CLINICAL GUIDELINE

Diabetes, GLP-1 Initiation Guidance for Primary Care

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:
The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

GLP-1 Initiation Guidance for Primary Care

Purpose of this document is to support initiation of GLP-1 agonists in primary care **when a decision to prescribe has been made in the line with local guidelines and formulary status.** Please refer the NHS GGC Guidelines for the Management of Type 2 Diabetes and NHS GGC Formulary pages for more information.

https://clinicalguidelines.nhsggc.org.uk/endocrine-system/acute-management/management-of-type-2-diabetes-mellitus/

https://ggcmedicines.org.uk/formulary/endocrine-system-6/drugs-used-in-diabetes/antidiabetic-drugs/glp-1-agonists/

Contents

1. Pre-treatment Assessment

See Appendix 1 for prescribing checklist. Ensure the following routine Type 2 Diabetes annual screening parameters are up to date, particularly:

1. HbA1c
2. Weight, height & BMI
3. Renal function
4. LFTs

2. Hba1c targets and monitoring requirements as per NHS GGC Type 2 Diabetes guidelines

- Individual or national targets for HbA1c reduction agreed with the patient.
- At 1 month: It is good practice to review the patient to check adherence, injection technique, injection sites and address any possible side-effects.
- At 3-6 months: It is good practice to offer an appointment to check HbA1c and weight.
    - Consider stopping medication if individualised targets not achieved OR HbA1c falls less than 5.0mmol/mol).

3. Side effects & Drug Interactions

The most common adverse effects are nausea, vomiting, diarrhoea and hypoglycaemia (in context of use with hypoglycaemic agents). The slowing of gastric emptying may reduce the extent and rate of orally administered medicinal products, refer to the individual drug's summary of product characteristics (SmPC) for more details. The individual SmPC should be consulted for full information with respect to adverse effects and drug interactions for each drug:

Dulaglutide: Trulicity 0.75mg 1.5mg 3mg 4.5mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Liraglutide: Victoza 6 mg/ml solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Semaglutide: Ozempic 0.25 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Oral Semaglutide: Rybelsus 3mg tablet – Summary of Product Characteristics (SmPC) – (emc) (medicines.org.uk)

4. Pregnancy & Breastfeeding

- Women of childbearing age can be prescribed a GLP-1 receptor agonist provided they are not at risk of pregnancy. Contraception should be used if sexually active.
- Women planning pregnancy in the future can use GLP-1 receptor agonist meantime, provided they are using adequate contraception. Referral to the pre-pregnancy service should be made for any women with diabetes planning a pregnancy within the next 6 months. The pre-pregnancy clinic will advise when the GLP-1 should be stopped pre-conception.
- Women of childbearing age should be advised of the potential risks as outlined in the BNF:
    - Pregnancy - Manufacturer advises avoid toxicity in animal studies (correct as of Jan 2022).
    - Breast feeding - Manufacturer advises avoid (correct as of Jan 2022).

5. Sick Day rules/ restarting after period of withholding

- Withhold during periods of illness such as diarrhoea, vomiting or when individuals are unable to eat and drink normally.
- Restart when eating and drinking normally.
- See Appendix 2 for advice regarding missed doses and need for re-titration of doses if prolonged periods off the medication.

6. Choice of GLP-1 agonist

Choice between weekly or daily subcutaneous preparations or oral can be made depending on patient factors such as those outlined in Table 1:

Table 1: patient factors to consider when prescribing GLP-1 agonist

Table 1. Patient factors	**Suggested GLP-1 agonist**
Adherence	Daily- liraglutide Weekly- semaglutide/dulaglutide
Manual dexterity/ease of use	Dulaglutide -single use pen with needle already fitted
Needle phobia	Dulaglutide-needle is hidden and individuals with needle phobia may find this preparation acceptable Semaglutide (oral) can be considered if subcutaneous administration is not acceptable.
3rd party administration required	Dulaglutide- risk of needle injury is minimal
Engagement	Dose titration in dulaglutide is optional. Can start at 1.5mg and leave on that dose. Others require dose titration.
Retinopathy	Semaglutide (oral or subcutaneous) **should not** be used in patients with proliferative retinopathy.
Cardiovascular benefit	GLP-1 agonists with proven CV benefit (currently dulaglutide[1], liraglutide[2] or subcutaneous semaglutide)[3] are preferred.

