Mid and South Essex Health and Care Partnership

NHS

MID AND SOUTH ESSEX MEDICINES OPTIMISATION COMMITTEE (MSEMOC)

SEMAGLUTIDE (RYBELSUS®) FOR TYPE 2 DIABETES MELLITUS

YELLOW - RECOMMENDED FOR RESTRICTED USE - for initiation by SPECIALISTS with relevant clinical experience in managing diabetes and for continuation in primary care

Name: generic (trade)	What it is	Indication	Decision status	NICE/SMC guidance
Semaglutide (Rybelsus®)	Oral glucagon-like peptide-1 (GLP-1) receptor agonist	Type 2 diabetes mellitus (T2DM)	Final	NICE - none SMC - approved for restricted use

MSEMOC recommendation:

- **Semaglutide (Rybelsus®) is recommended for restricted use as an ORAL GLP-1 receptor agonist when a GLP-1 receptor agonist is indicated in accordance with the type 2 diabetes mellitus – anti-hyperglycaemic treatment pathway. Semaglutide (Rybelsus®) must be initiated by SPECIALISTS with relevant clinical experience and training in managing diabetes and can be continued in primary care.**

- **Injectable forms of GLP-1 receptor agonists are first line where this class is indicated, due to better bioavailability and vascular outcome data. Semaglutide (Rybelsus®) should ONLY be used (as either monotherapy, or in dual therapy, or in triple therapy regimens):**

  i. **after a trial of injectable forms has been considered/attempted**
  AND
  ii. **for patients with established severe needle-phobia or marked limitations in manual dexterity**
  AND
  iii. **for patients with no access to support partners or carers.**

Monotherapy regime:

- **ONLY** in patients when control of blood glucose remains or becomes inadequate **(HbA1c ≥53 mmol/mol [7%] or greater than individualised target)**:
  - with a high cardiovascular risk **and**
  - if metformin is contraindicated/not tolerated **and**
  - in whom a sodium-glucose co-transporter 2 inhibitor (SGLT2i) is contraindicated

  And the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

Dual therapy regime:

- **With metformin or a sulphonylurea or pioglitazone or SGLT2i in patients when control of blood glucose remains or becomes inadequate (HbA1c ≥53 mmol/mol [7%] or greater than individualised target)**
  And the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

Triple therapy regime:

- **With metformin and a sulphonylurea, or metformin and a SGLT2 inhibitor, or metformin and pioglitazone, or pioglitazone and a sulphonylurea** in patients when control of blood glucose remains or becomes inadequate **(HbA1c ≥53 mmol/mol [7%] or greater than individualised target) And** the person has
  - 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 or alternative anti-glycaemic therapy options would have significant occupational implications, or weight loss would benefit other significant obesity-related comorbidities
- **Treatment should ONLY be continued if there is a reduction of at least 11 mmol/mol in HbA1c [1%] AND a weight loss of at least 3% of initial body weight at 6 months**.

Background information:

- Semaglutide (Rybelsus®) is an oral long-acting glucagon-like peptide 1 (GLP-1) receptor agonist, that exhibits GLP-1-mediated effects, including glucose-dependent potentiation of insulin secretion, decrease in glucagon secretion, delay of gastric emptying, and decrease in appetite.
- Semaglutide (Rybelsus®) is licensed for the management of T2DM in adults as a monotherapy when metformin is considered inappropriate due to intolerance or contraindications or in combination with other medicinal products for the treatment of diabetes.
- Semaglutide is available as a once weekly subcutaneous injection (Ozempic®) and as a once daily tablet (Rybelsus®). Ozempic® and Rybelsus® are not interchangeable because of the high pharmacokinetic variability of oral semaglutide.
- The dose regimen for the first month is 3mg once daily, then the dose should be increased to a maintenance dose of 7mg once daily. After at least one month with a dose of 7 mg once daily, the dose can be increased to a maintenance dose of 14 mg once daily to further improve glycaemic control.
- To aid absorption patients are required to strictly adhere to the administration directions, taking the tablet on an empty stomach 30 minutes before eating, drinking or taking other oral medicines.

