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

by Nicola Milne, Community Diabetes Specialist Nurse, Manchester

NICE NG28 (2015)	SIGN 154 (2017)	ADA/EASD consensus (2019)
If triple therapy with metformin and two other oral drugs is ineffective, not tolerated or contraindicated, HCPs should consider combination therapy with metformin, sulfonylurea and GLP-1 RA as below.	People with BMI ≥30 kg/m^2 (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.	Second-line use for people with established atherosclerotic CVD or indicators of high risk (age >55 years with coronary, carotid or lower extremity artery stenosis >50% or left ventricular hypertrophy). Use GLP-1 RA with proven CVD benefit: subcutaneous semaglutide>liraglutide>dulaglutide.
BMI ≥35 kg/m^2 (adjust for ethnicity) 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.	For people where heart failure or CKD predominates, use a GLP-1 RA with proven CVD benefit if an SGLT2 inhibitor is not tolerated or is contraindicated, or if eGFR is less than adequate for SGLT2i initiation. Use as third agent in those within this cohort who fail to meet HbA_{1c} target despite metformin and SGLT2i. Also 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/m^2 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 cardiovascular disease (CVD) (currently liraglutide and subcutaneous semaglutide).	GLP-1 RAs preferred to insulin if greater glucose-lowering effect of an injectable medication needed; insulin recommended if extreme, symptomatic hyperglycaemia.
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.	People unable to maintain glycaemic targets on basal insulin + oral medications can have treatment intensified with GLP-1 RAs, SGLT2 inhibitors or prandial insulin.

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 semaglutide).
- GLP-1 RA therapies are injectable, apart from oral semaglutide, and they have different profiles, which affect dosing frequency.

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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 cardiovascular disease (CVD) ● People with type 2 diabetes and established CVD ● People with type 2 diabetes and CKD or heart failure, 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 renal 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 ● 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 (0.6 vs 0.5 events per 100 patient-years respectively; hazard ratio, 1.15); retinopathy complications occurred in 3.0% of the semaglutide group and 1.8% in the placebo group (hazard ratio, 1.76) in SUSTAIN-6.

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

Table 1. 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 or 1.5 mg in a pre-filled pen	Weekly dose 0.75 mg as monotherapy and 1.5 mg as add-on therapy. For vulnerable people, 0.75 mg weekly can be considered as an add-on starting dose	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.
†Bioavailability varies between individuals, but 14 mg oral dose is approximately equivalent to 0.5 mg subcutaneous semaglutide.

Top ten tips for initiation

1. Consider guidelines positioning and reason for initiating.
2. Review for any prescribing cautions/contraindications: Always refer to product SmPC.
3. Review other medications: **Not to be prescribed with 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 twice daily, daily or weekly.
6. Assess for CVD, high risk of CVD and/or CKD, as some GLP-1 RA therapies 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 boxes below on nausea, abdominal pain and injection site reactions.
- Compliance: Studies suggest compliance may be low but better with weekly.
- 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, for 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 stopping 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.

Nausea

- Gastrointestinal adverse events are usually mild or moderate, dose-dependent, decline with continued treatment and do not affect glycaemic control.
- Exclude any other gastrointestinal pathology.
- If the person is unwell, check for ketones and review diagnosis.
- Reduce meal size, eat more often, reduce fat content (which slows gastric emptying).
- "Flex-pen" 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.

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

Injection site reactions

- Check injection technique.
- Change frequency of needle replacement.
- 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.

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
  - Stop taking and seek medical advice if any sudden onset of abdominal pain
- Demonstrate the range of devices to ensure person 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 rotating the site.
- 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.