1 Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial - The Lancet

2. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes | NEJM

3. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes | NEJM

7. Dosage and titration.

Table 2 summarised initial doses and titration options. Please refer to the BNF for additional information. See appendix 2 for advice about missed doses or restarting after prolonged period.

Table 2: GLP-1 agonist dosage and administration.

Device	Dosing regimen and available doses	How to initiate	Quantity to prescribe for 28 days
Dulaglutide (Trulicity)	Once weekly. 0.75 mg, 1.5 mg, 3.0mg and 4.5mg in a pen that delivers one of the four doses	1.5mg once weekly. For frailer patients or CKD, consider 0.75mg weekly initially, then up titrate at 4 weekly intervals if tolerated. May increase dose at 4 weekly intervals to 3.0mg then 4.5mg weekly, if HbA1c not to target	One box of 4 pens
Liraglutide (Victoza)	Once daily 1 pen delivers 3 different doses: 0.6 mg, 1.2 mg, or 1.8 mg. SMC doesn't recommend 1.8mg dose.	Initial dose 0.6 mg once daily for 1 week then 1.2 mg daily.	One box of 2 pens and 4mm needles prescribed separately
Semaglutide (Ozempic)	Once weekly 0.25 mg, 0.5 mg or 1 mg in a pen that delivers 4 doses of the given dose.	0.25 mg for 4 weeks then 0.5 mg for at least 4 weeks. Escalate to 1 mg if HbA1c not to target.	One box of one pen (4 needles supplied)
Semaglutide (Rybelsus)	3mg, 7mg and 14 mg tablets, one to be taken daily.	3 mg once daily for one month. Then, 7 mg once daily. Can be increased to 14 mg once daily after 4 weeks to further improve glycaemic control.	3mg, 7mg and 14 mg tablets

At present injectable GLP1 receptor agonists with proven cardiovascular benefit are preferred option. Oral semaglutide is reserved for individuals where subcutaneous preparations are not acceptable.

8. Cautions and contraindications

The purpose of this guide is to support initiation of GLP1 inhibitors when a decision to prescribe has been made in the line with local guidelines and formulary status. Contents of Table 3 below should be considered when initiating this medication. Please refer to individual SmPC for full details.

Table 3 Primary Care Contraindications and Precautions for use of Dulaglutide, Liraglutide or Semaglutide

Type 2 diabetes with suspected beta cell failure	Beta cell failure suggested by rapidly rising HbA1c with weight loss, and usually long duration of diabetes. Consider gliclazide/insulin instead. Consider SCI Gateway referral to secondary care for advice.
Type 1 diabetes/DKA	Not currently licensed. Occasionally prescribed 'off license' as adjuvant therapy to insulin in T1 diabetes but for specialist initiation only.
Renal impairment	No dose adjustment required for, until eGFR <15ml/min when should be stopped. Individuals with renal impairment may be more likely to have side-effects or at risk of dehydration from side-effects, so consider lower starting doses and slower up titration.
Pregnancy and Breastfeeding	Contraindicated
Diabetic retinopathy	Semaglutide: Caution in diabetic retinopathy in those treated with insulin but best avoided in active eye disease. No restrictions with dulaglutide or liraglutide
Liver impairment	Avoid in severe liver failure. Caution if history of bleeding oesophageal varices. No dose adjustment required. Consider referral to secondary care for advice in patients with liver disease not due to NAFLD.
Severe gastrointestinal disease	Caution in gastroparesis, or patients with other causes of nausea and vomiting. Consider SCI Gateway referral to secondary care for advice.
Pancreatitis	Patients should be told how to recognise signs and symptoms of acute pancreatitis and advised to seek medical attention if symptoms such as persistent, severe abdominal pain develop. Caution if previous pancreatitis. Consider SCI Gateway referral to secondary care for advice.
Frail Elderly	Consider benefit/risk ratio, particularly with regards to what alterative therapy would be, considering comorbidity, ability to self-manage and risk of hypoglycaemia. Consider lower starting doses and cautious up titrations. Frail elderly will have a higher HbA1c target and be aware that risk of hypoglycaemia is magnified in elderly.
Hypoglycaemia	Caution in use with other hypoglycaemia inducing medications e.g., sulphonylurea (SU) or insulin. If already on insulin, consider referral to local community DSN for support. If already on SU, consider reducing SU dose on initiation, particularly where individual is close to target.
Dehydration	All contraindicated in severe dehydration to reduce risk of acute kidney failure. Treat as acute kidney injury and stop during periods of infection/illness where dehydration an issue and kidneys compromised. Recommence when oral intake returns to normal.
Thyroid	Caution with personal or family history of medullary carcinoma of thyroid or MEN type 2 syndrome. Consider referral to secondary care for advice.
On insulin	Recommend referral to community Diabetes Nurse Specialist to support safe insulin titration on initiation of GLP1 agonist.

