Prescribing guideline: The combination of a glucagon like peptide-1 receptor agonist (GLP-1 RA) or dual long acting Glucose-dependent Insulinotropic Polypeptide agonist (GIP) with GLP-1RA and insulin for adults who have poorly controlled type 2 diabetes (T2DM)

AMBER INITIATION: RECOMMENDED FOR RESTRICTED USE – for initiation and stabilisation by community or secondary care and continuation in primary care.

The following guidelines provide information relating to the combination of GIP/GLP-1RA or GLP-1 RA and insulin therapy in adults with poorly controlled T2DM. The expectation is that these guidelines will enable prescribers in general practice to identify appropriate patients for referral to specialist care and support primary care in continuing and monitoring these medications once they have been stabilised by the diabetes specialist team.

As per the NICE guidelines 28 on the treatment of T2DM in adults and NICE TA 924 (Tirzepatide for treating T2DM) as follows:
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 mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjusted to BMI of 30 kg/m^2 (local adjustment agreed) 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/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team.

When should patients be referred to the specialist diabetes team:
A healthcare prescriber in general practice should refer a patient to a specialist diabetes team in the following scenarios:

- Where a patient is established on insulin therapy and requires further control with a GIP/GLP-1RA or GLP-1RA
- A patient is established on a GIP/GLP-1RA or GLP-1RA, but their diabetes control is suboptimal and may require additional insulin therapy.

The specialist diabetes team will review the patient according to the following inclusion criteria for the use of GIP/GLP-1RA or GLP-1RA in combination with insulin:

- Patient has seen a dietician or demonstrated an attempt to lose weight over the previous 6 months
- Suboptimal glucose control with a HbA1C ≥ 69mmol/mol
- Patients should have reasonable ß-cell functional capacity - therefore consideration should be given to the length of time a patient has been receiving insulin or the length of time they have had a diagnosis of diabetes. GIP/GLP-1RA or GLP-1 RAs may potentiate endogenous insulin secretion and therefore may have limited effect in those with poor beta cell reserve.
- Dipeptidyl peptidase-4 inhibitors should be stopped when adding a GIP/GLP-1RA or GLP-1RA.

- Patients who are on insulin analogues should be reviewed and switched to human insulin where possible (and if appropriate) before a GIP/GLP-1RA or GLP-1 RA is started.
- All patients should have had a retinal scan within the last year prior to initiating treatment.

The specialist diabetes team will initiate the appropriate GIP/GLP-1RA or GLP-1 RA
The following are the first line choices of GLP-1 RAs due to evidence of favourable cardiovascular outcomes:
Subcutaneous injection preparations of:

- Dulaglutide (Trulicity®)
- Semaglutide (Ozempic®)
- Liraglutide (Victoza®)

Tirzepatide (GIP/GLP-1RA) is an option for use with insulin (NICE TA 924). Note: The cardiovascular outcomes of tirzepatide (Mounjaro®) have not been established. SURPASS-CVOT aims to provide evidence of the CV safety and efficacy of tirzepatide as compared with dulaglutide. This trial is currently ongoing.

Liraglutide (Saxenda®) brand is not licensed for treatment of insufficiently controlled T2DM Use of Saxenda® is restricted to managing overweight and obesity and for prescribing by specialist multidisciplinary tier 3 weight management services only. It is not recommended for primary care prescribing.

No new initiation of exenatide (Bydureon BCise®)is recommended, but existing patients may remain on exenatide (Bydureon BCise®) provided they are achieving treatment goals and are at low risk of cardiovascular disease.

Oral Semaglutide (Rybelsus®) is, as per local agreement, restricted to patients who are unable to tolerate injections, those with needle phobia or those unable to self-administer and with no carer support. Patients covered by this guideline would be able to tolerate injections (as they are on/being considered for insulin) and therefore use of Rybelsus® is not applicable to these guidelines (**Note**: During the national shortage of GLP-1 RAs, this restriction is temporarily suspended until supply issues have resolved or national guidance is updated). The CV outcomes trials for oral semaglutide showed CV safety but does not show a statistically significant cardiovascular risk reduction.

Specialist diabetes team responsibilities on initiation is to discuss and confirm risks and benefits of treatment including hypoglycaemia, monitoring and actions to take. Patients should be informed of the risks, signs and symptoms of diabetic ketoacidosis and acute pancreatitis and advised to seek immediate medical attention if these develop.

When a GIP/GLP-1RA or GLP-1RA is used with insulin, a reduction of the insulin dose will be required initially to prevent the increased risk of hypoglycaemia and increased risk of retinopathy (due to sudden improvement in control of diabetes).

The following will be monitored by the specialist diabetes team:

1st Review: To review the patients' concordance, injection technique, injection sites and address any possible side-effects.
At 6 months: Record HbA1c, weight and confirm whether the GIP/GLP-1RA or GLP-1 RA meets NICE continuation criteria (below). Compare six-month measurements with targets recorded at base line.

The specialist service will prescribe and titrate the dose of a GIP/GLP-1RA or GLP-1RA to a stable maintenance dose for a minimum of 3 months before requesting primary care to take up on-going prescribing.

NICE NG 28 GIP/GLP-1RA or GLP-1 RA continuation criteria at SIX MONTHS

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

The monitoring of patients on combination insulin and GIP/GLP-1RA or GLP-1 RA therapy may be continued in primary care after being stabilised on a maintenance dose for a minimum of 3 months ONLY if the patient has already reached the expected 6-month target for continuation of therapy. Otherwise, monitoring of the treatment should be retained by the specialist diabetes team until after the 6-month review.

