How to use GLP-1 receptor agonist therapy safely and effectively

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What is the role of the incretin hormone GLP-1?

- Increases insulin secretion and insulin sensitivity.
- Increases beta-cell mass and maintains beta-cell function.
- Increases glucose disposal.
- Delays gastric emptying.
- Reduces appetite by increasing satiety.

What are GLP-1 RAs?

- Chemical modification of GLP-1 produces drugs that bind to the GLP-1 receptor, producing the same effects as the native protein.
- Current therapies all have a similar mechanism of action.
- Effects in type 2 diabetes include reductions in HbA_{1c} and weight. Some therapies have additionally demonstrated cardiovascular benefits (dulaglutide, liraglutide and injectable semaglutide).
- GLP-1 RA therapies are injectable, apart from oral semaglutide, and they have different profiles, which affect dosing frequency.

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National and international guidelines

NICE NG28 (2022)	SIGN 154 (2017)	ADA/EASD consensus (2022)
If triple therapy with metformin and two other oral drugs is not effective, not tolerated or contraindicated, consider triple therapy by switching one drug for a GLP-1 RA for adults with type 2 diabetes who have:	People with BMI ≥30 kg/m² (or ethnicity-adjusted equivalent) combined with oral glucose-lowering drugs, basal insulin or both as third- or fourth-line treatment, when adequate glycaemic control not achieved.	In people with established CVD, a GLP-1 RA with proven benefit should be used to reduce MACE, or an SGLT2i with proven benefit should be used to reduce MACE and HF and improve kidney outcomes. In individuals without established CVD but with multiple cardiovascular risk factors (e.g. age ≥55 years, obesity, hypertension, smoking, dyslipidaemia, albuminuria), a GLP-1 RA with proven benefit could be used to reduce MACE, or an SGLT2i with proven benefit could be used to reduce MACE and HF and improve kidney outcomes. In people with HF, CKD, established CVD, or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin.
BMI ≥35 kg/m² (adjust for people from Black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity.	As an alternative to insulin in people for whom combinations of oral glucose-lowering drugs did not produce adequate glycaemic control.	In people with CKD and an eGFR ≥20 mL/min/1.73 m² and a uACR >3.0 mg/mmol (>30 mg/g), an SGLT2i with proven benefit should be initiated to reduce MACE and HF and improve kidney outcomes (indications and eGFR thresholds may vary by region). If SGLT2i treatment is not tolerated or is contraindicated, a GLP-1 RA with proven cardiovascular outcome benefit could be considered to reduce MACE and should be continued until renal replacement therapy is indicated. Consider second-line use after metformin where there is compelling need to minimise weight gain or promote weight loss, or a compelling need to minimise hypoglycaemia.
BMI <35 kg/m² when insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.	Consider a GLP-1 RA with proven cardiovascular benefit for people with type 2 diabetes and established CVD.	GLP-1 RAs considered as efficacious for glycaemic management: • Very high efficacy: semaglutide and dulaglutide • High efficacy: Other GLP-1 RAs not included above GLP-1 RAs considered efficacious when weight loss is also required: • Very high efficacy: semaglutide • High efficacy: dulaglutide, liraglutide • Intermediate efficacy: Other GLP-1 RAs not listed above
Only continue GLP-1 RAs if the person has had a beneficial metabolic response: reduction of ≥11 mmol/mol (1.0%) in HbA_{1c} **and** a weight loss of ≥3% of initial body weight in 6 months.	Continue GLP-1 RA at each stage if **either** individualised HbA_{1c} target achieved **or** HbA_{1c} falls >5.5 mmol/mol (0.5%) in 3–6 months. Discontinue GLP-1 RA if ineffective.	Pioglitazone therapy, GLP-1 RA therapy and metabolic surgery have all been shown to reduce non-alcoholic steatohepatitis activity.

CKD=chronic kidney disease; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; HF=heart failure; MACE=major adverse cardiovascular events; uACR=urinary albumin:creatinine ratio.

