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GLP-1 Receptor Agonists in Type 2 Diabetes

As detailed in Oxfordshire's local Type 2 Diabetes Blood Glucose Management in Adults Guideline and NICE Guideline 28, GLP-1 Receptor Agonists are a treatment option that can be initiated by prescribers in Primary Care to manage blood glucose in patients with Type 2 Diabetes. NICE recommend use of a GLP-1 agonist in combination with metformin and a sulfonylurea if triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated. The recommendation is for patient with type 2 diabetes who:

- have a BMI of 35 kg/m^2 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/m^2 and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity‑related comorbidities.

This guideline aims to assist prescribers in deciding on the most appropriate GLP-1 Receptor Agonist for their patient. Before starting a patient on a GLP-1 Receptor Agonist, ensure patient is compliant with current medication and that all oral hypoglycaemic therapy is optimised. If the patient's HbA1c remains at 58 mmol/mol (7.5%) or greater (or above personalised agreed target), consider initiating a GLP-1 Receptor Agonist.

Oral semaglutide (Rybelsus®) should only be considered when subcutaneous injections are definitely not possible, such as in cases of needle phobia.

The choice of GLP1RAs should be those with evidence of cardiovascular outcomes (subcutaneous Semaglutide, Dulaglutide, Liraglutide).

Prescribers should consider stopping treatment if there is no response within 6 months of initiating treatment. Non-responders would be defined by NICE criteria as patients who fail to decrease their HbA1c by 1% point (10.1 mmol/mol if measured in IFCC units) and lose 3% of their body weight. The Agreement Form and Checklist will assist with this.

Exenatide (Byetta and Bydureon) and Lixisenatide (Lyxumia): Previously, both lixisenatide and exenatide were included in local guidance as first line options. Trials on cardiovascular benefits for both lixisenatide and daily exenatide have not demonstrated CV benefit, therefore the recommendation is to offer one of the options listed in the table below which have proven cardiovascular benefit. Weekly exenatide has been withdrawn. Only consider continuation of lixisenatide and daily exenatide in existing patients who are achieving treatment goals and are at low risk of cardiovascular disease.

It is good practice to discuss the possible risks of starting and not starting medication with patients. The table below is a quick reference guide, for additional advice please contact the Community Diabetes team. For full and up to date information, refer to the Summary of Product Characteristics (SPC) and BNF.

	Semaglutide *(SPC: Ozempic)*	**Dulaglutide** *(SPC: Trulicity)*	**Liraglutide** *(SPC: Victoza)*	**Oral Semaglutide** (SPC: Rybelsus)
Cost per Month	0.25mg: £73.25 0.5mg: £73.25 1mg: £73.25 (needles included)	0.75mg: £73.25 1.5mg: £73.25 3mg: £73.25 4.5mg: £73.25 (needles integrated in device)	1.2mg: £78.48 1.8mg: £117.72 (needles not included)	3mg, 30=£78.48. 7mg, 30=£78.48. 14mg, 30=£78.48
Frequency of Administration	Weekly 1 pen = 4 weekly doses	Weekly 1 pen = 1 weekly dose	Daily 1 pen = 15 doses/10 doses	Daily
Dosing	Administered once weekly at any time of the day, with or without meals. • Start at 0.25mg/week for 1 month • 0.5mg/week for 1 month (could be ongoing dose) • 1.0mg/week can be used If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose.	Administered once weekly at any time of day, with or without meals. • Monotherapy: 0.75mg/week • Add on therapy: 0.75-1.5mg/week • Can now be increased to 4.5mg/week but CV outcomes demonstrated at 1.5mg 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.	Administered once daily at any time, independent of meals. Itis preferable that Victoza is injected around the same time of the day. • Start at 0.6mg for 1 week then increase to 1.2mg • Can be increased to 1.8mg if partial response. If no response consider one of the more cost effective options.	ONLY TO BE USED IF PATIENT CANNOT USE INJECTABLE OPTIONS Initially 3mg daily increasing after one month to 7mg once daily. After a further month increase to max 14mg once daily if required. To be taken on an empty stomach, ≥30 min before food.
CV Benefit	Yes (26% MACE reduction)[1]	Yes (12% MACE reduction) with 1.5mg dose[2]	Yes (13% MACE reduction at 1.8mg)[3]	Studies ongoing
Glucose Lowering	Greatest benefit[4]	Benefit	Benefit	Greatest benefit
Weight Loss	Greatest benefit[4]	Benefit	Benefit	Greatest benefit