9. Appendix 1. Primary care prescribing checklist for GLP 1 agonist initiation (for patients <u>not</u> on insulin)

- ❑ Discuss commencing GLP-1 and targets
- ❑ Consider providing written information
- ❑ Recommend referral to Glasgow Weight Management Service (GWMS) if have not already
- ❑ Discuss contraception for women of childbearing age.
- ❑ Mode of action and expected side-effects
- ❑ Encourage smaller portions and reduced fatty foods to reduce risk of side-effects
- ❑ Advise on action if severe vomiting, dehydration, or abdominal pain should occur
- ❑ Sick day rules
- ❑ Timing of doses, and action required if missed dose(s)
- ❑ Demonstration of device, injection technique and suitable sites if subcutaneous administration.
- ❑ Advice on requirements for oral semaglutide if applicable (empty stomach, <120mls water, nil to eat or drink for 30mins, including other medications)
- ❑ Adjustments to oral medications (stop gliptins, consider dose reduction of sulphonylurea (SU)
- ❑ Blood glucose monitoring (only if on SU/insulin)
- ❑ Identification and management of hypoglycaemia (only if on SU/insulin)
- ❑ Storage of pens and safe disposal of needles if applicable
- ❑ Plan for dose titrations if applicable
- ❑ Arrange 3–6-month HbA1c and weight check

10. Appendix 2. Missed dose and re-starting after period of withholding

GLP-1 dose	Advice
Dulaglutide weekly subcutaneous (s/c) injection	
0.75 mg 1.5mg	Missed dose can be taken up to 3 days before next scheduled dose. If two or more consecutive doses are missed, restart dulaglutide at the same dose, and then titrate if required (see Table 2).
3.0mg 4.5mg	Missed dose can be taken up to 3 days before next scheduled dose. If two or more consecutive doses are missed, restart dulaglutide at 1.5mg weekly, and then titrate as required (see Table 2).
Liraglutide daily s/c injection	
0.6mg 1.2mg	Resume dosing with next scheduled dose. If dose is missed for more than 3 days, re-start with 0.6mg daily and titrate (see Table 2)
1.8mg	Resume dosing with next scheduled dose. If dose is missed for more than 3 days, re-start with 0.6mg daily and titrate (see Table 2)
Semaglutide weekly s/c injection.	
0.25mg	Missed dose can be taken within 5 days after missed dose.
0.5mg	Missed dose can be taken within 5 days after missed dose. If 2 doses missed, continue with 0.5 mg once weekly. If 3 or more doses missed, re-start with 4 weeks on 0.25 mg once weekly and up titrate as required (See Table 2)
1.0mg	Missed dose can be taken within 5 days after missed dose. If 2 doses missed, continue with 1 mg once weekly. If 3-4 doses missed, re-start with 4 weeks on 0.5 mg once-weekly before escalation to the maintenance dose of 1 mg once-weekly If 5 or more missed doses, then a full dose escalation should be performed (see Table 2)
Semaglutide daily oral tablet	
3mg	Resume dosing with next scheduled dose
7mg 14mg	If a morning dose is missed, the missed dose should be skipped and the next dose should be taken the following day. If a patient misses multiple days, clinical judgement should be used to determine the need for potential dose reductions. Consideration of clinical factors include, but are not limited to, the length of time missed and individual patient factors such as previous tolerability. The half-life (~1 week), and time to steady-state (4-5 weeks) can inform decision and suggests that in established use, several weeks can be missed before full dose titration is required.