Use of Liraglutide, Semaglutide, and Tirzepatide for Adults Living With Overweight and Obesity

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Primary Care Hacks

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Incretin Therapy	Indication	Standard Dose Escalation Schedule (in Weeks)[A]									Further Considerations (see also *Prescribing Considerations and Special Precautions for Use*)
		1	2	3	4	5–8	9–12	13–16	17–20	21–24	
Liraglutide (Saxenda®)[3,4]	Weight management, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of: • ≥30 kg/m², or • 27–30 kg/m² in the presence of ≥1 weight-related comorbidity.[B],[C]	**0.6 mg (od)[D]**	**1.2 mg (od)[D]**	**1.8 mg (od)[D]**	**2.4 mg (od)[D]**	**3.0 mg (od)[D]**					• No dose adjustment is required according to age, but therapeutic experience is limited in patients aged ≥75 years and use is not recommended in these patients • No dose adjustment is required in mild/moderate renal impairment (CrCl ≥30 ml/min) or mild/moderate hepatic impairment • Avoid in severe renal impairment (CrCl <30 ml/min), including ESRD • Not recommended in patients with severe hepatic impairment; should be used cautiously in mild/moderate hepatic impairment.
Semaglutide (Wegovy®▼)[5–8]	Weight management, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of: • ≥30 kg/m², or • 27–30 kg/m² in the presence of ≥1 weight-related comorbidity.[B],[E] To reduce the risk of major adverse CV events in adults with established CVD and BMI ≥27 kg/m²,[B] as an adjunct to a reduced-calorie diet and increased physical activity.	**0.25 mg (once weekly)**				**0.5 mg (once weekly)**	**1.0 mg (once weekly)**	**1.7 mg (once weekly)**	**2.4 mg (once weekly)[F]**		• No dose adjustment is required according to age, but there is limited therapeutic experience in patients aged ≥85 years • No dose adjustment is required in mild/moderate/severe renal impairment; avoid in ESRD (eGFR <15 ml/min/1.73 m²) • No dose adjustment is required in hepatic impairment; exercise caution when prescribing in severe hepatic impairment.
Tirzepatide (Mounjaro®▼)[9,10]	Weight management, as an adjunct to a reduced-calorie diet and increased physical activity in adults with an initial BMI of: • ≥30 kg/m², or • 27–30 kg/m² in the presence of ≥1 weight-related comorbidity.[B],[G]	**2.5 mg (once weekly)**				**5 mg (once weekly)**	**7.5 mg (once weekly)[H]**	**10 mg (once weekly)[H]**	**12.5 mg (once weekly)[H]**	**15 mg (once weekly)[H]**	• No dose adjustment is required according to age, but there are limited data available for patients aged ≥85 years • No dose adjustment is required in renal impairment (including ESRD) • No dose adjustment is required in hepatic impairment; exercise caution when prescribing in severe hepatic impairment.

Footnotes

[A] **Slower dose titration can be a useful strategy to aid long-term adherence**

[B] **NICE recommends lower BMI thresholds (usually, reduced by 2.5 kg/m²) for people of South Asian, Chinese, other Asian, Middle Eastern, Black African, or African–Caribbean family backgrounds**[4,7,10]

[C] NICE TA664[4] recommends liraglutide for overweight or obesity if it is prescribed by a specialist, multidisciplinary, tier-3 weight-management service and is provided according to the commercial arrangement for the drug. NICE recommends provision in patients with all of the following: a BMI of ≥35 kg/m²; nondiabetic hyperglycaemia (HbA_{1c} of 42–47 mmol/mol or fasting plasma glucose of 5.5–6.9 mmol/l); and high risk of CVD, based on risk factors.[4] After 12 weeks of treatment with the 3.0 mg/day dose, treatment should be discontinued if patients have not lost ≥5% of their initial bodyweight[3]

[D] If escalation to the next dose is not tolerated for 2 weeks consecutively, consider discontinuing treatment[3]

[E] NICE TA875[7] recommends semaglutide if it is used for a maximum of 2 years, is prescribed within a specialist weight-management service providing multidisciplinary management, and is provided according to the commercial arrangement for the drug; NICE recommends provision in patients with ≥1 weight-related comorbidity and either a BMI ≥35 kg/m² or a BMI of 30–34.9 kg/m² if the patient meets the criteria for referral to specialist weight-management services in NICE NG246;[11],[A] if weight loss is <5% of initial weight after 6 months of treatment, consider stopping semaglutide;[7] as the SELECT trial has demonstrated CV benefits of semaglutide irrespective of weight loss, it may be worth considering continuation independent of weight loss when used for CV indications[8]