PROPOSED ASSESSMENT AGAINST THE ETHICAL FRAMEWORK – to be agreed by committee

Evidence of Clinical Effectiveness

Vs empaglifozin in patients with T2DM uncontrolled on metformin (PIONEER 2 Trial, Rodbard et al. 2019)

- Objective: To validate the efficacy and safety of oral semaglutide versus empagliflozin in subjects with T2DM
- Design: The trial design included a randomised, open-label, multinational 52-weeks trial, conducted at 108 sites in 12 countries. The randomisation was assigned 1:1 and patients received either semaglutide or empagliflozin
- Patients: 822 adult patients with type 2 diabetes and an HbA1c of 7.0-10.5% (53mmol/mol-91mmol/mol) receiving a dose of metformin ≥ 1500mg or maximum tolerated. The patients were half (49.5%) female, mean age was 58 years, the mean duration of diabetes is 7.4 years and the mean body weight is 91.6kg. Although, the paper states 822 were randomised, results were only provided for 821 patients as one patient in the oral semaglutide group enrolled at two different sites; only data from the first randomization were included in the efficacy and safety analyses
- Intervention and comparison: 411 patients were intervened with semaglutide initiated at 3mg once daily, escalated to 7mg at week 4 and 14mg after week 87. 410 patients were given Empaglifozin as the comparator and initiated at 10mg once in the morning and escalated to 25mg at week 8.
- Outcomes: The primary end point was a change in HbA1c and the secondary end point was change in body weight (kg), both measured from baseline to week 267. 400 (97.1%) patients in the oral semglutide group and 387 (94.4%) in the empagliflozin group completed the trial.
  semaglutide 14mg provided a superior reduction in HbA1c compared to empaglifozin 25mg at week 26 (-1.3% [-14mmol/mol] vs. -0.9% [-9mmol/mol]), and at week 52. The mean baseline HbA1c was 65mmol/mol (8.1%). At week 26, a 95% confidence interval: -6.6 to -3.3, p<0.0001. At week 52, a 95% confidence interval: -5.5 to -3.3, p<0.0001. With regards to weight reductions with oral semaglutide 14mg the mean overall body weight at baseline was 91.6kg, with 95% confidence interval :- 0.7 to 0.5, p=0.7593 at week 26 and 95% confidence interval: -0.9 to -0.5, p=0.6231 at week 52

Vs subcutaneous liraglutide and placebo in type 2 diabetes, a randomised, double-blind, phase 3a trial (PIONEER 4, Pratley et al. 2019.)

- Objective: To validate the efficacy and safety of oral semaglutide versus liraglutide and versus placebo in subjects with T2DM
- Design: The trial design is a randomised, double-blind, double-dummy, active-controlled, placebo-controlled, 52-week multinational trial. The trail collected patients from 100 sites across 12 countries. Patients were randomly assigned (2:2:1) using an interaction web-response system and stratified by background glucose-lowering medication and country of origin.
- Patients: Patients eligible were adults with type 2 diabetes with HbA1cs of 7.0-10.5% (53mmol/mol-91mmol/mol) receiving a dose of metformin ≥ 1500mg or maximum tolerated, with or without a sodium-glucose co-transport 2 inhibitor (SGLT2i). 711 adults were recruited for the trial and there were no confounding factors between the 2 treatment groups. The mean HbA1c was 64mmol/mol (8.0%), mean age of 56 years, 48% were female, mean duration of diabetes was 7.6 years and the mean body weight was 94kg
- Intervention and comparison: The intervention was oral semaglutide as fixed dose escalations of 3mg once daily for 4 weeks, then 7mg once daily for 4 weeks followed by an escalation to 14mg once daily until 52 weeks. The comparator, subcutaneous liraglutide was initiated at 0.6mg with dose escalation to 1.2mg after 1 week and to the maintenance dose of 1.8mg after 2 weeks. This trial used a double-dummy and so a placebo was also provided to one treatment group for 52 weeks to compare the trial product against.
- Outcomes: The primary endpoint was change from baseline to week 26 in HbA1c. The confirmatory secondary endpoint was change from baseline to week 26 in bodyweight.
  Mean change from baseline in HbA1c at week 26 was −1·2% (SE 0·1) with oral semaglutide, −1·1% (SE 0·1) with subcutaneous liraglutide, and −0·2% (SE 0·1) with placebo. Oral semaglutide was non-inferior to subcutaneous liraglutide in decreasing HbA1c (estimated treatment difference [ETD] −0·1%, 95% CI −0·3 to 0·0; p<0·0001) and superior to placebo (ETD −1·1%, −1·2 to −0·9; p<0·0001) by use of the treatment policy estimand. At week 52, there was significantly greater reduction with oral semaglutide vs. subcutaneous liraglutide from baseline (ETD -0.3%, 95% CI -5 to -2; p=0.0002) and vs. placebo (ETD -1.0%, 95% CI -13 to -8; p<0.0001).

