

**Factsheet**  
**Subcutaneous SEMAGLUTIDE<sup>▼</sup> (Ozempic<sup>®</sup>),  
DULAGLUTIDE<sup>▼</sup> (Trulicity<sup>®</sup>) and LIRAGLUTIDE 1.2mg (Victoza<sup>®</sup>)  
Treatment of Type 2 Diabetes Mellitus**

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Document Control		
Date	Version	Action
July 2016	1.0	New guideline
August 2019	1.1	Subcutaneous semaglutide added as the preferred GLP-1 receptor agonist Agreed by NCL Medicines Optimisation Network: 6 <sup>th</sup> August 2019 Ratified by NCL Joint Formulary Committee: 19 <sup>th</sup> August 2019

**FACTSHEET TO FACILITATE PRESCRIBING**

PLEASE NOTE THIS IS NOT A SHARED CARE GUIDELINE, NOR IS IT A FULL SUMMARY OF DRUG INFORMATION. ALWAYS REFER TO THE MOST RECENT BNF AND/OR SUMMARY OF PRODUCT CHARACTERISTICS.

**Disclaimer**

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# Factsheet – subcutaneous SEMAGLUTIDE<sup>▼</sup> (Ozempic<sup>®</sup>), DULAGLUTIDE<sup>▼</sup> (Trulicity<sup>®</sup>) and LIRAGLUTIDE 1.2 mg (Victoza<sup>®</sup>)

## *Type 2 Diabetes Mellitus*

As per local formulary agreement subcutaneous semaglutide (Ozempic<sup>®</sup>), dulaglutide or liraglutide 1.2 mg (Victoza<sup>®</sup>) should only be initiated under the direction of a specialist in diabetes for the management of type 2 diabetes mellitus.

The use of these medicines for patients outside the [approved indications](#), including liraglutide (Saxenda<sup>®</sup>) for weight-loss is not recommended.

### **Checklist and actions for GP:**

- Ensure documented communication has been received from the diabetes specialist with an indication for use (see [Indication](#)) and evidence that the specialist has counselled the patients on subcutaneous semaglutide/dulaglutide/liraglutide
- Ensure that the patient meets the criteria for treatment
- Conduct necessary monitoring (see [Clinical Monitoring](#))
- Prescribe the drug treatment as described below. The term “as directed” should not be used.
- Refer patients back to the diabetes specialist 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**

Three glucagon-like peptide 1 (GLP-1) receptor agonists are available within North Central London:

- **Subcutaneous semaglutide (Ozempic<sup>®</sup>) is preferred due to superior glycaemic control and weight loss**
- Alternatives:
  - Dulaglutide is restricted for patients:
    - who are needle-phobic and cannot use the semaglutide pen device.
    - with impaired manual dexterity (e.g. due to severe arthritis) and cannot use the semaglutide pen device.
    - with learning difficulty or mental health issues and require GLP-1 receptor agonist administration by a third-party as the dulaglutide device minimises the risk of needle-stick injury
  - Liraglutide 1.2 mg (Victoza<sup>®</sup>) is restricted for patients with concurrent gastrointestinal conditions e.g. inflammatory bowel disease

### **Indication**

#### Triple therapy with metformin and sulphonylurea

GLP-1 receptor agonists (see [Product Choice](#)) may be initiated as a triple therapy regimen (in combination with metformin and sulphonylurea) for those who fail to have optimal glycaemic control despite fully titrated triple oral therapy. They will only be used when control of blood glucose remains or becomes inadequate (HbA1c  $\geq$  58mmol/mol or other higher level agreed with the individual) **and either** of the following criteria are met:

- Body mass index (BMI)  $\geq$  35 kg/m<sup>2</sup> (adjusted for people from black, Asian and other minority ethnic groups;  $\geq$  30Kg/m<sup>2</sup> if Asian origin) and specific psychological or medical problems associated with obesity
- BMI < 35 kg/m<sup>2</sup> 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)

#### Dual therapy with metformin, or triple therapy with metformin and pioglitazone

GLP-1 receptor agonists (see [Product Choice](#)) in combinations with metformin alone or metformin and pioglitazone may occasionally be advised by Specialists in Diabetes (e.g. if the patient is at serious risk from the consequences of hypoglycaemia or unable to tolerate a sulphonylurea). The eligibility criteria are identical to described under 'Triple therapy with metformin and sulphonylurea'

#### In combination with insulin

GLP-1 receptor agonists (see [Product Choice](#)) may be used in combination with insulin in the following circumstances:

- Control of blood glucose remains or becomes inadequate ( $\text{HbA1c} \geq 58\text{mmol/mol}$ , or other higher level agreed with the individual) for patients prescribed maximum tolerated basal insulin  $\pm$  oral antihyperglycaemic drugs and
  - 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)
- Control of blood glucose becomes inadequate ( $\text{HbA1c} \geq 58\text{mmol/mol}$ , or other higher level agreed with the individual) for patients prescribed GLP-1 receptor agonist + metformin + sulphonylurea.

Use in combination with insulin should only be under specialist care advice with ongoing support from a consultant-led multidisciplinary team.

Patients who would have fulfilled the criteria for GLP-1 receptor agonist therapy but who were commenced on insulin treatment should be considered for co-administration of insulin and GLP-1 receptor agonist therapy with the potential to wean off insulin if possible.