[F] If semaglutide is not tolerated at 2.4 mg, maintain at 1.7 mg for 4 more weeks then re-escalate afterwards[6]

[G] NICE TA1026[10] recommends prescribing tirzepatide for adults with a BMI of ≥35 kg/m² and ≥1 weight-related comorbidity;[A] if weight loss is <5% of initial weight after 6 months of treatment, consider stopping tirzepatide

[H] Individualise tirzepatide above 5 mg depending on individual treatment goals, increasing dose by 2.5 mg after ≥4 weeks at current dose; 5 mg, 10 mg, and 15 mg are the recommended maintenance doses.[9]

This table is based on the authors' interpretation of summaries of product characteristics and relevant guidance. HCPs are asked to report all suspected adverse drug reactions to products with a Black Triangle symbol (▼) through the Yellow Card Scheme: yellowcard.mhra.gov.uk.

Brand Names of Incretin Therapies for Different Indications[3,5,9,12–15]

Drug	Brand Name (Maximum Dose) for Weight Management	Brand Name (Maximum Dose) for T2D	Notes
Liraglutide	**Saxenda®** (up to 3.0 mg daily)	**Victoza®** (up to 1.8 mg daily)	• Liraglutide is now available as a generic in the UK (for T2D)[13]—e.g. as **Diavic®**.
Semaglutide	**Wegovy®▼** (up to 2.4 mg weekly)	**Ozempic®** (up to 2.0 mg weekly)	—
Tirzepatide	**Mounjaro®▼** (up to 15 mg weekly)		• In the UK, tirzepatide is currently only branded as Mounjaro®▼ • In the US, the FDA has approved Mounjaro®▼ for T2D and Zepbound® for weight management.[15]

Practical Considerations—Injection, Storage, Driving[3,5,9]

- Incretin therapies are injected **subcutaneously** in the **abdomen, thigh, or upper arm**
- Needles must be prescribed separately for liraglutide and tirzepatide when used for weight management; 4 mm needles will usually be suitable
- **Injection sites should be rotated**
  - if the individual also injects insulin, they should inject the incretin therapy into a different site
- Do not forget to issue a **sharps bin**—a 1.8-litre bin is usually adequate
- Store incretin therapies in a refrigerator at 2–8°C, away from the cooling element; do not freeze incretin therapies
  - **liraglutide:** after first use, store at <30°C (preferably, at 2–8°C in a refrigerator); pens should be discarded after 30 days, even if they still contain medication
  - **semaglutide:** after first use, store at <30°C (preferably, at 2–8°C in a refrigerator) for up to 6 weeks
  - **tirzepatide:** may be stored unrefrigerated for ≤30 days at <30°C
- **Incretin therapies have a negligible impact on the ability to drive or use machines**
  - however, if using incretin therapies alongside insulin/SUs, the usual advice and precautions should be given to avoid hypoglycaemia when driving/operating machinery. Ensure adherence with DVLA requirements.

Behavioural Modifications and Interventions[3,5,9,11,16–26]

- **Consider recommending behavioural modifications to all people with overweight or obesity**
  - offer a brief intervention to people living with overweight or obesity, using **ASK, ASSESS, ADVISE, AGREE, and ASSIST**;[19] see also PHE guidance
  - in these discussions, be aware of weight bias, stigma, and how language matters
  - use specific conversation techniques that have been shown to support brief, effective, and well-received conversations about weight loss
- Adequate support of behavioural modifications, as well as mental health care, needs to be considered **during** and **before** incretin therapy initiation
- Consider **multicomponent interventions**, involving behaviour modification strategies and motivational interviewing; key areas to support include:
  - **nutrition** (including eating behaviours and diet content)
  - **increased physical activity** (including maintenance of muscle mass)—discuss the importance of resistance training to aid preservation of muscle mass and function
  - **stress management**
  - **sleep health**
- Set **personalised goals** that are realistic and achievable
  - use a **SMART** goal-setting framework[23]
- Behavioural modifications and comprehensive obesity care in primary care should focus on **whole health gain,** not just weight loss, as this approach has been shown to improve long-term weight and behavioural outcomes[24,25]
- **Be aware that mental illness can impact obesity management efforts;** screen patients for potential mental illnesses that need to be addressed.[26]

Women's Health and Incretin Therapies[3,5,9,27,28]

