NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Diabetes: GLP-1RA and other incretin mimetics
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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Lead Author:	Samina Ali
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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 RA and other incretin mimetics: Initiation Guidance for Primary Care

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

Incretins are gut hormones that aid in digestion and blood glucose control. They include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Incretin mimetics are medications that mimic the functions of incretin hormones.

These functions include among others:

- **Stimulating the release of insulin** by the pancreas after eating, even before blood sugars start to rise.
- **Inhibiting the release of glucagon** by the pancreas, therefore reducing liver glucose production.
- **Slowing glucose absorption into the bloodstream** by reducing the speed at which the stomach empties after eating, leading to earlier feelings of satiety.

Contents

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
5. Note most recent retinopathy screening result

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) and/or weight reduction of less than 5% from baseline. However, it may be appropriate for those with high CV risk on incretin mimetics with proven CV benefit to continue regardless of weight loss.

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 linked below should be consulted for full information with respect toadverse effects and drug interactions for each drug:

Dulaglutide: Trulicity® 0.75mg 1.5mg 3mg 4.5mg solution for injection in pre-filled pen (SmPC)

Liraglutide: Victoza® 6 mg/ml solution for injection in pre-filled pen (SmPC)

Semaglutide: Ozempic® 0.25 mg solution for injection in pre-filled pen (SmPC)

Oral Semaglutide: Rybelsus® 3mg tablet – Summary of Product Characteristics (SmPC)

Tirzepatide: Mounjaro® KwikPen 2.5mg solution for injection in pre-filled pen (SmPC)

Pregnancy & Breastfeeding

- Women of childbearing age can be prescribed an incretin mimetic provided they are not at risk of pregnancy. Contraception should be used if sexually active.
- Possible interaction between tirzepatide and oral contraception. Review as per UKMEC contraception choices, and consider switch to a non-oral option or adding a barrier method as per CKS statement for 4 weeks at initiation and dose changes.
- Women planning pregnancy in the future can use incretin mimetic 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 incretin mimetic should be stopped pre-conception.
- Women of childbearing age should be advised of the potential risks as outlined in the BNF:
    - Breast feeding - Manufacturer advises avoid (correct as of June 2024).
    - Pregnancy - Manufacturer advises avoid toxicity in animal studies (correct as of June 2024).

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.

Choice of incretin mimetic

Choice between weekly or daily subcutaneous preparations or oral can be made depending on patient factors such as those outlined in Table 1. All of these options are on the GGC formulary and suitable for initiation in primary care.

Table 1: suggested incretin mimetic depending on determining factors

Determining factors	**Suggested incretin mimetic**
Adherence	Daily- liraglutide Weekly- semaglutide (subcutaneous)/dulaglutide/tirzepatide
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) and tirzepatide **should not routinely** be used in patients with *proliferative* retinopathy (see Appendix 3). Advice can be sought via cMDT/SCI Gateway if compelling reason to consider
Cardiovascular benefit	Incretin mimetic with proven CV benefit (currently dulaglutide[1], liraglutide[2] or subcutaneous semaglutide[3]) are preferred.
Treatment failure with current GLP1-RA	Tirzepatide
Supply issues	Tirzepatide
Individuals with obesity related complications e.g. obstructive sleep apnoea, steatotic liver disease	Tirzepatide
Switching between incretin mimetics	In primary care we suggest re-titrating from lowest dose, particularly as often switch is due to missed doses. In some cases those established on top doses could be switched to a higher dose. Please seek advice if considering that.

Dosage and titration

Table 2 summarises 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: incretin mimetic 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 (Diavic®)	Once daily 1 pen delivers 3 different doses: 0.6 mg, 1.2 mg or 1.8 mg.	Initial dose 0.6 mg once daily for 1 week then 1.2 mg daily. Dose can be titrated to 1.8mg if needed.	2-3 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 pen (comes with 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
Tirzepatide (Mounjaro®)	2.5mg, 5mg, 7.5mg, 10mg, 12.5mg and 15mg once weekly. NB 5mg, 10mg and 15mg are maintenance doses	2.5mg once weekly for 4 weeks then 5mg once weekly**.** NB – please note that the majority of glucose reduction occurs with the 5mg treatment dose. Doses higher than 5mg can be considered see below.	One Kwikpen and 1 box 4mm needles prescribed separately

Higher doses (>5mg) of tirzepatide can be prescribed following discussion with specialist diabetes services if patient has not achieved HbA1c reduction of at least 5mmol/mol or weight reduction of at least 5% from baseline within 6 months of starting tirzepatide or further weight loss would benefit obesity related complications.

Cautions and contraindications

The purpose of this guide is to support initiation of incretin mimetic 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.

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. Patients on tirzepatide with significant renal impairment should be aware of potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time (likely under secondary care, likely benefits outweigh risk).
Pregnancy and Breastfeeding	Contraindicated
Diabetic retinopathy	Semaglutide and tirzepatide: Caution in proliferative diabetic retinopathy especially in those treated with insulin or high HbA1c. (See Appendix 3 flowchart).
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 MASLD. Patients on tirzepatide with significant liver impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time (likely under secondary care)
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 to recognise signs and symptoms of acute pancreatitis and advised to seek medical attention if such symptoms 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 likely higher HbA1c target. Consider lower starting doses and cautious up titrations.
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 when close to target.
Dehydration	All contraindicated in severe dehydration to reduce risk of acute kidney failure. 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 Receptor agonist.

