BEDFORDSHIRE, LUTON AND MILTON KEYNES(BLMK) AREA PRESCRIBING COMMITTEE (APC)

Guidance for Prescribing Glucagon-like peptide 1 (GLP 1) agonists for adults with Type 2 Diabetes (T2DM)

(December 2022)

The recommendations in this guidance sheet written by the Medicines Optimisation team with the support of the BLMK Long-Term Conditions (LTC) Diabetes group aligns with current NICE guidance for prescribing and monitoring of GLP-1 agonists for adults with type 2 diabetes and should be read in conjunction with the Summary of Products Characteristics (SPC) of each agent.

The following organisations contribute to and participate in the BLMK APC – Bedfordshire, Luton and Milton Keynes Clinical Commissioning Group; Bedfordshire Hospitals NHS Foundation Trust; Cambridgeshire Community Services NHS Trust; Central and North West London NHS Foundation Trust; East London NHS Foundation Trust; Milton Keynes University Hospital NHS Foundation Trust

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Glucagon-like peptide 1 (GLP 1) agonists for adults with Type 2 Diabetes (T2DM)

Background

GLP-1 agonists bind to and activate GLP-1 receptors to stimulate insulin secretion, lowering glucagon secretion when blood glucose is high, and delaying gastric emptying in the early post-prandial phase.

NICE Guideline NG28 Type 2 diabetes in adults: management set tight limits on when a GLP- 1 agonist can be offered as a cost-effective option for the treatment of adults with type 2 diabetes(T2DM). The recommendation in this document therefore aligns with current NICE guidance for prescribing and monitoring of GLP-1 agonists and should be read in conjunction with the Summary of Products Characteristics (SPC) of each agent. There are currently 5 Glucagon-like peptide (GLP 1) agonists(mimetics) licensed for use by subcutaneous(s/c) injection: - Liraglutide (Victoza®), Semaglutide (Ozempic®), Dulaglutide (Trulicity®), Exenatide (Byetta®, Bydureon®), Lixisenatide (Lyxumia®). In addition, an oral preparation of Semaglutide (Rybelsus®) has been licensed for use.

Indication and place in therapy

For the treatment of adults with insufficiently controlled type 2 diabetes (T2DM) to improve glycaemic control as an adjunct to diet and exercise.

As per NICE NG28 :
If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated, or contraindicated, consider triple therapy by switching one drug for a GLP-1 agonist for adults with type 2 diabetes 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.

GLP-1 agonist continuation criteria

Only continue GLP-1 agonist therapy if the adult with type 2 diabetes(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).

Initiation of injectable GLP-1 agonist

GLP1-agonist preparations can be initiated by **Diabetes Specialist Team** or a **General Practice Diabetes Specialist** or **healthcare professional(HCP) in GP Practice** with relevant expertise and experience in management of type 2 diabetes(T2DM). The Integrated Community Diabetes Service [ICDS] or Integrated Diabetes Service [IDS] across BLMK are able to support with training and education. Initiation should be in accordance with NICE recommendations and licensed indications- *Refer to SPC.*

Initiation of Oral Semaglutide (Rybelsus®)

Oral semaglutide (Rybelsus®) can be initiated by **Diabetes Specialist Team** or a **General Practice Diabetes Specialist** or **healthcare professional (HCP) in GP Practice** with relevant expertise and experience in management of type 2 diabetes(T2DM). It can be offered where subcutaneous(s/c) preparation is not tolerated, unsuitable or based on patient preference. Patient should be counselled on specific daily dosing requirements.

Prescribers should note that the effect of switching between oral and s/c semaglutide cannot easily be predicted because of the high pharmacokinetic variability of oral semaglutide. Clinical effectiveness should be considered when making switching decisions between formulations. An oral dose of semaglutide 14 mg once daily is comparable to s/c semaglutide 0.5 mg once weekly.

Preferred Formulary Choices

Joint first line choices:

Subcutaneous injection preparations of: -

- Dulaglutide (Trulicity®) once weekly – NB: maintenance dose of dulaglutide is usually 1.5mg. For additional glycaemic control doses >1.5mg can be considered in exceptional circumstances and only after consultation with the Specialist Diabetes Team. Maximum recommended dose is 4.5mg.
- Liraglutide (Victoza®) once daily – NB: maximum recommended dose of liraglutide is 1.8mg.
- Semaglutide (Ozempic®) once weekly – NB: maximum recommended dose of semaglutide is 1 mg. Weekly doses higher than 1mg are not recommended.

Joint first line choice (if the subcutaneous injection preparations outlined above are unsuitable)

- Oral Semaglutide (Rybelsus®) – once daily. NB: maximum recommended dose is 14mg daily.