- **Incretin therapies are not recommended during breastfeeding and pregnancy**
  - **women of childbearing potential should use contraception**[27]
- For women planning pregnancy:
  - liraglutide: discontinue before attempting to conceive
  - semaglutide: discontinue ≥2 months before attempting to conceive
  - tirzepatide: discontinue ≥1 month before attempting to conceive
- **Specific OCP advice for tirzepatide:**
  - **women with a normal BMI:** no dose adjustment of OCP is required
  - **women with obesity or overweight:** switch to a non-oral contraceptive method, or add a barrier method of contraception upon initiation or dose escalation of tirzepatide (for 4 weeks)
- Follow the British Menopause Society's tool for clinicians when considering prescribing incretin-based therapies in women using HRT.[28]

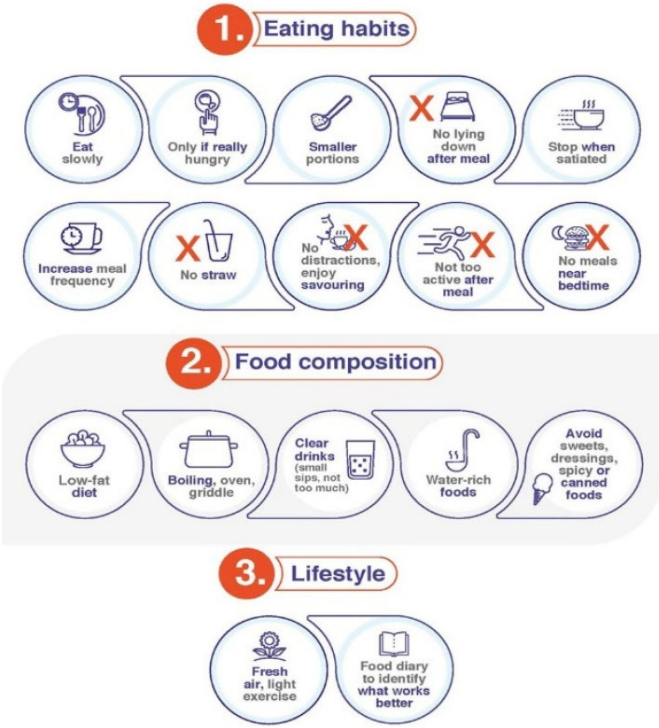
Side Effects[3,5,6,9,29–34]

- The side effects of incretin therapies can lead to nonadherence and discontinuation—in one study of GLP-1 RA use, 21.2% of people had discontinued therapy by 12 months and only 48.6% were adherent[29]
- **The most common adverse effects (prevalence ≥10%) are mostly GI in nature.** GI side effects mostly occur during dose escalation, usually fade with time, and are typically mild/moderate in severity
  - examples include nausea, vomiting, diarrhoea, constipation, abdominal pain, abdominal distension, dyspepsia, flatulence, and belching
- Hair loss (likely due to telogen effluvium; usually transient and reversible),[30,31] fatigue, headache, dizziness, and a small increase in resting HR (around 3 bpm on average, and not clinically significant) can also commonly occur.

Managing GI Side Effects

- **Incretin therapies should be used with caution in people with severe GI disease**, e.g. severe gastroparesis
- **GI side effects are dose-dependent, so consider slower dose escalation or drug holidays** (temporary cessation of incretin therapy) for those who are struggling with GI side effects in the early weeks of therapy
  - a lower maintenance dose can be considered for individuals unable to tolerate the usual maintenance dose
- Advise patients reporting GI side effects to adopt the following mitigating strategies:
  - eat slowly, stop eating as soon as you start to feel full, and avoid eating when not feeling hungry
  - eat smaller portion sizes and eat more frequently during the day, but avoid eating late in the day
  - maintain good hydration, aiming for ≥2–3 litres of fluids daily (not including alcohol)
    - limit intake of alcohol and fizzy drinks, especially if experiencing nausea or dyspepsia
  - avoid eating high-fat, ultra-processed, and spicy foods
  - increase fibre and water intake if experiencing constipation
  - consider short-term use of PPIs, antiemetics, laxatives, and antidiarrhoeal medications for those with disabling side effects
- Consider alternative causes of GI symptoms if persistent despite mitigation strategies, or if red-flag features are present.

Minimising Occurrence/Severity of GI Adverse Effects: General Guidance[32]



Gorgojo-Martínez J, Mezquita-Raya P, Carretero-Gómez J et al. Clinical recommendations to manage gastrointestinal adverse events in patients treated with glp-1 receptor agonists: a multidisciplinary expert consensus. *J Clin Med* 2022; **12** (1): 145.

