg once per week. Prescribe the 0.5mg/dose pen.
- After four weeks, increase to 1mg once per week. Prescribe the 1mg/dose pen.
- The product literature advises increasing to 1mg if glycaemic target not met on 0.5mg. However, as there is no difference in cost but the benefits in clinical trials were with the 1mg dose, we recommend 1mg dose unless limited by side effects.