Renal Impairment	Do not use if eGFR <15ml/min			
Side Effects	Most side effects are gastrointestinal. Nausea is likely to be temporary, advise patient to stop eating before full to minimise nausea. • Dulaglutide 1.5mg and Semaglutide 0.5 & 1mg all have similar rates of side effects Dulaglutide 0.75mg has a lower risk of side effects			
Contraindications	• Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis. • Congestive heart failure NYHA class IV • Patients under 18 years old • Pregnancy and breast feeding • Gastroparesis • History of pancreatitis	• Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis. • Congestive heart failure. • Patients under 18 years old • Pregnancy and breast feeding • Gastroparesis • History of pancreatitis	• Type 1 diabetes mellitus • Treatment of diabetic ketoacidosis. • CCF (NYHA class IV) • Patients under 18 years old • Pregnancy and breast feeding • Inflammatory Bowel Disease • Gastroparesis • Significant liver impairment • History of pancreatitis	• End-stage renal disease • Treatment of diabetic ketoacidosis • CCF (NYHA class IV) • Pregnancy, ensure contraception in women and discontinue at least 2 months before a planned pregnancy. Lactation. • History of pancreatitis
Cautions	• An increased risk of developing diabetic retinopathy complications has been observed. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, caution in those with a high HbA1c (>9%, 75mmol/mol) and/or retinopathy grade R2/R3/M1/P1. • If HbA1c >9% (75mmol/mol) and no retinopathy, risk of worsening of retinopathy is low. • Therapeutic experience in patients ≥75 years of age is limited • severe hepatic impairment	• Patients ≥ 75y old (0.75 mg once weekly can be considered as a starting dose) • delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products	• Monitor INR on warfarin • Thyroid Disease • delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products	• Renal or severe hepatic impairment • Advise patients of symptoms of pancreatitis; discontinue if suspected. • Diabetic retinopathy • Bariatric surgery • Elderly (≥75 years).

	• delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products			
	All: Be alert to the signs and symptoms of **acute pancreatitis**. Instruct patients to seek prompt medical care if they experience persistent severe abdominal pain. Discontinue GLP-1 Receptor Agonist if pancreatitis is suspected. If pancreatitis is confirmed, appropriate supportive treatment should be initiated and the patient carefully monitored until recovery and a GLP-1 Receptor Agonist should not be restarted.			
	All: MHRA safety alert: Serious and life-threatening cases of **diabetic ketoacidosis** have been reported in patients with type 2 diabetes on a combination of a GLP-1 agonist and insulin, particularly after rapid discontinuation or reduction of concomitant insulin. GLP-1 receptor agonists are not substitutes for insulin, and any reduction of insulin should be done in a stepwise manner with careful glucose self-monitoring. If unsure, please contact the Community Diabetes Team for advice on diabetesdialogue@nhs.net.			
	All: When added to existing therapy of sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. NICE recommend seeking specialist care advice and ongoing support from a consultant-led multidisciplinary team when offering a GLP-1 mimetic in combination with insulin. Contact the Community Diabetes Team for advice on diabetesdialogue@nhs.net.			
Storage	• Before first use: Store in a refrigerator (2°C to 8°C) • After first use: Store below 30°C or in a refrigerator (2°C to 8°C).	• Store in a refrigerator (2 °C – 8 °C). • In use: Trulicity may be stored unrefrigerated for up to 14 days at a temperature not above 30 °C.	• Before first use: Store in a refrigerator (2°C–8°C). • After first use: Store below 30°C or store in a refrigerator (2°C–8°C).	• Store in the original blister package in order to protect from light and moisture. • This medicinal product does not require any special temperature storage conditions.

References

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