NHS
South West London

Glucagon-like peptide-1 (GLP-1) Mimetics

Prescribing considerations

- Always prescribe by brand name as different products may exist within each drug class with varying indications
- Should only be initiated by clinicians who are adequately trained and competent to provide training for patients on how to use the injectable device
- See SWL joint formulary for further information regarding formulary choices and prescribing criteria
- See 'Oral Semaglutide Information Sheet' for further information on semaglutide tablets (Rybelsus®▼)

Indication

Treatment of adults with insufficiently controlled type 2 diabetes mellitus (T2DM) to improve glycaemic control as an adjunct to diet and exercise:

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 mimetic for adults with T2DM who:

- Have a body mass index (BMI) of 35 kg/m2 or higher (adjust accordingly for people from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity **or**
- Have a BMI lower than 35 kg/m2 and:
  - For whom insulin therapy would have significant occupational implications **or** weight loss would benefit other significant obesity related comorbidities

Mechanism of action

GLP-1 mimetics bind to, and activate, the GLP-1 receptor to increase insulin secretion, suppress glucagon secretion, and slow gastric emptying. GLP-1 mimetics require beta cell function to be effective.

Treatment options

Liraglutide (Victoza®):

Dose titration is listed in the BNF and see table below.

Missed dosing advice: If a dose is more than 12 hours late, the missed dose should not be taken and the next dose to be taken at the normal time.

Delivery device: 6mg/ml solution for injection in a Multi-dose daily pre-filled pen. 1 pen contains 15 doses/10 doses (needles not supplied with pen).

Cardiovascular (CV) benefit, reduction in major adverse cardiac events (MACE): 13% MACE reduction at 1.8mg.

Dulaglutide (Trulicity®)

Dose titration is listed in the BNF and see table below.

Missed dosing advice: Any missed dose should be administered if there are at least 72 hours until next scheduled dose.

Delivery device: Single use pre-filled pen (0.75mg to 4.5mg doses available in each pen supplied in packs of 4). 1 pen contains 1 weekly dose (needles integrated in device).

Cardiovascular benefit, reduction in MACE: 12% MACE reduction with 1.5mg dose (Evidence for benefit in primary prevention).

Semaglutide injection (Ozempic®▼)

Dose titration is listed in the BNF and see table below.

Missed dosing advice: Any missed dose should be administered within 5 days.

Delivery device: Available in 250mcg, 500mcg and 1mg multi-dose pre-filled pens. 1 pen contains 4 weekly doses (needles supplied with pen).

Cardiovascular benefit, reduction in MACE: 26% MACE reduction (Evidence for benefit in secondary prevention).

Semaglutide tablets (Rybelsus®▼)

Dose titration is listed in the BNF and see table below.

Missed dosing advice: If a dose is missed, the missed dose should be skipped and the next dose should be taken the following day.

Delivery device: Available as 3mg, 7mg or 14mg oral tablets to be taken daily. To be taken whole on an empty stomach, with a sip of water (max 120 ml). Wait at least 30 minutes after a dose before eating, drinking, or taking other oral medicines.

Cardiovascular benefit, reduction in MACE: Non-inferiority to placebo was proven. Superiority could not be proved due to study design.

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Table summary of treatment options

GLP-1 mimetic	Liraglutide (Victoza®)	Dulaglutide (Trulicity®)	Semaglutide injection (Ozempic®)	Semaglutide tablets (Rybelsus®)
Dose titration	Starting: 0.6mg daily for at least 1 week. Maintenance: 1.2mg daily for at least 1 week. Max dose is 1.8mg daily	Monotherapy: 0.75mg once weekly. Add on therapy: 0.75mg to 1.5mg once weekly for at least 1 month. If required increase to 3mg once weekly for at least 1 month then if required up to 4.5mg once weekly.	Starting: 0.25mg once weekly for 1 month Maintenance: 0.5mg once weekly for at least 1 month. If required increase dose up to 1.0mg once weekly.	Starting: 3mg once daily for 1 month Maintenance: 7mg once daily. If required increase further after 1 month to 14mg daily.
Missed dosing advice	If a dose is more than 12 hours late, the missed dose should not be taken and the next dose to be taken at the normal time.	Any missed dose should be administered if there are at least 72 hours until next scheduled dose.	Any missed dose should be administered within 5 days.	If a dose is missed, the missed dose should be skipped and the next dose should be taken the following day.
Delivery device	Multi-dose daily pre-filled pen 1 pen=15 doses/10 doses (needles not supplied with pen)	Single use pre-filled pen 1 pen=1 weekly dose (needles integrated in device)	Multi-dose pre-filled pen 1 pen=4 weekly doses (needles supplied with pen)	Oral tablet taken daily. To be taken whole on an empty stomach, with a sip of water (max 120 ml). Wait at least 30 minutes after a dose before eating, drinking, or taking other oral medicines.
CV benefit, major adverse cardiac events (MACE) reduction	Yes. 13% MACE reduction at 1.8mg.	Yes. 12% MACE reduction with 1.5mg dose. (Evidence for benefit in primary prevention)	Yes. 26% MACE reduction (Evidence for benefit in secondary prevention)	Non-inferiority to placebo was proven. Superiority could not be proved due to study design.