Monitoring requirements after the 6-month review in primary care:

1. Monitor HbA1c levels every 3 months until stable for 6 months. Then measure HbA1c 6 monthly thereafter.
2. BMI should be calculated and recorded at each visit. Any weight reduction or increase should be recorded at **12 months**.
3. Change in insulin requirements should be recorded at each visit – this will help establish a trend which may be useful for the specialists should the patient need to be referred back if their diabetes becomes unstable.
4. Monitor renal function every 6 months- if patients eGFR falls below 15ml/min, seek urgent advice from the specialist diabetes team.
5. Patients should have regular annual retinal screening.

Prescribers in primary care should refer back to the specialist diabetes team for review or advice where:

1. A patient is unable to tolerate GIP/GLP1RA or GLP-1 RA or if the GIP/GLP1RA or GLP-1RA must be discontinued for other medical reasons.
2. Diabetes control becomes unstable based on number of hypoglycaemia episodes or HbA1c becomes out of target.
3. Patient develops any acute/serious diabetes complications.
4. Patients with worsening diabetic retinopathy.
5. If pancreatitis is suspected, the GIP/GLP1RA or GLP-1RA should be discontinued; if acute pancreatitis is confirmed then the GIP/GLP1RA or GLP-1 RA should not be restarted.
6. The patient is a woman with diabetes who is planning a pregnancy or becomes pregnant. If the patient becomes pregnant, GIP/GLP1RA or GLP-1RA treatment should be stopped immediately and the patient urgently referred to the **specialist care**.

Stopping Criteria for GIP/GLP1RA or GLP-1 RA therapy (applicable at any time point)

- Patient choice
- Drug intolerance
- Occurrence of any contra-indication to treatment
- Failure to meet continuation criteria
- Failure to attend for blood tests and clinical reviews
- Pregnancy or planning a pregnancy

Related safety alerts:

MHRA warning June 2019: GLP-1 receptor agonists: reports of diabetic ketoacidosis when concomitant insulin was rapidly reduced or discontinued in patients with T2DM (June 2019). Healthcare professionals are advised that any dose reduction of insulin should be done in a stepwise manner with careful blood glucose self-monitoring, particularly when GIP/GLP-1RA or GLP-1 agonist therapy is initiated. Patients should be informed of the risks, signs and symptoms of diabetic ketoacidosis and advised to seek immediate medical attention if these develop.

Contact details for the diabetes team

Herts Valleys integrated diabetes service (HIDS):
Community Diabetes Specialist Service
Sandridge Gate
Ronsons Way
St Albans
AL4 9XR
Telephone: 01727 732073
Email: hids.diabetes@nhs.net

Acute (HIDS) service:
Michael Clements Diabetes centre
Watford General Hospital,
Vicarage Road,
Watford,
Herts.
WD18 0HB
Telephone: 01923 244 366

All referrals to the HIDS team should be made through ERS using SOPC form.

East and North Herts - HCT Community Diabetes Service

Tel: 0300 123 7571
Email: HCT.CommunityENDiabetes@nhs.net
All referrals to the HCT Community diabetes service should be made through ESR.

East and North Herts - Acute Diabetes Service

Acute patient advice line: 01438 288 301
E-mail: diabetes.enh-tr@nhs.net

Community Diabetes Service West Essex
Diabetes Patient Advice Line (9:30-12:30): 0333 015 3481

Diabetes Appointment Line: 01702 372081

Diabetes Health Care Professional Line: 01702 372082 (09:00-17:00)

Email: Diabetes.one@nhs.net

Healthcare professionals can refer patients by completing the referral form.

Version	2.0 - Published June 2024 – Updated to include a). Addition of Tirzepatide following NICE TA924. b). Addition of information on oral semaglutide (Rybelsus ®) as an option for use during market shortages for GLP-1 RA. c) Updates on contact details for diabetes teams.
Developed by	Pharmacy and Medicines Optimisation Team, Hertfordshire and West Essex (HWE) ICB with relevant HWE ICS stakeholders.
Approved by	Hertfordshire & West Essex Area Prescribing Committee
Date approved / updated	November 2023 (Tirzepatide approved in line with NICE TA 924). Comparison document updated following product launch and addition to drug tariff in May 2024.
Review date	This HWE APC recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.
Superseded version	1.0 Prescribing guideline: The combination of a glucagon like peptide-1 (GLP-1) agonist and insulin for patients who have poorly controlled type 2 diabetes (T2DM) – Hertfordshire Medicines Management Committee (January 2022)

References

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- Buckinghamshire Clinical Commissioning Group and Buckinghamshire Healthcare NHS Trust. Glucagon-like peptide (GLP-1) agonists for adults with type 2 diabetes initiation in secondary or primary care. Accessed November 2021- http://www.bucksformulary.nhs.uk/docs/Guideline_109FM.pdf
- Bedfordshire Clinical Commissioning Group and Luton Clinical Commissioning Group. Bedfordshire and Luton joint prescribing committee (JPC). Overarching shared care guideline for Glucagon-like-peptide-1 (GLP 1) agonists. Accessed November 2021- https://medicines.blmkccg.nhs.uk/wp-content/uploads/2020/05/GLP-1-agonist-overarching-shared-care-guideline-Final-December-2020.pdf