Hertfordshire and West Essex Integrated Care System

NHS Hertfordshire and West Essex Integrated Care Board

Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) and dual long-acting Glucose-dependent Insulinotropic Polypeptide agonist (GIP) with GLP-1 RA in adults with Type 2 Diabetes (T2DM)

- There are currently four GLP-1 RAs (dulaglutide, exenatide, liraglutide and semaglutide) and one long-acting dual GIP/GLP-1 RA (tirzepatide) licensed in the UK for the management of adults with T2DM.
- Treatment should be individualized based on patient preferences and patient characteristics. Liraglutide (Victoza®), dulaglutide (Trulicity®) and semaglutide (Ozempic®) have proven cardiovascular (CV) benefits.
- No new patients should be initiated on exenatide (Bydureon BCise®). Existing patients who are on exenatide are to be reviewed and treatment should only continue in those who are achieving treatment goals and are at low risk of CV disease. Where patients are not meeting treatment goals, the patient should preferably be switched to a GLP-1 RA with CV benefits.
- GREEN initiation- **Semaglutide (Ozempic®) or semaglutide (Rybelsus®)* or dulaglutide (Trulicity®) or liraglutide (Victoza®)-** Initiation and dose titration in primary care restricted to patients with no or mild diabetic retinopathy by clinician with special interest and relevant training.
- AMBER INITIATION- **Semaglutide (Ozempic®) or semaglutide (Rybelsus®)* or dulaglutide (Trulicity®) or liraglutide (Victoza®)-** Initiation by specialists in secondary and community setting in patients with moderate or severe retinopathy or maculopathy.
- AMBER INITIATION- Patients who are on liraglutide 1.8mg may continue with this dose but new patients should only be titrated to this dose if weekly GLP-1 RAs are not tolerated.
- AMBER INITIATION- **Tirzepatide (Mounjaro®)-** initiation by specialists in community, secondary or tertiary care and continuation in primary care. Primary care clinicians with special interest in diabetes may initiate.
- AMBER INITIATION- **Combination GIP/GLP-1RA or GLP-1RA and insulin therapy-** for initiation and stabilisation by specialist community or secondary care services and continuation in primary care.

***Oral **semaglutide (Rybelsus®)** is restricted for use in patients who are unable to tolerate injections, or those with needle phobia or those unable to self-administer and with no carer support. The CV outcomes trials for oral semaglutide showed CV safety but does not show a statistically significant cardiovascular risk reduction. (**Note**: During the national shortage of GLP-1 RAs, this restriction is temporarily suspended until supply issues have resolved or national guidance is updated).

NICE Clinical Guideline 28 (T2DM in adults) and NICE TA 924 (Tirzepatide for treating T2DM)

NICE makes recommendations for when GLP-1 RAs can be considered in adults with T2DM; Hertfordshire and West Essex Area Prescribing Committee Recommendations are in line with NICE guidance:

If TRIPLE therapy with metformin and 2 other oral drugs is not effective, not tolerated, or contra-indicated, consider triple therapy by switching one drug for a GLP-1 mimetic for adults with T2DM 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.

➢ Only continue GLP-1 mimetic therapy if the person with T2DM 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 in 6 months) [NICE NG28].