By use of the trial product estimand, oral semaglutide had significantly greater decreases in HbA1c than both subcutaneous liraglutide (ETD −0·2%, 95% CI −0·3 to −0·1; p=0·0056) and placebo (ETD −1·2%, −1·4 to −1·0; p<0·0001) at week 26. Oral semaglutide resulted in superior weight loss (−4·4 kg [SE 0·2]) compared with liraglutide (−3·1 kg [SE 0·2]; ETD −1·2 kg, 95% CI −1·9 to −0·6; p=0·0003) and placebo (−0·5 kg [SE 0·3]; ETD −3·8 kg, −4·7 to −3·0; p<0·0001) at week 26 (treatment policy). By use of the trial product estimand, weight loss at week 26 was significantly greater with oral semaglutide than with subcutaneous liraglutide (−1·5 kg, 95% CI −2·2 to −0·9; p<0·0001) and placebo (ETD −4·0 kg, −4·8 to −3·2; p<0·0001). Adverse events were more frequent with oral semaglutide (n=229 [80%]) and subcutaneous liraglutide (n=211 [74%]) than with placebo (n=95 [67%].

Cardiovascular outcomes of oral semaglutide in subjects with T2DM (PIONEER 6)

- Objective: investigation of cardiovascular outcomes of semaglutide in T2DM
- Design: The trial design included a randomised, event-driven, double-blind, placebo-controlled, multinational cardiovascular outcomes trial. The trial was conducted at 214 sites in 21 countries. Randomisation was stratified according to evidence of established cardiovascular disease or chronic kidney disease, or the presence of cardiovascular risk factors only.
- Patients: 3183 patients, (placebo, n= 1592) who were either ≥50 years old with T2DM with established cardiovascular disease (previous cardiovascular, cerebrovascular, or peripheral vascular disease), chronic heart failure (New York Heart Association class II or class III), or moderate kidney disease (eGFR 30-59 mL/min/1.73m2) (n=2,695; 84.7%), or ≥60 years with at least one cardiovascular risk factor (n=488; 15.3%) were enrolled.
  Baseline characteristics, including age (overall mean 66 years), duration of diabetes (14.9 years), mean bodyweight (90.9 kg) and HbA1c (66 mmol/mol [8.2%]) were similar between the groups.
  Patients treated with any GLP-1 RA, dipeptidyl peptidase 4 inhibitor or pramlintide within 90 days before screening were excluded. Patients were on a standard of regimen for diabetes and cardiovascular risk management.
  At baseline, most patients were taking metformin (77.4%) or insulin (60.6%) and 32.3% were taking sulfonylureas and 9.6% on SGLT2 inhibitors9. At baseline, 94% of patients overall were taking cardiovascular medication. This included:
  • Antihypertensives (93.8%-94%)
  • Lipid-lowering drugs (84%-86.4%)
  • Antithrombotics (78.4%-80.3%)
  • Diuretics (39.0%-40.2%)
- Intervention and comparison: Oral semaglutide initiated at 3mg once daily for 4 weeks, escalated to 7mg for a following 4 weeks and then 14mg once daily for the duration of the study. The comparator in the study was of 1592 patients taking placebo.