Non-Formulary (no new initiations/existing patients may remain on these medicines):

- Exenatide (Bydureon BCise ®)- once weekly preparation
- Exenatide (Byetta®) – twice daily preparation
- Lixisenatide (Lyxumia®)- once daily preparation

Not recommended: -

- Xultophy® (insulin degludec/liraglutide combination)

Co-prescribing a GLP-1 agonist with other blood glucose lowering agents

- With dipeptidyl peptidase 4 inhibitors (DPP 4) inhibitors: *not advisable to combine as they both work on same pathway and would be a waste of resources.*
- With metformin, thiazolidinedione: *can be combined.*
- With a sodium-glucose co-transport - 2(SGLT2) inhibitor: *acceptable to combine but note high cost when combined.*
- With a sulphonylurea (SU): *can be combined* (*consider reducing the dose of SU if there is risk of hypoglycaemia).*
- With insulin – *offer in line with NICE Guideline NG28 i.e., only offer combination therapy with a GLP-1 agonist and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team or* ***Diabetes Specialist Team.***

Table 1: GLP-1 AGONIST CONTRAINDICATIONS AND PRECAUTIONS- Please see individual **SPC** for comprehensive information

Type 2 diabetes and suspected beta cell failure	Consider insulin instead as GLP-1 agonists requires effective beta cell function.
Type 1 diabetes /diabetes ketoacidosis (DKA)	Contraindicated.
Renal Impairment	**Semaglutide (s/c and oral):** No dose adjustment for mild, moderate, or severe renal impairment. Not recommended in end-stage renal disease. **Dulaglutide:** No dose adjustment for mild, moderate, or severe renal impairment (eGFR < 90 to ≥ 15 mL/min/1.73 m^2). Contraindicated if estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 **.** **Liraglutide:** No dose adjustment for mild, moderate, or severe renal impairment**.** Not recommended in end-stage renal disease.
Hepatic impairment:	**Semaglutide (s/c and oral):** No dose adjustment required. Caution in severe liver impairment due to lack of data**.** **Dulaglutide:** No dose adjustment. **Liraglutide:** No dose adjustment for mild, moderate hepatic impairment. Not recommended for use in patients with severe hepatic impairment.
Pregnancy, paternal exposure, and breastfeeding	All contraindicated. Women of childbearing potential are recommended to use contraception when treated with GLP-1 agonists. Discontinue treatment before planning pregnancy. Consult individual **SPC** for comprehensive information. (e.g., Semaglutide SPC recommends at least 2 months before due to long half-life).
Diabetic Retinopathy	**Semaglutide:** Caution in patients with diabetic retinopathy treated with insulin due to an increased risk of developing diabetic retinopathy complications.
Gastrointestinal disease	Not recommended in severe gastrointestinal disease e.g., gastroparesis, as GLP-1 agonists are associated with transient gastrointestinal adverse reactions, including nausea, vomiting and diarrhoea.
Pancreatitis	GLP-1 agonists have been associated with a risk of developing acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected GLP-1 agonist should be discontinued; if confirmed it should not be re-started.

Thyroid disease	**Liraglutide:** Caution in patients with pre-existing thyroid disease. **Semaglutide:** Caution if patients are being treated with semaglutide at same time as with levothyroxine, monitoring of thyroid parameters should be considered.
Hypoglycaemia	Increased risk of hypoglycaemia in patients treated with GLP-1 agonists with a sulphonylurea (SU) or insulin. Risk can be lowered by reducing dose of SU or insulin.
Dehydration	Advise of potential risk of dehydration, particularly in relation to gastrointestinal adverse reactions and to take precaution to avoid fluid depletion.
Clinically relevant drug interactions and advice on management	Please see individual **SPC** for comprehensive information Discuss with Diabetes Specialist Team and seek advice on any aspect of patient care that is of concern and may affect treatment.

Pre-treatment Assessments

Ensure routine type 2 diabetes(T2DM) annual screening tests are up to date, particularly:

- HbA1c
- Weight, Height, and BMI
- Renal Function

Recommended Monitoring and Follow up

After initiation patient should be monitored/followed up at the following intervals.

- At 1 month – review compliance, injection technique, injection site and discuss any possible side-effects.
- At 3 months – check HbA1c, weight, review compliance and discuss any possible side-effects.
- At 6 months – check efficacy of treatment by checking HbA1c and weight. Compare measurements with those taken at baseline and confirm whether patient meets NICE continuation criteria.
- At 12 months - Consider discontinuing treatment if the response at 6 months is not maintained, taking into consideration the progressive nature of type 2 diabetes.