Comparative data

Name of drug	Liraglutide (Victoza®)	Dulaglutide (Trulicity®)	Semaglutide (Ozempic)®	Semaglutide (Rybelsus)®	Tirzepatide (Mounjaro®)
Formulation	Subcutaneous	Subcutaneous	Subcutaneous	Oral	Subcutaneous
Mechanism of action	GLP-1 RA	GLP-1 RA	GLP-1 RA	GLP-1 RA	Dual GIP and GLP-1RA
Frequency	Daily	Weekly	Weekly	Daily	Weekly
Dosing information	Administered once daily at any time, independent of meals. It is preferable that Victoza is injected around the same time of the day. • Start at 0.6mg daily for 1 week then increase to 1.2mg • Patients who are on liraglutide 1.8mg may continue with this dose but new patients should not be titrated to this dose as it is not cost effective. If a dose is more than 12 hours late, the missed dose should not be taken and the next dose should be taken at the normal time. Should be stored in a refrigerator (2-8°C). After first use store under 30°C. or store in a refrigerator (2-8°C).	Administered once weekly at any time of day, with or without meals. Only approved for add on therapy: 1.5mg/week. (Locally and as per NICE we do not recommend monotherapy). For additional glycaemia control the dose can be increased after at least 4 weeks to 3mg once weekly. The 3mg dose may be increased after at least 4 weeks to 4.5mg once weekly, the maximum dose is 4.5mg weekly. For potentially vulnerable populations 0.75mg once weekly can be considered as a starting dose. 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. Should be stored in a refrigerator (2-8°C) but may be stored unrefrigerated for up to 14 days at up to 30°C.	Administered once weekly at any time of the day, with or without meals. The starting dose is 0.25mg semaglutide once weekly. After 4 weeks the dose should be increased to 0.5mg once weekly. After at least 4 weeks with a dose of 0.5mg once weekly, the dose can be increased to 1mg once weekly to further improve glycaemic control. Weekly doses higher than 1mg are not recommended. If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. Should be stored in a refrigerator (2-8°C). After first use store under 30°C or store in a refrigerator (2-8°C).	Administered once daily at any time on waking with a sip of water (up to 120ml), on an empty stomach, swallowed whole. Should wait at least 30 minutes before eating or drinking or taking any other medicinal products. Initially 3mg daily increasing after one month to 7mg daily. After a further month increase to max 14mg daily to further improve glycaemic control. Taking two 7mg tablets to achieve the effect of 14mg is not recommended. If a dose is missed, the missed dose should be skipped and the next dose should be taken the following day.	Administered once weekly at any time of the day, with or without meals. The starting dose is 2.5mg tirzepatide once weekly. After 4 weeks the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose. The maximum dose is 15 mg once weekly. If a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. Should be stored in a refrigerator (2-8°C) but may be stored unrefrigerated for up to 30 days at up to 30°C.

CV benefit	Yes	Yes	Yes	Not established	Not established
Effect on HbA1C	Lowering effect	Lowering effect	Lowering effect	Lowering effect	Lowering effect
Effect on weight	Benefit	Benefit	Benefit	Benefit	Benefit
Renal Impairment	No dose adjustment required for patients with mild, moderate or severe renal impairment. Avoid in patients with end stage renal disease (eGFR<15ml/min) due to the lack of evidence.				No dose adjustment required for patients with renal impairment. Caution should be exercised in patients with severe renal impairment and end stage renal disease due to limited experience.
Hepatic Impairment	Not recommended for use in patients with severe hepatic impairment.	No dosage adjustment	No dose adjustment is required for patients with hepatic impairment. Experience with the use in patients with severe hepatic impairment is limited.		No dose adjustment is required for patients with hepatic impairment. Caution should be exercised in patients with severe hepatic due to limited experience.
Contraindications	• Hypersensitivity to active substance or excipients. • Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis • Congestive heart failure NYHA class IV • Pregnancy and breast feeding • Inflammatory bowel disease and diabetic gastroparesis	• Hypersensitivity to active substance or excipients. • Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis • Pregnancy and breast feeding • Severe gastroparesis and severe gastrointestinal disease as no studies have been conducted	• Hypersensitivity to active substance or excipients. • Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis • Congestive heart failure NYHA class IV • Pregnancy and breast feeding		• Hypersensitivity to active substance or excipients. • Type 1 diabetes mellitus (Not indicated) • Treatment of diabetic ketoacidosis (Not indicated) • Pregnancy and breast feeding
	The US license for the GLP-1 RAs and dual GIP with GLP-1 RA also includes the following contraindications: • personal or family history of medullary thyroid carcinoma • in those with multiple endocrine neoplasia syndrome type 2 (MEN 2)				
Cautions	• Goitre development has been reported in clinical trials and in particular in patients with pre-existing thyroid disease. • Delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products.	• Delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. • Be alert to the signs and symptoms of acute pancreatitis. If pancreatitis is suspected, dulaglutide should be discontinued; if acute pancreatitis is	• An increased risk of developing diabetic retinopathy has been observed. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. • Therapeutic experience in patients ≥75 years of age is limited. • Delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. • Be alert to the signs and symptoms of acute pancreatitis. If pancreatitis is suspected,		• Delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. • Caution should be exercised in patients with a history of pancreatitis. • Therapeutic experience in patients ≥85 years of age is limited. • Severe gastroparesis and severe gastrointestinal disease as no studies have been conducted.

