### Assessing suitability

<table>
<thead>
<tr>
<th>People to consider</th>
<th>Prescribe with caution</th>
<th>Unsuitable people</th>
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<tbody>
<tr>
<td>People with type 2 diabetes and high BMI, adjusted for ethnicity</td>
<td>People in whom weight loss would cause concern (e.g. frailty)</td>
<td>Type 1 diabetes</td>
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<tr>
<td>People with type 2 diabetes and significant risk of cardiovascular disease (CVD)</td>
<td>People with a history of gallstones</td>
<td>Children (although liraglutide is licensed for use in adolescents and children aged ≥10 years with type 2 diabetes)</td>
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<tr>
<td>People with type 2 diabetes and established CVD</td>
<td>Women of child-bearing age (ensure adequate contraception)</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>People with type 2 diabetes and CKD or heart failure, unsuitable for SGLT2 inhibitors</td>
<td>People with irritable bowel syndrome or gastro-oesophageal reflux disease (GORD)</td>
<td>History of, or risk factors for, pancreatitis*</td>
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<td>People with renal or hepatic impairment</td>
<td>History of medullary thyroid cancer or multiple endocrine neoplasia type 2</td>
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<tr>
<td></td>
<td>Active proliferative or pre-proliferative retinopathy*</td>
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*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 GLP-1 RA if ineffective.

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**NICE NG28 (2015)**

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.

**SIGN 154 (2017)**

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.

**ADA/EASD consensus (2019)**

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/m² (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 HbA₁c target despite metformin and SGLT2i.
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. |
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<tbody>
<tr>
<td>BMI &lt;35 kg/m² when insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.</td>
<td>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).</td>
<td>GLP-1 RAs preferred to insulin if greater glucose-lowering effect of an injectable medication needed; insulin recommended if extreme, symptomatic hyperglycaemia.</td>
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<tr>
<td>Only continue GLP-1 RAs if the person has had a beneficial metabolic response: reduction of ≥211 mmol/mol (1.0%) in HbA₁c and a weight loss of ≥3% of initial body weight in 6 months.</td>
<td>Continue GLP-1 RA at each stage if either individualised HbA₁c target achieved or HbA₁c falls &gt;5.5 mmol/mol (0.5%) in 3–6 months. Discontinue GLP-1 RA if ineffective.</td>
<td>People unable to maintain glycaemic targets on basal insulin + oral medications can have treatment intensified with GLP-1 RAs, SGLT2 inhibitors or prandial insulin.</td>
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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 HbA₁c 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.

**Citation:** Milne N (2020) How to use GLP-1 receptor agonist therapy safely and effectively. Diabetes & Primary Care 22: 135–6.
Table 1. Tailoring the drug and device to the individual.

<table>
<thead>
<tr>
<th>Device/tablet</th>
<th>Dosing regimen and available doses</th>
<th>How to initiate</th>
<th>Other information</th>
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<tbody>
<tr>
<td>Dulaglutide</td>
<td>Once weekly 0.75 mg or 1.5 mg in a pre-filled pen</td>
<td>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</td>
<td>One-use disposable device with hidden needle</td>
</tr>
<tr>
<td>Exenatide, extended-release (Bydureon)</td>
<td>Once weekly 2 mg</td>
<td>Fixed dose 2 mg weekly</td>
<td>One-use disposable device with hidden needle</td>
</tr>
<tr>
<td>Exenatide (Byetta)</td>
<td>Twice daily 5 μg or 10 μg in a pre-filled pen</td>
<td>Initial dose 5 μg per dose for at least one month. May increase to 10 μg per dose for further glycaemic control</td>
<td>Pen device requires attachable needle</td>
</tr>
<tr>
<td>Lixisenatide (Lyxumia)</td>
<td>Once daily 10 mg or 20 mg in separate pre-filled pens that deliver each dose</td>
<td>Initial dose 10 mg once daily for 2 weeks, then increase to 20 mg</td>
<td>Pen device requires attachable needle</td>
</tr>
<tr>
<td>Liraglutide (Victoz).</td>
<td>Once daily 0.6 mg once daily for at least 1 week, then 1.2 mg daily</td>
<td>Escalate to 1.8 mg, if further glycaemic control required or in people with established CVD*</td>
<td>Pen device requires attachable needle</td>
</tr>
<tr>
<td>Semaglutide, subcutaneous (Ozempic)</td>
<td>Once weekly 0.25 mg, 0.5 mg or 1 mg in separate pre-filled pens that deliver each dose</td>
<td>Initial dose 0.25 mg for 4 weeks, then 0.5 mg for at least 4 weeks</td>
<td>Pen device requires attachable needle (included with pen)</td>
</tr>
<tr>
<td>Semaglutide, oral (Rybelsus)</td>
<td>Once daily 3 mg, 7 mg or 14 mg tablets</td>
<td>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*</td>
<td>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: ht tps://www.medicines.org.uk/emc).</td>
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*Scottish Medicines Consortium has not approved 1.8 mg on grounds of cost-effectiveness.

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.

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 glimepiride or insulin).
  - Suggest targets for continuation of treatment.

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.
4. Doses of sulfonylureas and/or insulin may need to be reduced to avoid initial hypoglycaemia.
5. Consider efficacy: Longer-acting GLP-1 RAs seem to benefit both fasting and post-prandial glucose control.
6. Consider whether oral or injectable and dosing frequency: Oral: twice daily, daily or weekly.
7. Evaluate people for underlying dermatological disease.
8. Consider tolerability: Clinical studies suggest that the GLP-1 RAs have comparable adverse event profiles.
9. Consider device characteristics, if injectable.

Underlying cause | Comments
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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