Table 2: GLP-1 AGONIST DOSAGE AND ADMINISTRATION

Drug	Dulaglutide (Trulicity®) SPC	Semaglutide (Ozempic®) SPC	Liraglutide (Victoza®) SPC	Semaglutide (Rybelsus®) SPC
Starting dose	1.5 mg s/c once weekly. If >75 years, 0.75 mg s/c once weekly. Titrate if tolerated.	0.25 mg s/c once weekly for 4 weeks.	0.6 mg s/c once daily for at least one week.	3 mg once daily for 1 month.
Titration if tolerated	1.5 mg s/c once weekly.	Increase to 0.5 mg s/c once weekly for at least 4 weeks. Increase again, if necessary to 1 mg s/c weekly after 4 weeks.	Increase to 1.2 mg s/c daily for at least 1 week, then increase, if necessary (seek advice from Diabetes Specialist Team), to 1.8mg s/c once daily.	Increase to 7mg once daily after 1 month. Increase again to 14mg after 1 month.
Maintenance dose	1.5 mg s/c one weekly. Doses > 1.5mg s/c once daily only in exceptional cases and following discussion with Diabetes Specialist Team.	1 mg s/c once weekly	1.2 mg s/c once daily. If further increase to 1.8mg s/c once daily is necessary, seek advice from Diabetes Specialist Team.	14mg once daily
Method of Administration	Injected subcutaneously in the abdomen, in the thigh or in the upper arm.			Oral
When to administer	At any time of day. Not related to meals.	At any time of day. Not related to meals.	At any time of day. Not related to meals.	On an empty stomach at any time of the day. Wait at least 30mins before eating or drinking or taking other oral medicines (NB: intake with food or large volumes of water decreases the absorption of semaglutide).
Missed dose	Administer at least 3 days (72 hours) until the next schedule dose.	Can be given up to 5 days after the missed dose.	If a dose is more than 12 hours late, the missed dose should not be taken. The next dose should be taken at the normal time	Skip and take the next dose the following day.

Conditions requiring dose adjustment advice and guidance

Healthcare professionals in General Practice may seek advice and guidance (as appropriate) from the **Diabetes Specialist Team** *(if any of these applies):*

- Problems arise tolerating the GLP 1 agonist or if the GLP 1 agonist must be discontinued for other medical reasons.
- Patient develops any acute/serious diabetes complications.
- The patient is a woman with diabetes who is planning a pregnancy or becomes pregnant. If the patient becomes pregnant, treatment should be stopped immediately, and the patient urgently referred to the **Diabetes Specialist Team.**
- The patient is receiving maintenance dose and following shared decision making, higher dose (within marketing authorisation) would be beneficial
- Use of a GLP 1 agonist outside NICE guideline recommendation is being considered

Use of GLP-1 agonists in combination with insulin in patients with type 2 diabetes

NICE NG28 contains very little detail pertaining to the use of insulin in combination with GLP 1-agonists.

For adults with type 2 diabetes, only offer combination therapy with a GLP-1 agonist and insulin along with specialist care advice and ongoing support from a consultant-led multidisciplinary team. See appendix 3 for agreed local inclusion criteria.

Criteria for continuation of therapy

Patients receiving GLP-1 agonist	6-month review	Only continue GLP-1 agonist therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight.
	12-month review	Consider discontinuing treatment if the response at 6 months is not maintained, taking into consideration the progressive nature of type 2 diabetes.
Patients receiving insulin and GLP-1 agonist combination	6-month review	The GLP 1 agonist should be stopped if the HbA1c has not fallen by at least 5mmol/mol.
	12-month review	The GLP 1 agonist should be stopped if none of the following apply • Improvement in HbA1c ≥ 11mmol/mol [1.0%] **and** weight reduction ≥ 3% Or • Improvement in HbA1c ≥ 11mmol/mol [1.0%] **and** patient is taking human insulin Or • Improvement in HbA1c ≥ 5mmol/mol [0.5%] **and** weight reduction ≥ 10%
	Beyond 12 months	Consider discontinuing treatment if the response at 12 months is not maintained, taking into consideration the progressive nature of type 2 diabetes.