	• Be alert to the signs and symptoms of acute pancreatitis. If pancreatitis is suspected, liraglutide should be discontinued; if acute pancreatitis is confirmed then liraglutide should not be restarted. • Potential risk of dehydration if affected take precautions to avoid fluid depletion.	confirmed then dulaglutide should not be restarted. • Potential risk of dehydration if affected take precautions to avoid fluid depletion.	semaglutide should be discontinued; if acute pancreatitis is confirmed then semaglutide should not be restarted. • Potential risk of dehydration if affected take precautions to avoid fluid depletion.		• Non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, as no studies have been conducted. • Contains benzyl alcohol. Patients with hepatic or renal impairment should be informed of the potential risk of metabolic acidosis due to accumulation of benzyl alcohol over time. • Be alert to the signs and symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued; if acute pancreatitis is confirmed then tirzepatide should not be restarted. • Potential risk of dehydration if affected take precautions to avoid fluid depletion.
Special considerations	• Some patients may prefer daily injections to help maintain a routine. • Does not come with needles but compatible with BD Viva®	• May be more suitable for patients with a needle phobia as needle is hidden. • Once weekly administration means fewer injections.	• Once weekly administration means fewer injections. • Comes with needles to deliver the 4 doses available in each pen.	• Appropriate for needle phobic patients as oral therapy.	• Once weekly administration means fewer injections. • Does not come with needles but compatible with BD Viva®

<u>Very common or common side effects listed as per SPC</u> (NB: This list is not exhaustive; please refer to BNF/SPC for further information)

All GLP-1 RAs- nausea, diarrhoea, hypoglycemia, vomiting, abdominal pain, fatigue, dyspepsia, GORD, eructation, flatulence and abdominal distention.
Liraglutide (Victoza®)- nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, headache, dizziness, increased heart rate, constipation, gastritis, toothache and rash.
Dulaglutide (Trulicity®)- hypoglycaemia, decreased appetite, constipation.
Semaglutide (Ozempic®)- hypoglycaemia (when used with insulin or other oral antidiabetic drugs), decreased appetite, dizziness, diabetic retinopathy complications, constipation, gastritis and cholelithiasis.
Semaglutide (Rybelsus®)- hypoglycaemia (when used with insulin or other oral antidiabetic drugs), decreased appetite, diabetic retinopathy complications, constipation, gastritis and dizziness.
Tirzepatide (Mounjaro®)- hypersensitivity reactions, hypoglycaemia (when used with metformin + SLG2i or sulfonylurea or insulin), decreased appetite, dizziness, hypotension related events, constipation, hair loss, heart rate increase, lipase and amylase increase.
(▼Ozempic, Rybelsus and Tirzepatide are black triangle drugs, all side effects should be reported using the yellow card system at: www.mhra.gov.uk/yellowcard)

Cardiovascular Outcome Trial (CVOT) Data from Randomised Controlled Trials (RCTs)

RCTs for the cardiovascular outcomes of the GLP-1 RAs and dual GIP and GLP-1RA are available:

- **Liraglutide (Victoza®):** LEADER study. 13% MACE (Major Adverse Cardiovascular Event) reduction at 1.8mg. NICE concluded that the results showed a clinically meaningful reduction of CV mortality and mortality from all causes in participants treated with liraglutide compared to placebo. The benefit could be due to the higher dose of liraglutide used in the trial, NICE concluded that this is not sufficient evidence to recommend a dosage of 1.8mg daily.
- **Dulaglutide (Trulicity®):** REWIND study. 12% MACE reduction with 1.5mg dose. The trial showed it manages glycaemic control in middle-aged and older people with T2DM with either previous CV disease or CV risk factors.
- **Semaglutide (Ozempic®):** SUSTAIN-6 study. 26% reduction with MACE. The lower CV risk with semaglutide was principally driven by a statistically significant decrease in the rate of non-fatal stroke and a non-significant decrease in non-fatal myocardial infarction. There was no significant difference in the rate of CV death.
- **Semaglutide (Rybelsus®):** PIONEER-6 showed CV safety but was not powered to demonstrate superiority of semaglutide versus placebo and therefore did not show statistically significant CV risk reduction. A larger CV outcome study for oral semaglutide (SOUL) is currently underway.
- **Tirzepatide (Mounjaro®):** SURPASS-CVOT aims to provide evidence of the CV safety and efficacy of tirzepatide as compared with dulaglutide. This trial is currently ongoing.

Drug Interactions (NB: This list is not exhaustive; please refer to BNF/SPC for further information http://www.medicines.org.uk/emc/)

Warfarin- when starting oral semaglutide (Rybelsus®) or subcutaneous semaglutide (Ozempic®) or liraglutide (Victoza®), frequent monitoring of INR (International Normalised Ratio) is recommended.

Levothyroxine - when starting oral semaglutide (Rybelsus®), monitoring of thyroid parameters should be considered 6-8 weeks after initiation for those on concomitant levothyroxine. (There may be an opportunity to move levothyroxine to dosing at bedtime to ensure both medicines continue to be taken on an empty stomach. Levothyroxine does not specifically need morning dosing).

