North Central London
Joint Formulary Committee

Factsheet

GLP-1 mimetic therapy Factsheet

Subcutaneous semaglutide▼ (Ozempic®), dulaglutide▼ (Trulicity®), liraglutide 1.2mg (Victoza®) and oral semaglutide (Rybelsus®)

Treatment of adults with Type 2 Diabetes Mellitus

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Document Control		
Date	**Version**	**Action**
July 2016	1.0	New guideline
August 2019	1.1	Change to preferred GLP-1 mimetic
November 2019	1.2	Supply quantities added
October 2022	2.0	Change to preferred GLP-1 mimetic. Implemented NG28 recommendation 1.7.20. Agreed by NCL Shared Care Group: October 2022

Disclaimer
Factsheets support GPs in taking ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

This document is intended for use by healthcare professionals to aid the treatment of patients within NCL. It should not be used for marketing purposes. If you identify information within this document that is inaccurate, please report to admin.ncl-mon@nhs.net.

GLP-1 mimetic therapy Factsheet

Type 2 Diabetes Mellitus (adults)

Contents

GLP-1 mimetic therapies (see Product choice) for the treatment of adults with type 2 diabetes mellitus should be initiated under the direction of a clinician experienced with GLP-1 mimetics, for an approved indication. Contact your Community Diabetes Service if you are not experienced with these medicines.

GLP-1 mimetic therapies (Saxenda®, Wegovy®) for weight management in diabetic and non-diabetic patients should not be prescribed in primary care.

Checklist and actions for GP:

- Ensure documented communication has been received from the initiating prescriber with an indication for use (see Indication) and evidence that the initiating prescriber has counselled the patient
- Ensure that the patient meets the criteria for treatment
- Conduct necessary monitoring (see Clinical Monitoring)
- Prescribe the drug treatment (see Prescription quantities). The term “as directed” should not be used.
- Refer patients back to the initiating prescriber if the patient:
    - Is intolerant of side effects
    - Is non-adherent with medicines, or this is suspected
    - Does not achieve an adequate response at 6 months (see Continuation criteria)

Product choice

Refer to NCL guidance Antihyperglycaemic agents for Type 2 diabetes (adults) for full information.

Preferred:

- Semaglutide subcutaneous (Ozempic®)
- Dulaglutide subcutaneous (Trulicity®)

Alternative:

- Semaglutide oral (Rybelsus®) – *only where subcutaneous treatment is not possible and prescriber has confirmed patient can adhere to administration instructions:*
    - *Tablets 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.*
- Liraglutide subcutaneous 1.2mg dose (Victoza®) – *for existing patients only (not usually recommended for new adults)*

Not recommended:

- Liraglutide subcutaneous 1.8mg dose (Victoza®) – not considered cost-effective
- Lixisenatide subcutaneous (Lyxumia®)
- Exenatide subcutaneous (Byetta/Bydureon®)

GLP-1 mimetics specifically for weight loss in diabetic and non-diabetic patients is outside of the scope of this guideline. Liraglutide subcutaneous 3mg dose (Saxenda®) is the only GLP-1 mimetic recommended in line with NICE TA664 and should only be prescribed in secondary care.

Indication

Refer to NCL guidance Antihyperglycaemic agents for Type 2 diabetes (adults) for full information.

Triple therapy with two oral antihyperglycaemic drugs

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider substituting ineffective therapy for a GLP-1 mimetic (see Product Choice) for adults with type 2 diabetes who have:

- Body mass index (BMI) ≥ 35 kg/m^2 (adjusted for people from black, Asian and other minority ethnic groups;) and specific psychological or medical problems associated with obesity *or*
- BMI < 35 kg/m^2 and
    - therapy with insulin would have significant occupational implications (e.g. Class 2 driver, working at heights), *or*
    - weight loss would benefit other significant obesity-related comorbidities (including sleep apnoea, non-alcoholic fatty liver disease [NAFLD], CKD secondary to obesity, musculoskeletal issues due to obesity)

In combination with insulin

If therapy with maximum tolerated basal insulin with or without oral drugs is not effective, consider a GLP-1 mimetic (see Product Choice) in combination with insulin for adults with type 2 diabetes where

- insulin escalation (switching to biphasic or adding a bolus insulin) would have significant occupational implications (e.g. Class 2 driver, working at heights) *or*
- weight loss would benefit other significant obesity-related comorbidities (including sleep apnoea, non-alcoholic fatty liver disease [NAFLD], CKD secondary to obesity, musculoskeletal issues due to obesity)

Alternatively, if therapy with GLP-1 memetic and 2 other oral drugs is not effective, consider substituting ineffective therapy with insulin.