Key References

- Ozempic 0.5 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)- Accessed 20/05/2022
- Victoza 6 mg/ml solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)- Accessed 20/05/2022
- TRULICITY 0.75mg 1.5mg 3mg 4.5mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)-Accessed 20/05/2022
- Rybelsus - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)- Accessed 20/05/2022
- Bydureon (BCise) - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) – Accessed 31/05/2022
- Byetta 10 micrograms solution for injection, prefilled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)- Accessed 31/05/2022
- Lyxumia 10 micrograms solution for injection - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)- Accessed 31/05/2022
- NG28 Type 2 diabetes in adults: management – Accessed – 31/05/2022

Contact Details for Diabetes Specialist Teams

Bedford/Central Bedfordshire

North and Central Beds - Integrated Community Diabetes Service
Telephone: 01234 792297
Fax: 01234 792180

South Bedfordshire- Integrated Community Diabetes Service
Telephone: 01582 718431

Bedfordshire Hospital Foundation Trust (BHFT) - Bedford Hospital Site
Diabetes Specialist Nurses:
Advice line: 01234 730586
Fax: 01234 792180

Luton

Luton - Integrated Community Diabetes Services
Telephone: 0333 405 313
Email: ccs-tr.diabetesluton@nhs.net
MDT Referral: blmkicb.diabetespharmacist@nhs.net

Bedfordshire Hospital Foundation Trust (BHFT) - Luton and Dunstable Hospital Site
Diabetes Specialist Nurses:
Telephone: 01582 718050

Milton Keynes

Milton Keynes Integrated Diabetes Service
NPMC@Willen
Beaufort Drive
Willen
Milton Keynes
MK15 9EY

Tel No. 01908 619765
Email: mk.ids@mkuh.nhs.uk

Appendix 1. **Definitions**

The following definitions will apply wherever the following terms appear:

Diabetes Specialist Team – Integrated Community Diabetes Service [ICDS] or Integrated Diabetes Service [IDS], Specialist [Diabetes] Primary Care Pharmacists, Secondary/Tertiary Care Specialist Diabetes Teams.

General Practice Diabetes Specialist – Healthcare professional in General Practice with appropriate specialist expertise in management of diabetes and have experience/training in the use of these medicines. (Excludes Specialist [Diabetes] Primary Care Pharmacists who are covered by the 'Diabetes Specialist Team' definition above).

Appendix 2. **Prescribing checklist for GLP 1 agonist initiation**

 Discuss commencing GLP-1 agonist and targets (HbA1c and Weight).

 Consider providing patient information (written or electronic copies).

 Discuss lifestyle options including referral to appropriate weight management programme (including digital options).

 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)*.

 Adjustments to oral medications (stop DPP-4, consider dose reduction of SU and insulin)

 Blood glucose monitoring (only if on SU/insulin).

 Identification and management of hypoglycaemia. Adjustments to doses of SU/insulin.

 Storage of pens and safe disposal of needles *(if applicable).*

 Plan for GLP-1 agonist dose titrations.

 Arrange 3-month HbA1c and weight check

 Discuss discontinuation of GLP-1 agonist if criteria for continuation are not met

Appendix 3: **GLP-1 agonists in combination with insulin**

NICE NG28 contains very little detail pertaining to the use of insulin in combination with GLP 1-agonists.

Inclusion Criteria for use of GLP1 agonists in combination with insulin in patients with type 2 diabetes: -

- Clinician should give consideration to the length of time a patient has been receiving insulin / duration of time since diagnosis of diabetes as GLP 1 agonists potentiate endogenous insulin secretion and therefore may have limited efficacy in patients with limited beta cell functional capacity.
- Consider patient acceptability (insulin and GLP 1 agonist regimens will involve multiple daily injections).
- Patients who are on an insulin analogue should be reviewed and switched to human insulin where possible (and if appropriate) before a GLP 1 agonist is started.
- Review dose of basal insulin before starting a GLP 1 agonist – consider reducing the dose of basal insulin in patients at increased risk of hypoglycaemia when adding a GLP 1 agonist. Any reduction in insulin dose should be calculated and recorded.
- The patient must fit the following criteria for starting a GLP 1 agonist:

1) Body mass index (BMI) ≥ 35 kg/m² in those of European family origin (adjust accordingly for people from Black, Asian, and other minority ethnic groups) and specific psychological or other medical problems associated with obesity

or

Body mass index (BMI) < 35 kg/m², and weight loss would benefit other significant obesity-related comorbidities

2) Patient's HbA1c still not to target agreed with the individual, **AND ONLY IF**:

- there are concerns associated with intensifying the insulin regimen (e.g., clinical reasons, practical reasons, or patient refuses).

or

- further weight gain (expected with intensification of insulin) would be of significant concern (e.g., patient has obesity co-morbidities – sleep apnoea, mobility / musculoskeletal issues / CHD / heart failure/ NASH)

or

- previous attempts at intensification of insulin regimen have been unsuccessful in reducing HBA1c to acceptable target.

3) Agreement that the GLP-1 agonist will be discontinued at 6 month or 12-month review date, and beyond if the required criteria for continuation are not met**.**