- Outcomes: The primary outcome measured was the time from randomisation to the first occurrence of a major adverse cardiovascular event (MACE), a composite of death from cardiovascular cases (including undetermined causes of death), nonfatal myocardial infarction or nonfatal stroke.
  The proportion of patients with the first occurrence of MACE was found to be 61 events in 1591 (3.8%) patients on oral semaglutide + standard of care (SOC) and 76 events in 1952 (4.8%) patients on placebo + SOC. These results showed the absolute risk reduction (ARR) to be 1%, hazard ratio: 0.79 (95% confidence interval: 0.57 to 1.11), p<0.0001 (non-inferiority), p=0.17 (superiority).
  The secondary endpoint outcomes (individual components of the composite primary outcome) are listed below:
  • Death from cardiovascular causes: HR: 0.49 (95% confidence interval: 0.27 to 0.92)
  15 events in 1591 patients (0.9%) in oral semaglutide + SOC, 30 events in 1592 patient (1.9%) in placebo + SOC
  • Nonfatal myocardial infarction: HR: 1.18 (95% confidence interval: 0.73 to 1.90), 37 events in 1591 patients (2.3%) in oral semaglutide + SOC, 31 events in 1592 patients (1.9%) in placebo + SOC
  • Nonfatal stroke: HR: 0.74 (95% confidence interval: 0.35 to 1.57),12 events in 1591 (0.8%) patients in oral semaglutide + SOC, 16 events in 1592 (1.0%) patients in placebo + SOC
  Death from any cause occurred in 23 of 1591 patients (1.4%) in the oral semaglutide group and 45 of 1592 (2.8%) in the placebo group (hazard ratio, 0.51; 95% CI, 0.31 to 0.84). Gastrointestinal adverse events leading to discontinuation of oral semaglutide or placebo were more common with oral semaglutide.
  The mean overall HbA1c at baseline was 66mmol/mol (8.2%). Oral semaglutide + SOC versus placebo + SOC had an estimated treatment difference of -7.6mmol/mol (-0.7%).
  The mean overall body weight at baseline was 90.9kg. Oral semaglutide + SOC versus placebo + SOC had an estimated treatment difference of-3.4kg.
  Due to these outcomes, the cardiovascular risk profile of oral semaglutide was deemed non-inferior to placebo.

Meta-Analysis of RCTs for Oral Semaglutide

A meta-analysis was conducted of RCTs with a parallel or cross-over design and a treatment duration of at least 12 weeks that compared oral semaglutide with placebo or any other glucose lowering agent in adults with T2DM. The included RCTs were the 10 phase IIIa trials of the PIONEER Clinical Trials Programme plus one additional trial. The total number of patients included across the RCTs was 9890. Compared with placebo, oral semaglutide reduced HbA1c and body weight (Weighted Mean Difference (WMD) –0.89% [CI95% −1.07; −0.71] and − 2.99 kg, [CI95% −3.69; −2.30], respectively). Oral semaglutide was also superior to other active comparators (including liraglutide, empagliflozin and sitaglipitin) in terms of lowering HbA1c (WMD –0.35%, [CI95% −0.43 to −0.26]) and reduction of body weight (WMD −1.48 kg, [CI95% −2.28 to −0.67]), and had a favourable effect on systolic blood pressure