Contraindications (Individual product license contains full list)

- Ketoacidosis
- Pancreatitis
- Renal impairment
    - Avoid exenatide standard-release and liraglutide injection if estimated glomerular filtration rate (eGFR) is less than 30 mL/min
    - Avoid exenatide modified-release injection if eGFR is less than 50 mL/min
    - Avoid liraglutide and semaglutide in end-stage renal disease
- Severe hepatic impairment: avoid liraglutide
- Severe gastrointestinal disease: avoid exenatide, liraglutide (for example if diabetic gastroparesis or inflammatory bowel disease), lixisenatide, and dulaglutide

Cautions (Individual product license contains full list)

- History of pancreatitis: discontinue if symptoms of acute pancreatitis occur
- Hepatic impairment: caution with semaglutide
- Elderly people: may cause weight loss
- Severe heart failure: use liraglutide and semaglutide with caution
- Thyroid disease: history of medullary thyroid cancer or multiple endocrine neoplasia type 2 disease (for liraglutide)
- Retinopathy: use semaglutide with caution (see monitoring section below)
- Poor glycaemic control: HbA1c more than 91 mmol/mol (10.5%)
- Current insulin treatment (see GLP-1 and insulin section below)

Monitoring

- Only continue GLP-1 mimetic therapy if the adult with T2DM has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and weight loss of at least 3% of initial body weight) in 6 months
- Ensure all patients are up to date with their retinopathy screening programme prior to initiation of semaglutide; it is recommended that a retinal screening result should be available in the last 6 months prior to initiation. Whilst on treatment with semaglutide, patients should attend regular retinopathy screening as recommended by the programme. Ideally, retinopathy screening should occur every 12 months, or up to 18 months allowing for slippage in local screening appointments. If the previous retinal screen was completely normal, at present an interval of up to 24 months is acceptable. Longer than this and active retinopathy may be present, so the retinal screen should be updated before GLP-1 initiation

GLP-1 and insulin

This combination is Amber-2 on the SWL Joint Formulary. Initiation by a specialist, stabilisation (approximately three months), then continuation in primary care under an individual management plan.

MHRA/Safety alerts

GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued (June 2019)

Noteworthy Interactions (Individual product license contains full list)

- Beta-blockers: the warning signs of hypoglycaemia (such as tremor) may be masked during concurrent treatment with a beta-blocker
- Warfarin: exenatide and liraglutide possibly enhance the anticoagulant effect of warfarin. Monitor the international normalized ratio (INR) during concurrent treatment with warfarin
- Other antidiabetic drugs: due to the increased risk of hypoglycaemia, the dose of concomitant sulfonylurea may need to be reduced
- Co-prescribing a gliptin with a GLP-1 mimetic is not recommended as both work through the same (incretin) pathway
- The blood glucose-lowering effects of GLP-1 mimetics may be enhanced by:
    - Alcohol
    - Anabolic steroids
    - Disopyramide
    - Monoamine oxidase inhibitors
    - Testosterone
- The blood glucose-lowering effects of GLP-1 mimetics may be antagonized by:
    - Corticosteroids
    - Diuretics (thiazide and related, and loop)
    - Oestrogens and progestogens

Information on adverse effects (Individual product license contains full list)

- Acute pancreatitis (rare): advise the person to seek urgent medical advice if symptoms such as severe upper abdominal pain, nausea, and/or vomiting develop. Advise to discontinue treatment if pancreatitis is suspected
- Gastrointestinal: decreased appetite, altered taste, nausea, vomiting, dyspepsia, burping, gastro-oesophageal reflux, constipation, diarrhoea, gallbladder disorders (liraglutide)
- Headache, dizziness, drowsiness, alopecia, hyperhidrosis
- Renal impairment (exenatide and liraglutide)
- Atrioventricular block, sinus tachycardia, delayed gastric emptying (dulaglutide)
- Skin reactions including rash, angioedema, urticaria, and pruritus

Sick Day rules

If taken during an acute illness that can lead to dehydration, there is an increased risk of developing serious side-effects and therefore should be temporarily stopped. Further information can be found in the sick day rules section.

Disposal

For GLP-1 pens that have a removable needle, these should be disposed of in a sharps bin, which can be prescribed. The full bins can usually be collected by the local council.

Links to local borough sharps disposal information

- Croydon
- Kingston
- Merton
- Richmond
- Sutton
- Wandsworth

Some GLP-1 pens can now be recycled to reduce plastic waste. Novo Nordisk has one such recycling scheme called PenCycle for their insulin and GLP-1 pre-filled plastic pens. Signpost these patients to the PenCycle website. Patients can collect a PenCycle return box from their nearest participating pharmacy, or order directly from Novo Nordisk.

References

- BNF online (Last accessed 01/05/2024)
- Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: The PIONEER programme (Last accessed 01/05/2024)
- Prescribing Guide for GLP-1 Receptor Agonists in Type 2 Diabetes. Hereford and Worcestershire Clinical Commissioning Group (Last accessed 01/05/2024)
- SPCs for individual products (Last accessed 01/05/2024)
- SWL Joint Medicines Formulary (Last accessed 01/05/2024)

Document History

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Updates: Link to oral semaglutide information sheet updated, and other minor amendments due to change in oral semaglutide formulary status.