Advice for Missed Doses[3,5,9,34]

	Day of Usual Administration	Number of Days After Missed Dose					
		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Semaglutide	Missed dose	Administer catch-up dose as soon as possible (within 5 days)				Skip dose and administer next dose on usual day	
Tirzepatide	Missed dose	Administer catch-up dose as soon as possible (within 4 days)				Skip dose and administer next dose on usual day	

After a dose of semaglutide or tirzepatide is missed (regardless of whether a catch-up dose is taken), individuals can then resume their regular once-weekly dosing schedule.
Note: the time between any two doses must always be ≥72 hours.

	0–12 hours after a missed dose	12–24 hours after a missed dose
Liraglutide	Administer catch-up dose as soon as possible	Skip dose and administer next dose on usual day

If >3 days have elapsed since the last dose, reinitiate liraglutide at 0.6 mg daily and follow the usual dose escalation schedule.[34]

Special Considerations for People With T2D and Overweight/Obesity[3,5,9,12,14,40–44]

- Incretin therapies are **not** currently licensed for use in people with T1D and overweight/obesity
- Deprescribe any DPP4 inhibitor if initiating an incretin therapy
- Based on the findings of a systematic review and meta-analysis, people **without** T2D may achieve significantly greater mean weight loss with GLP-1 RAs than people **with** T2D[40]
- **Risk of hypoglycaemia is low if the incretin therapy is not used alongside insulin or SUs**
  - people with T2D taking insulin or SUs may need to lower the dosage of these medications initially when starting incretin therapies, to reduce the risk of hypoglycaemia
  - SMBG is necessary when adjusting the dose of SU or insulin, and a stepwise approach to insulin reduction is recommended
- **DKA risk**
  - the MHRA (2019)[41] warns of reports of DKA when insulin is rapidly reduced or discontinued alongside GLP-1 RAs
  - any dose reduction of insulin should be done in a stepwise manner, with careful SMBG
- **Retinopathy—be aware that pre-existing DR may be worsened if HbA_{1c} is rapidly lowered on initiation or escalation of incretin therapy**
  - use all incretin therapies with caution in patients who have DR requiring active ophthalmology follow up, suboptimal glycaemic control (HbA_{1c} ≥86 mmol/mol), and are currently being treated with insulin[42–44]
  - ensure that all people living with T2D being considered for incretin therapies are up to date with retinal screening.

Prescribing Considerations[3,5,9,34–39]

- Incretin therapies can be administered at any time of the day, with or without meals
  - injections of semaglutide and tirzepatide should be scheduled on the same day each week, but the time can be varied
  - if a change of day is required for semaglutide or tirzepatide, **the time between the two doses during transition must be ≥3 days (≥72 hours)**
- **All incretin therapies delay gastric emptying and therefore have the potential to impact the absorption of coadministered oral medications;** however, no dose adjustments are required for most oral medications
  - if individuals are taking oral medications with a **narrow therapeutic index** (e.g. digoxin, lithium, warfarin), closer monitoring may be warranted according to clinical judgement
  - **specific OCP advice is required for tirzepatide** (see *Women's Health and Incretin Therapies*)
- **Sick day guidance** may be required:[35,36] during any intercurrent dehydrating illness (e.g. diarrhoea or vomiting), a temporary pause of incretin therapy may be required to avoid worsening of any GI or other symptoms
  - the incretin therapy can be restarted when the patient is eating and drinking as normal and recovered from illness
- Incretin therapies can be used as adjunctive treatment after bariatric surgery for those with suboptimal weight loss or weight regain, offering a viable alternative to revision surgery.[37] However, this approach should be discussed with a specialist in bariatric surgery and medicine
- **Contraindications:**
  - hypersensitivity to the active substance or any of the excipients present in the incretin therapy
  - according to the US SPCs, all incretin therapies are contraindicated in individuals with MEN2 or with a personal or family history of MTC[38]
    - however, a 2023 systematic review and meta-analysis found that **semaglutide use in RCTs and real-world studies was not associated with an increased risk of any types of cancer (including pancreatic and thyroid cancer).**[39]

Special Precautions for Use[3,5,9,45]

Adverse Effect	Frequency	Notes
Acute pancreatitis	≤1% (uncommon)	• Use with caution in people with a history of pancreatitis • Discontinue if pancreatitis is suspected.
Acute gallbladder disease (cholelithiasis, cholecystitis)	≤1% (uncommon)[A]	• Significant or rapid weight loss can increase the risk of gallstones[45] • If gallbladder disease is suspected, consider gallbladder imaging and appropriate clinical follow up as indicated.[45]
Pulmonary aspiration	—	• Cases of pulmonary aspiration have been reported in people undergoing GA or deep sedation who are receiving incretin therapies • Before such procedures, the increased risk of residual gastric content (due to delayed gastric emptying) should be considered • UK societies have developed a consensus statement giving guidance on the perioperative management of incretin therapies: individuals should continue to take their GLP-1 and GIP RAs throughout the perioperative period.