Be aware of the risk of diabetic ketoacidosis if concomitant insulin was rapidly reduced or discontinued (MHRA Drug Safety Update, 2019). GLP-1 memetic use in combination with insulin should only be under specialist care advice with ongoing support from a consultant-led multidisciplinary team (NICE NG28).

Continuation criteria

NICE recommend that GLP-1 mimetics (see Product Choice) should only be continued if the patient has a beneficial metabolic response within 6 months, defined as:

- Reduction of at least 11mmol/mol (1.0%) in HbA1c, *and*
- Weight loss of at least 3% of initial body weight

In exceptional circumstances, the requirement to achieve 3% weight loss may be waived if a reduction of at least 11mmol/mol (1%) in HbA1c has been achieved. These circumstances include patients in whom insulin (or insulin intensification) is the only alternative treatment, and in whom insulin (or insulin intensification) would have significant occupational implications.

Subcutaneous semaglutide (Ozempic®), dulaglutide, oral semaglutide, and liraglutide (Victoza®) are not licensed for weight loss, nor approved within NCL for this indication. Therefore patients who fail to achieve a reduction in HbA1c of at least 11mmol/mol (1%) yet achieve 3% weight loss should discontinue treatment.

Initiation, Dose and Administration

Semaglutide 0.5 - 1 mg weekly injection

The starting dose is 0.25 mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After at least 4 weeks the dose can be increased to 1 mg once weekly to further improve glycaemic control. Semaglutide 0.25 mg is not a maintenance dose.

- Semaglutide is administered once weekly at any time of the day, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site can be changed without dose adjustment. The day of weekly administration can be changed if necessary as long as the time between two doses is at least 3 days (>72 hours). Patients can then resume their regular once weekly dosing schedule.
- If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Refer to Prescription quantities for injectables for prescribing support.

Dulaglutide 1.5 mg – 4.5mg weekly injection

The recommended dose is 1.5 mg dulaglutide once weekly. The dose can be increased to 3 mg and then 4.5 mg in four weekly intervals for additional glycaemic control. For potentially vulnerable patients, such as patients > 75 years, 0.75 mg once weekly can be considered.

- Dulaglutide is injected subcutaneously in the abdomen, thigh or upper arm. The dose can be administered at any time of day, with or without meals.
- If a dose is missed, it should be administered as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days (72 hours), the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule. The day of weekly administration can be changed if necessary, as long as the last dose was administered 3 or more days (72 hours) before.

Refer to Prescription quantities for injectables for prescribing support.

Semaglutide 7mg – 14mg daily tablet

The starting dose is 3 mg semaglutide once daily. After 30 days the dose should be increased to 7 mg once daily. After at least 30 days the dose can be increased to 14 mg once daily to further improve glycaemic control. Semaglutide 3 mg is not a maintenance dose.

- Semaglutide should be taken on an empty stomach at any time of the day (usually in the morning). It should be swallowed whole with a sip of water. Patients should wait at least 30 minutes before eating or drinking or taking other oral medicinal products

Liraglutide 1.2 mg daily injection

Liraglutide is not recommended for new patients owing to better HbA1c lowering and weight loss with semaglutide subcutaneous (SUSTAIN 10) and less convenient that dulaglutide (once weekly pre-filled pen).

The starting dose is liraglutide 0.6 mg subcutaneously once daily. After at least one week, if tolerated the dose should be increased to 1.2 mg (liraglutide 1.8 mg should NOT be prescribed as it is not considered cost-effective in North Central London).

- Liraglutide is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, in the thigh or in the upper arm. The injection site and timing can be changed without dose adjustment. However, it is preferable that liraglutide is injected around the same time of the day, when the most convenient time of the day has been chosen.

Refer to Prescription quantities for injectables for prescribing support.

Adverse Effects

All GLP-1 mimetics:

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
  - Nausea, diarrhoea, vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, gastro-oesophageal reflux disease, eructation and flatulence are very common or common.
  - At the beginning of therapy, gastrointestinal adverse reactions may occur more frequently and usually diminish within a few days or weeks on continued treatment. Advise patients to reduce meal size, avoiding high-fat or spicy food and moderating intake of alcohol and fizzy drinks (Wharton et al 2021). Short-term use of antiemetic treatment may be considered. Take steps to avoid dehydration which could cause deterioration of renal function.
  - GLP-1 mimetic dose escalation should not be carried out until the gastrointestinal symptoms have resolved. If symptoms occur on dose escalation, consider temporary reduction in dosage followed by rechallenge.
  - If adverse effects prevent use of a recommended dose therapy should be discontinued (semaglutide injection ≥ 0.5 mg, dulaglutide injection ≥ 1.5 mg, liraglutide injection ≥ 1.2 mg, (semaglutide tablets ≥ 7 mg).
- Hypoglycaemia
  - Hypoglycaemia is very common when used in combination with insulin or sulphonylurea. If recurrent symptomatic hypoglycaemia, consider reduction in the dosage of insulin or sulphonylurea.
  - Be aware of the risk of diabetic ketoacidosis if concomitant insulin is rapidly reduced or discontinued (MHRA Drug Safety Update, 2019).
- Injection site reactions – if severe, consider cessation of treatment
- Cholelithiasis (gallstones) and fatigue are common
- Increase in heart rate is common though not associated with cardiovascular harm – routine monitoring is not required