#### **Continuation criteria**

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

- Reduction of at least  $11\text{mmol/mol}$  (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  $11\text{mmol/mol}$  (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 and liraglutide 1.2 mg (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  $11\text{mmol/mol}$  (1%) should discontinue treatment.

#### **Dose and Administration**

##### Semaglutide 0.5 - 1 mg WEEKLY subcutaneous injection (for use in individuals 18 years and older)

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 with a dose of 0.5 mg *once weekly*, 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.

#### Dulaglutide 1.5 mg WEEKLY injection (for use in individuals 18 years and older)

The recommended dose for dulaglutide when used in combination with other glucose-lowering medicinal products including insulin, is 1.5 mg *once weekly* by subcutaneous injection. 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.

#### Liraglutide 1.2 mg DAILY injection (for use in individuals 18 years and older)

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.

When subcutaneous semaglutide, dulaglutide or liraglutide is added to sulfonylurea therapy or basal insulin, a reduction in the dose of sulfonylurea or basal insulin should be considered to reduce the risk of hypoglycaemia. See [Clinical Monitoring](#) section.

## **Adverse Effects**

### Semaglutide adverse effects

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
  - Nausea and diarrhoea are very common, whereas vomiting, abdominal pain, abdominal distension, constipation, dyspepsia, gastritis, GORD, eructation and flatulence are 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. Short-term use of antiemetic treatment may be considered. Take steps to avoid dehydration which could cause deterioration of renal function.
  - Escalation of dose from 0.25 mg to 0.5 mg, and from 0.5mg to 1.0mg, 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 semaglutide 0.5 mg cannot be tolerated, therapy should be discontinued (the 0.25 mg dose should not be continued long-term as unlikely to be cost-effective).
- Hypoglycaemia

- Hypoglycaemia is very common when used in combination with insulin or sulphonylurea. If recurrent symptomatic hypoglycaemia occurs, consider reduction in the dosage of insulin or sulphonylurea.
- 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 (0.25 mg weekly) before considering any dose increase AND cautious adjustment of insulin dosage. Specialist advice is recommended for such patients.
- Dizziness, cholelithiasis (gallstones) and fatigue are 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 adverse effects

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
  - Nausea, diarrhoea, vomiting and abdominal pain are very common, whereas dyspepsia, constipation, flatulence, abdominal distension, GORD, eructation are common.
  - Short-term use of antiemetic treatment may be considered. Take steps to avoid dehydration which could cause deterioration of renal function.
  - If dulaglutide 1.5 mg cannot be tolerated consider trial at dose of 0.75 mg followed by escalation to 1.5 mg when symptoms resolve (0.75 mg dose should not be continued long-term as unlikely to be effective).
- Hypoglycaemia
  - Hypoglycaemia is very common when used in combination with prandial insulin, metformin or metformin with sulphonylurea. If this occurs consider reduction in the dosage of insulin or sulphonylurea.
- Fatigue, sinus tachycardia and first degree atrioventricular block are common
- Injection site reactions are uncommon – if severe, consider cessation of treatment with dulaglutide
- 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 adverse effects

The most frequently reported adverse effects are listed below:

- Gastrointestinal disorders
  - Nausea and diarrhoea are very common, whereas vomiting, constipation, abdominal pain, and dyspepsia are common.
  - At the beginning of liraglutide therapy, these gastrointestinal adverse reactions may occur more frequently and usually diminish within a few days or weeks on continued treatment.
  - Short-term use of antiemetic treatment may be considered. Take steps to avoid dehydration which could cause deterioration of renal function.
  - Escalation of dose from 0.6 mg to 1.2 mg should not be carried out until the symptoms have resolved.

- If symptoms occur on dose escalation to 1.2 mg consider temporary reduction in dosage followed by rechallenge at 1.2 mg. If liraglutide 1.2 mg cannot be tolerated liraglutide therapy should be discontinued (the 0.6 mg dose should not be continued long-term as unlikely to be cost-effective)
- Headache – common and are usually self-limiting
- Nasopharyngitis – common and are usually self-limiting
- Hypoglycaemia – common and very common when liraglutide is used in combination with a sulphonylurea or insulin respectively
  - Major hypoglycaemia has primarily been observed when combined with a sulphonylurea or insulin.
    - If this occurs consider reduction in dosage of sulphonylurea or insulin.
- Injection site reactions – if severe, consider cessation of treatment with liraglutide
- 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](#) and [liraglutide](#).

### 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<sup>2</sup>)
  - *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 receptor agonists 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<sup>2</sup>)
  - *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<sup>2</sup>)
  - *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 subcutaneous 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)
- For a full list of drug interactions, refer to the Summary of Product Characteristics as there are differences between [subcutaneous semaglutide](#), [dulaglutide](#) and [liraglutide](#).

### **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)
- Self-monitoring of blood glucose is not needed in order to adjust the dose of these GLP-1 receptor agonists. 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 receptor agonists 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 receptor agonists 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.
- Subcutaneous semaglutide, dulaglutide and liraglutide are contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

## Contact Details

<b>Barnet Diabetes Integrated Practice Unit (IPU)</b> Diabetes Service	<a href="mailto:CLCHT.barnetdiabetes@nhs.net">CLCHT.barnetdiabetes@nhs.net</a> or 020 8732 6824
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## References

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