Appendix 1. Primary care prescribing checklist for incretin mimetic initiation(for individuals <u>not</u> on insulin, if on insulin refer to community DSN)

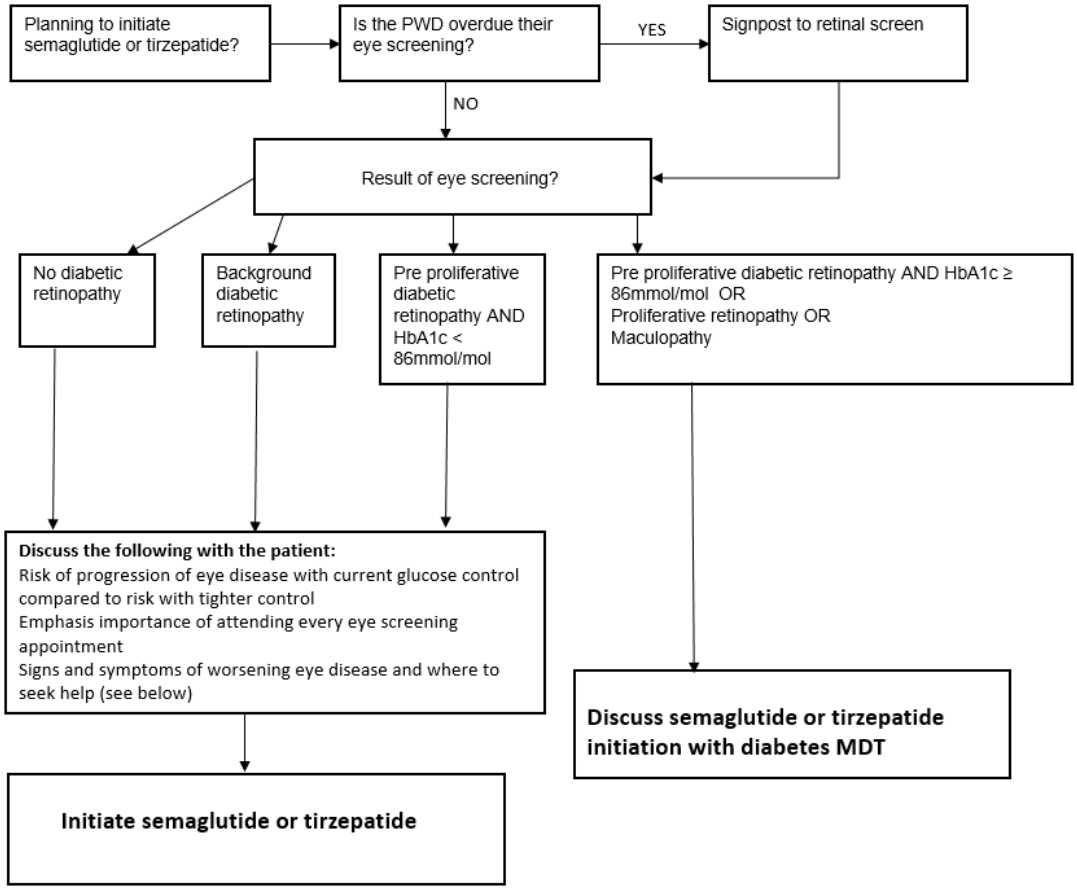
- ❑ Discuss commencing incretin mimetic and HbA1c and/or weight targets
- ❑ Reiterate importance of attending diabetes eye screening appointments
- ❑ Consider providing written information
- ❑ Recommend referral to local weight management services if have not already
- ❑ Discuss contraception for women 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

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

Dulaglutide weekly subcutaneous 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 subcutaneous 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 subcutaneous 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.
Tirzepatide subcutaneous injection	
2.5mg	Missed dose can be taken up to 4 days before next scheduled dose.
5mg 7.5mg 10mg 12.5mg 15mg	If 1 or2 doses are missed, restart at the same dose if the drug was well tolerated prior to period of withholding. If 3 or more doses are missed, restart treatment at 5mg regardless of the dose received prior to withholding period and up titrate as required (See Table 2).

Appendix 3: Retinopathy

Care should be taken in patients with HbA1c ≥86mmol/mol as rapid improvement of glycaemic control can *temporarily* worsen retinopathy. If patients have pre-proliferative or proliferative retinopathy AND HbA1c ≥86mmol/mol discuss with specialist diabetes services (asynchronous review is reasonable). If patient is under the ophthalmology team consider flagging to them that tirzepatide has been started to allow them to bring forward review. People do not require their screening to be brought forward if they did not have proliferative retinopathy on last screen.



If person has symptoms of worsening eye disease (e.g. any new change in vision or new eye symptoms) following initiation of the incretin mimetic, they should be referred to ophthalmology if they are under their care. If they are not under ophthalmology care, then they should be referred to their local optometrist urgently.

Consider slower titration of incretin mimetic if HbA1c >86mmol/mol and there is concern there may be worsening of eye symptoms flowing rapid improvement of glycaemic control.

For further information on grading of diabetic retinopathy, see Scottish diabetic retinopathy grading scheme

PWD= person with diabetes

References

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