Rosuvastatin: With oral semaglutide (Rybelsus®) the total exposure of rosuvastatin was increased by 41%. For those who have been prone to statin related side effects, they can be asked to be alert to this, or pre-emptive dose reduction could be made where suitable. Doses could also be reduced where symptoms suggest this is needed.

Narrow Therapeutic Index Medicines (e.g. warfarin, digoxin) – monitor especially at initiation of tirzepatide (Mounjaro®) and following dose increases.

Oral contraceptives – No dose adjustment of oral contraceptives is required in women with normal BMI. Limited information about the effect of tirzepatide (Mounjaro®) on oral contraceptives in women with obesity or who are overweight. It is advised switching to a non-oral contraceptive method or add a barrier method of contraception upon initiating tirzepatide therapy (for 4 weeks), or after each dose escalation (for 4 weeks).

Drug and Dose	Medicine to prescribe by brand name (all GLP-1 RAs and dual acting GIP with GLP-1RA should be prescribed by brand name)	Quantity to prescribe	Annual cost to prescribe*
Dulaglutide 0.75mg WEEKLY	Trulicity® 0.75mg/0.5ml solution for injection, pre-filled pen	1 box of 4 pens for 28 days' supply (each pen contains 1 dose)	£955
Dulaglutide 1.5mg WEEKLY	Trulicity® 1.5mg/0.5ml solution for injection, pre-filled pen		
Dulaglutide 3mg WEEKLY	Trulicity® 3mg/0.5ml solution for injection, pre-filled pen		
Dulaglutide 4.5mg WEEKLY	Trulicity® 4.5mg/0.5ml solution for injection, pre-filled pen		
Semaglutide 0.25mg WEEKLY	Ozempic® 0.25mg/0.19ml solution for injection, 1.5ml pre-filled pen	**1 Box of 1 Pen for 28 days' supply (each pen contains 4 doses)**	£955
Semaglutide 0.5mg WEEKLY	Ozempic® 0.5mg/0.37ml solution for injection, 1.5ml pre-filled pen		
Semaglutide 1.0mg WEEKLY	Ozempic® 1mg/0.74ml solution for injection, 3ml pre-filled pen		
Semaglutide 3mg or 7mg or 14mg	Rybelsus® 14mg, 7mg or 3mg tablets box of 30	1 box of 30 tablets for 30 days' supply	£955
Liraglutide 1.2mg daily#	Victoza® 6mg/ml solution for injection, 3ml pre-filled pen	1 box 2 pens for 30 days' supply (each pen contains 15 doses)	£955
Liraglutide 1.8mg daily#	Victoza® 6mg/ml solution for injection, 3ml pre-filled pen	3 pens for 30 days' supply (each pen contains 10 doses)	£1,432
Tirzepatide 2.5mg WEEKLY#	Mounjaro® KwikPen 2.5mg/0.6ml solution for injection, 2.4ml pre-filled pen	**1 Box of 1 Pen for 28 days' supply (each pen contains 4 doses)**	£1,199
Tirzepatide 5mg WEEKLY#	Mounjaro® KwikPen 5mg/0.6ml solution for injection 2.4ml pre-filled pen		£1,199
Tirzepatide 7.5mg WEEKLY#	Mounjaro® KwikPen 7.5mg/0.6ml solution for injection 2.4ml pre-filled pen		£1,395
Tirzepatide 10mg WEEKLY#	Mounjaro® KwikPen 10mg/0.6ml solution for injection 2.4ml pre-filled pen		£1,395
Tirzepatide 12.5mg WEEKLY#	Mounjaro® KwikPen 12.5mg/0.6ml solution for injection 2.4ml pre-filled pen		£1,590
Tirzepatide 15mg WEEKLY#	Mounjaro® KwikPen 15mg/0.6ml solution for injection 2.4ml pre-filled pen		£1,590

*The price as per the Dictionary of Medicines and Devices (accessed 5th April 2024)

The needle is not included. Locally preferred cost-effective option for compatible needles is BD Viva.

Version	2.1 – Updated to include additional contraindications for GLP-1 RAs/dual GIP with GLP-1 RA in line with US license (September 2024)
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 – GLP-1RA comparison document – Hertfordshire Medicines Management Committee March 2022 2.0 – Published June 2024 – Updates include a). Addition of Tirzepatide to the GLP-1 RA comparison document. b). Addition of information on oral semaglutide (Rybelsus ®) as an option for use during market shortages for GLP-1 RA.

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