[A] Cholelithiasis is listed as a common (≤10%) adverse effect of semaglutide[5] and liraglutide.[3]

Follow Up[3,7,10,11,17,46–53]

- **Provide long-term, multicomponent, multimodal, multidisciplinary follow up to all people living with overweight or obesity**
- **Set personalised goals that:**
  - emphasise long-term, realistic, sustained weight loss
  - promote weight maintenance and prevention, improvement, and resolution of obesity-related diseases, disorders, and complications
- Consider agreeing a realistic 'best weight' (i.e. a weight that a person can achieve and maintain in the context of their life circumstances)[46]
- **Evaluation of response to incretin therapies is crucial:**
  - consider intensification of therapy or additional therapeutic options (e.g. metabolic surgery) if individualised goals are not achieved
  - consider stopping incretin therapies if <5% of the initial weight has been lost after 6 months of the highest tolerated dose of tirzepatide or semaglutide, or after 12 weeks of the highest tolerated dose of liraglutide[3,7,10]
  - ensure appropriate/optimal prescribing; consider deprescribing medications that may no longer be indicated due to the health benefits of weight loss (e.g. antihypertensives)
  - consider reassessing goals of therapy during treatment course
  - long-term use of pharmacotherapy is recommended
- **Explain that regular physical activity is beneficial for weight maintenance** and improves cardiometabolic risk factors, health-related quality of life, and mood disorders[48]
  - in weight management interventions, aerobic and resistance exercise supports improvements in cardiorespiratory fitness, mobility, strength, and **muscle mass**; support strategies to minimise muscle loss
  - resistance training in particular can promote weight maintenance and modest increases in muscle mass
- **Set a defined timescale for follow up**
  - consider regular monitoring, as clinically indicated, to assess obesity and its related diseases, disorders, and complications (consider using the *Type 2 Diabetes CVRM Review Checklist*)
  - remember that managing obesity-related diseases, disorders, and complications is part of obesity management
- **Be aware of the risks of weight cycling on cardiometabolic health and adopt strategies that focus on sustained changes that maintain healthy habits over time**[49,50]
- Be aware that incretin therapies **may increase the risk of mental health disorders and suicidal behaviours.**[51] Assess mental health in all individuals on incretin therapies and manage as clinically indicated
  - a recent systematic review and meta-analysis found that, in individuals living with overweight/obesity and/or diabetes, GLP-1 RA treatment is not associated with an increased risk of psychiatric adverse events or worsening depressive symptoms compared to placebo and is associated with improvements in QoL, restrained eating, and emotional eating behaviour.[53]

BMI=body mass index; **bpm**=beats per minute; **CrCl**=creatinine clearance; **CV**=cardiovascular; **CVD**=cardiovascular disease; **CVRM**=cardiovascular–renal–metabolic; **DKA**=diabetic ketoacidosis; **DPP4**=dipeptidyl peptidase-4; **DR**=diabetic retinopathy; **DVLA**=Driver & Vehicle Licensing Agency; **eGFR**=estimated glomerular filtration rate; **ESRD**=end-stage renal disease; **FDA**=Food and Drug Administration; **GA**=general anaesthesia; **GI**=gastrointestinal; **GIP**=glucose-dependent insulinotropic polypeptide; **GLP-1**=glucagon-like peptide-1; **HbA_{1c}**=glycated haemoglobin; **HCP**=healthcare professional; **HR**=heart rate; **HRT**=hormone-replacement therapy; **LTC**=long-term condition; **MEN2**=multiple endocrine neoplasia type-2; **MHRA**=Medicines and Healthcare products Regulatory Agency; **MTC**=medullary thyroid carcinoma; **NG**=NICE Guideline; **OCP**=oral contraceptive pill; **od**=once daily; **PHE**=Public Health England; **PPI**=proton pump inhibitor; **QoL**=quality of life; **RA**=receptor agonist; **RCT**=randomised controlled trial; **SMART**=Specific, Measurable, Achievable, Rewarding, Timely; **SMBG**=self-monitoring of blood glucose; **SPC**=summary of product characteristics; **SU**=sulfonylurea; **TA**=Technology Appraisal; **T1D**=type 1 diabetes; **T2D**=type 2 diabetes.