Assessing suitability

People to consider	Prescribe with caution	Unsuitable people
● People with type 2 diabetes and high BMI, adjusted for ethnicity ● People with type 2 diabetes and significant risk of CVD ● People with type 2 diabetes and established CVD ● People with type 2 diabetes and CKD or heart failure who are unsuitable for SGLT2 inhibitors	● People in whom weight loss would cause concern (e.g. frailty) ● People with a history of gallstones ● Women of child-bearing age (ensure adequate contraception) ● People with irritable bowel syndrome or gastro-oesophageal reflux disease (GORD) ● People with severe renal impairment (see ***Table 1***) or hepatic impairment ● Active proliferative or pre-proliferative retinopathy†	● Type 1 diabetes ● Children (although liraglutide is licensed for use in adolescents and children aged ≥10 years with type 2 diabetes) ● Pre-conception/pregnant women ● History of, or risk factors for, pancreatitis* ● History of medullary thyroid cancer or multiple endocrine neoplasia type 2

* For example: idiopathic acute pancreatitis, gallstones, alcohol abuse, trauma and hypertriglyceridaemia.

† Non-significant increase in retinopathy with liraglutide versus placebo in LEADER (hazard ratio, 1.15), and a significant increase in retinopathy complications with injectable semaglutide (hazard ratio, 1.76) in SUSTAIN-6.
For more information and recommendations, see *At a glance factsheet: GLP-1 receptor agonists and diabetic retinopathy*.

SmPC for semaglutide advises caution in people with background retinopathy who are taking insulin therapy.

Adverse effects

Nausea

- Usually mild or moderate, dose-dependent, declines with continued treatment.
- Exclude any other gastrointestinal pathology.
- If the person is unwell, check for ketones and review diagnosis.
- Advise to reduce meal size, eat more slowly, and reduce fat intake and spicy food content.
- "FlexPen" devices (Victoza) can dial up smaller doses in "clicks". Some **specialist teams** may use these to uptitrate more gradually.
- Short-term antiemetic.
- Once-weekly treatment.

Injection site reactions

- Check injection technique.
- Ensure use of a new needle each injection.
- Evaluate people for underlying dermatological disease.
- Consider a change in preparation as some people react to the excipient, rather than the active GLP-1 RA.

Abdominal pain

- Unusual, and likely to be associated with an underlying cause rather than being a side effect of GLP-1 RAs.

Until the relationship between GLP-1 RAs and pancreatitis is resolved:
Avoid prescribing to people with risk factors for pancreatitis, such as severe hypertriglyceridaemia or excessive alcohol use, or persons with previously diagnosed pancreatitis.

Underlying cause	Comments
Dyspepsia	● Due to delayed gastric emptying ● Consider short-term use of dyspeptic agents
Constipation	● Consider osmotic laxatives if due to delayed gastric emptying ● Encourage fluids if due to reduced oral intake
Pancreatitis	● Consider especially if the patient is unwell or has a history of gallstones, elevated triglycerides or alcohol abuse ● Consider hospital admission ● Stop GLP-1 RA, check amylase levels and monitor closely

Table 1. Recommended use of GLP-1 receptor agonists in chronic kidney disease.

GLP-1 receptor agonist	Renal function (eGFR)
Exenatide immediate-release (twice-daily)	Avoid if eGFR <30
Liraglutide	Can use down to eGFR 15
Exenatide modified-release (once-weekly)	Avoid if eGFR <50
Lixisenatide	Avoid if eGFR <30, caution if eGFR 30–50
Dulaglutide	Can use down to eGFR 15
Semaglutide (injectable or oral)	Can use down to eGFR 15

eGFR=estimated glomerular filtration rate (in mL/min/1.73 m^2).

Tailoring the drug and device to the individual.

Device/tablet	Dosing regimen and available doses	How to initiate	Other information
Dulaglutide (Trulicity)	Once weekly 0.75 mg, 1.5 mg, 3.0 mg or 4.5 mg in pre-filled pens	Weekly dose 0.75 mg as monotherapy; 1.5 mg, 3.0 mg and 4.5 mg as add-on therapy. For vulnerable people, 0.75 mg weekly can be considered as an add-on starting dose. At least 4 weeks between each dose titration	One-use disposable device with hidden needle
Exenatide, extended-release (Bydureon)	Once weekly 2 mg	Fixed dose 2 mg weekly	One-use disposable device with hidden needle
Exenatide (Byetta)	Twice daily 5 µg or 10 µg in a pre-filled pen	Initial dose 5 µg per dose for at least one month. May increase to 10 µg per dose for further glycaemic control	Pen device requires attachable needle
Lixisenatide (Lyxumia)	Once daily 10 mg or 20 mg in separate pre-filled pens that deliver each dose	Initial dose 10 mg once daily for 2 weeks, then increase to 20 mg Starter kit has both strength pens	Pen device requires attachable needle
Liraglutide (Victoza)	Once daily One pen delivers three different doses: 0.6 mg, 1.2 mg or 1.8 mg	Initial dose 0.6 mg once daily for at least 1 week, then 1.2 mg daily Escalate to 1.8 mg if further glycaemic control required or in people with established CVD*	Pen device requires attachable needle
Semaglutide, subcutaneous (Ozempic)	Once weekly 0.25 mg, 0.5 mg or 1 mg in separate pre-filled pens that deliver each dose	Initial dose 0.25 mg for 4 weeks, then 0.5 mg for at least 4 weeks Escalate to 1 mg if further glycaemic control required	Pen device requires attachable needle (included with pens)
Semaglutide, oral (Rybelsus)	Once daily 3 mg, 7 mg or 14 mg tablets	Initial dose 3 mg daily for 4 weeks, then 7 mg for at least 4 weeks. Increase to 14 mg if further glycaemic control required	Take on an empty stomach at any time of day. Swallow tablet whole (do not split, crush or chew) with a sip of water (up to 120 mL). Wait ≥30 minutes before eating, drinking or taking other oral medicines. Monitor thyroid profile in those also treated with levothyroxine (see SmPC: bit.ly/346a9Ul).