Semaglutide specific adverse effects

- Diabetic retinopathy
    - In the cardiovascular outcome study, diabetic retinopathy complications occurred in more patients treated with semaglutide (3.0%) compared to placebo (1.8%). This was observed in insulin-treated patients with known diabetic retinopathy. The treatment difference appeared early and persisted throughout the trial.
    - The worsening of diabetic retinopathy with semaglutide in some insulin-treated patients with pre-existing proliferative retinopathy or maculopathy is likely to reflect a rapid improvement in glycaemic control and is a well-known phenomenon which is seen with other treatment modalities (eg insulin, bariatric surgery). This 'early worsening' of retinopathy is likely to be avoided by
        - Ensuring such patients are under close ophthalmology follow-up
        - Aiming to reduce HbA1c by no more than 2% over 3 months. This can be achieved by slower titration of semaglutide dose i.e. leaving the patient for more than 4 weeks at the lowest dose before considering any dose increase AND cautious adjustment of insulin dosage. Specialist advice is recommended for such patients.
- Dizziness is common
- Semaglutide is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

Dulaglutide specific adverse effects

The most frequently reported adverse effects are listed below:

- Fatigue, sinus tachycardia and first degree atrioventricular block are common
- Dulaglutide is a black triangle drug and as such is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

Liraglutide specific adverse effects

- Headache – common and are usually self-limiting
- Nasopharyngitis – common and are usually self-limiting
- Dizziness is common
- Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently thyroid adverse events and were reported in 0.5%, 1% and 0.8% of patients respectively.

For a full list of adverse effects, refer to the Summary of Product Characteristics for subcutaneous semaglutide, dulaglutide, liraglutide and oral semaglutide.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use

Semaglutide special warnings and precautions for use

- Should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
- Avoid in patients with congestive heart failure NYHA class IV.
- Caution when using in patients with diabetic retinopathy treated with insulin as an increased risk of developing diabetic retinopathy complications has been observed (see Adverse effects: Diabetic retinopathy).
- Not recommended for use in patients with end-stage renal disease (eGFR < 15 mL/min/1.73 m^2)
    - *Treatment may be recommended by Specialists in Diabetes however care should only transfer if the GP is in agreement to take clinical and prescribing responsibility.*

- Experience with the use of semaglutide in patients with severe hepatic impairment is limited.
- Avoid in pregnancy and lactation. Should be discontinued at least 2 months before a planned pregnancy due to the long half-life.
- Use of GLP-1 mimetics has been associated with a risk of developing acute pancreatitis (see Clinical monitoring: Pancreatitis)

Dulaglutide special warnings and precaution for use

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Avoid in patients with severe gastrointestinal disease including severe gastroparesis.
- Should not presently be used in patients with congestive heart failure due to lack of clinical experience.
- Not recommended for use in patients with end stage renal disease (eGFR < 15 mL/min/1.73 m^2)
    - *Treatment may be recommended by Specialists in Diabetes however care should only transfer if the GP is in agreement to take clinical and prescribing responsibility.*
- No dosage adjustment is required in patients with hepatic impairment.
- Avoid in pregnancy and lactation.
- Use of dulaglutide has been associated with a risk of developing acute pancreatitis (see Clinical monitoring: Pancreatitis)

Liraglutide special warnings and precaution for use

- Should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Avoid in patients with inflammatory bowel disease and diabetic gastroparesis.
- Avoid in those with congestive heart failure NYHA class IV.
- Not recommended for use in patients with end stage renal disease (eGFR < 15 mL/min/1.73 m^2)
    - *Treatment may be recommended by Specialists in Diabetes however care should only transfer if the GP is in agreement to take clinical and prescribing responsibility.*
- Not recommend for use in patients with severe hepatic impairment.
- Avoid in pregnancy and lactation.
- Use of liraglutide has been associated with a risk of developing acute pancreatitis (see Clinical monitoring: Pancreatitis).

For a full list of special warnings and precautions for use, refer to the Summary of Product Characteristics for subcutaneous semaglutide, dulaglutide and liraglutide.