*Scottish Medicines Consortium has not approved 1.8 mg on grounds of cost-effectiveness.

Top ten tips for initiation

1. Consider guidelines positioning and reason for initiation.
2. Review for any prescribing cautions/contraindications: Always refer to up-to-date product SmPC.
3. Review other medications: **Not to be prescribed with a DPP-4 inhibitor**. Doses of **sulfonylureas and/or insulin may need to be reduced** to avoid initial hypoglycaemia.
4. Consider efficacy: Longer-acting GLP-1 RAs seem to benefit both fasting and post-prandial glucose control.
5. Consider whether oral or injectable and dosing frequency: oral is daily; injectables are weekly, daily or twice daily.
6. Assess for CVD, high risk of CVD and/or CKD, as some GLP-1 RA therapies (currently dulaglutide, liraglutide and injectable semaglutide) have demonstrated benefit in these cohorts.
7. Consider tolerability: Clinical studies suggest that the GLP-1 RAs have comparable adverse event profiles.
8. Consider device characteristics, if injectable.
9. Consider cost-effectiveness.
10. Ensure effective education for the person with type 2 diabetes and their families and carers.

Top ongoing considerations for effective use of GLP-1 RAs

- Side effects: See ***Adverse effects*** section (previous page) for information on nausea, abdominal pain and injection site reactions.
- Compliance: Studies suggest compliance may be low but better with weekly agents.
- Contraception: Ensure adequate contraception for women of child-bearing potential. GLP-1 RAs of shorter duration and that delay gastric emptying may undermine the efficacy of oral contraception.
- Pregnancy: Any risks of using GLP-1 RAs in pregnancy are unclear. Ensure GLP-1 RAs are not used in pregnancy and that weekly GLP-1 RAs are stopped at least 3 months prior to conception.
- Sick-day guidance: GLP-1 RAs may be associated with acute kidney injury in persons with severe gastrointestinal symptoms and dehydration. Consider pausing if at risk of dehydration until well again.
- Intensification: As per product SmPC.
- Monitoring and achieving targets: NICE recommends measuring HbA_{1c} in adults with type 2 diabetes every:
  - 3–6 months (tailored to each person), until HbA_{1c} is stable on unchanging therapy.
  - 6 months once HbA_{1c} and therapy are stable.

Essential education

- Discussion of mode of action, to include anticipated benefits.
- Discuss potential side effects:
  - Postprandial fullness and nausea (suggest the person eats smaller meals more frequently and stops when they start to feel full).
  - Possible worsening of GORD.
  - Diarrhoea and headaches.
  - Stop taking and seek medical advice if any sudden onset of abdominal pain.
- Demonstrate the range of devices to ensure individual choice.
- Assess the person's understanding and ability to use the agreed device, if injectable, and dosing instructions if oral.
- Discuss injection sites and the importance of site rotation.
- Stress the importance of needle safety, including disposal.
- Arrange appropriate monitoring and review.
  - Advise about titration (if appropriate).
  - Discuss blood glucose monitoring (especially if used with gliclazide or insulin).
  - Suggest targets for continuation of treatment.

See also

- At a glance factsheet: GLP-1 receptor agonists and diabetic retinopathy
- PCDS consensus statement: A strategy for managing the supply shortage of the GLP-1 RAs Ozempic and Trulicity