Drug Interactions

- Warfarin
    - When starting semaglutide, dulaglutide or liraglutide, no initial warfarin dose adjustment is recommended however the manufacturer of semaglutide and liraglutide recommend more frequent monitoring of INR (International Normalised Ratio)
- Levothyroxine
    - When starting oral semaglutide, the effective dose of levothyroxine may increase by 33% if taken at the same time. Monitoring of thyroid function tests is advised. Consider changing the timing of levothyroxine administration to bedtime to avoid this interaction.
- For a full list of drug interactions, refer to the Summary of Product Characteristics as there are differences between subcutaneous semaglutide, dulaglutide, liraglutide and oral semaglutide.

Clinical Monitoring

- The HbA1c, U&E and weight, should be reassessed at 3 months and then 6 months. Thereafter to repeat 6 to 12 monthly according to clinical response (if Hb1Ac is higher than the Personalised HbA1c target, HbA1c should be rechecked every 3 months)
    - See NCL GLP-1RA Continuation criteria
- Self-monitoring of blood glucose is not needed in order to adjust the dose of these GLP-1 mimetics. However, when initiating treatment in combination with a sulphonylurea, blood glucose self-monitoring may become necessary to adjust the dose of the sulphonylurea.
    - Also consider whether the patient prescribed sulphonylurea and/or insulin should be self-monitoring in accordance with DVLA guidelines
- Use of GLP-1 mimetics have been associated with the risk of pancreatitis. Patients should be counselled and monitored for signs of acute pancreatitis (e.g. persistent, severe abdominal pain) and if suspected the GLP-1 mimetics should be stopped. This should be reported to the MHRA via the Yellow Card scheme.
- Patients with pre-existing thyroid disorders may be at risk of thyroid disorders such as increased blood calcitonin, goitre and thyroid neoplasm. Such patients should be monitored clinically. There is no need to routinely monitor calcitonin levels, thyroid function or perform thyroid USS. If pre-existing thyroid disorders worsen or new thyroid disorders develop while on treatment they should be investigated in the normal way.

Prescription quantities for injectables

The table below details the total quantity to be prescribed.

Drug + Dose	Medicine to prescribe	Quantity to prescribe for 28 days
Semaglutide injection (needles supplied with pen)		
Semaglutide 0.25mg **weekly** (starting dose only)	Semaglutide 0.25mg/0.19ml solution for injection, 1.5ml pre-filled pen	1 box of 1 pen (each pen contains 4 doses)
Semaglutide 0.5mg **weekly**	Semaglutide 0.5mg/0.37ml solution for injection, 1.5ml pre-filled pen	1 box of 1 pen (each pen contains 4 doses)
Semaglutide 1.0mg **weekly**	Semaglutide 1mg/0.74ml solution for injection, 3ml pre-filled pen	1 box of 1 pen (each pen contains 4 doses)
Dulaglutide injection (needles integrated in device)		
Dulaglutide 0.75mg **weekly** (starting dose only)	Dulaglutide 0.75mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)
Dulaglutide 1.5mg **weekly**	Dulaglutide 1.5mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)
Dulaglutide 3.0mg **weekly**	Dulaglutide 3.0mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)
Dulaglutide 4.5mg **weekly**	Dulaglutide 4.5mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens (each pen contains 1 dose)
Liraglutide injection (needles not supplied with pen)		
Liraglutide 0.6mg **daily** (starting dose)	Liraglutide 6mg/ml solution for injection, 3ml pre-filled pen	1 pen‡ (each pen contains 30 doses)
Liraglutide 1.2mg† **daily**	Liraglutide 6mg/ml solution for injection, 3ml pre-filled pen	1 box of 2 pens‡ (each pen contains 15 doses)

† Liraglutide 1.8mg daily is not locally approved – this dose is not cost-effective

‡ 30 day supply

References

- Summary of Product Characteristics (via eMC): Ozempic® revised Mar 2021 (accessed Apr 2022)
- Summary of Product Characteristics (via eMC): Trulicity® revised Oct 2021 (accessed Apr 2022)
- Summary of Product Characteristics (via eMC): Victoza® revised Sept 2022 (accessed Apr 2022)
- Summary of Product Characteristics (via eMC): Rybelus® revised Nov 2020 (accessed Apr 2022)
- National Institute for Health and Care Excellence, Type 2 diabetes in adults: management NICE guideline Published: March 2022 www.nice.org.uk/guidance/ng28
- Wharton et al. 2021. Managing the gastrointestinal side effects of GLP-1 receptor agonists in obesity: recommendations for clinical practice https://doi.org/10.1080/00325481.2021.2002616

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