Safety

- Overall, the safety profile of oral semaglutide is similar to that of subcutaneous (SC) semaglutide (Ozempic®). Most of the adverse events (AEs) reported with oral semaglutide were mild, nonserious and recovered by the end of the trials. AEs leading to premature treatment discontinuation were higher with oral semaglutide than with comparator. Treatment discontinuations were driven primarily by gastrointestinal (GI) AEs (nausea, diarrhoea, vomiting and constipation).
- Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Caution is exercised in patients with a history of pancreatitis
- Patients treated with semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with semaglutide
- In patients with diabetic retinopathy treated with insulin and SC semaglutide, an increased risk of developing diabetic retinopathy complications has been observed, a risk that cannot be excluded for orally administered semaglutide. Caution should be exercised when using semaglutide in patients with diabetic retinopathy. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy, but other mechanisms cannot be excluded. Long term glycaemic control decreases the risk of diabetic retinopathy.
- MHRA warning (June 2019) – Diabetic ketoacidosis has been reported in insulin-dependent patients whom had rapid discontinuation or dose reduction of insulin when treatment with a GLP-1 receptor agonist is started semaglutide was not subject to the EU review. At the time of publication of the MHRA warning, no UK reports of diabetic ketoacidosis in association with semaglutide has been received. However, the theoretical risk of ketoacidosis when changes are made to insulin dose cannot be excluded.

Limitations and Comments

- Semaglutide® is denoted as a 'black triangle' (▼) product. It is therefore subject to additional monitoring.
- Long term outcome and safety data is limited at this point in time due to the short durations of the trials.
- Trial end points and objectives were in line with EMA guidance on medicines for diabetes
- The safety profile of oral semaglutide appears to be consistent with that of subcutaneous semaglutide and the other GLP-1 receptors agonists.
- Oral semaglutide requires daily administration at least 30 minutes away from food, drink and other medications. Some patients may prefer the ease of a weekly injectable GLP-1 receptor agonist.
- Due to the high variability in the absorption of oral semaglutide, an important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy.
- Discontinuation rates for oral semaglutide were significantly higher than for placebo (although similar to other GLP-1 receptor agonists)
- Some uncertainty remains about the long term effect of semaglutide (both oral and SC) on the development of AEs of diabetic retinopathy and related complications
- The cardiovascular outcomes trials did not show a statistically significant CV risk reduction. Due to the large variability in exposure, the different route of administration, and taken into account that not all patients will tolerate the highest dose of 14 mg, it remains uncertain if the exposure obtained with oral semaglutide is sufficient for the entire population to exhibit the CV effect.
- The studies were initiated & sponsored by Novo Nordisk

Cost of treatment and Cost Effectiveness:

- No cost effectiveness evidence is available for Rybelsus®, however the Scottish Medicines Consortium has accepted Rybelsus® for restricted use within NHS Scotland because oral semaglutide (Rybelsus®) costs the same per day as subcutaneous semaglutide (Ozempic®).

Semaglutide (Rybelsus®) costs:

Rybelsus® strength and formulation	Price for 30 tablets
3mg Tablets	£78.48
7mg Tablets	£78.48
14mg Tablets	£78.48
Costs based on Drug tariff prices (June 2021).	

Comparative unit costs:

Drug	Example of maintenance regimen	Pack cost	Cost per patient per year (ex VAT)

Rybelsus® oral tablets	**14 mg daily**	**£78.48**	**£954.82**
Semaglutide (Ozempic®) injection	1 mg once weekly	£73.25	£954.86
Dulaglutide (Trulicity®) injection	1.5 mg once weekly	£73.25	£954.86
Exenatide (Bydureon®) injection	2 mg once weekly	£73.36	£956.30
Exenatide (Byetta®) injection	10 mcg twice daily	£81.89	£996.33
Liraglutide (Victoza®) injection	1.8 mg once daily	£117.72	£1,432.26
Lixisenatide (Lyxumia®) injection	20 mcg daily	£57.93	£755.16
Costs based on Drug tariff prices (June 2021). This table does not imply therapeutic equivalence of drugs or doses.			

The needs of the population:

- The needs of the population may be high as there is no alternative licensed oral GLP-1RA available.
- The cardiovascular outcomes trials did not show a statistically significant CV risk reduction
- There may be a benefit for patient cohorts who are unable to tolerate injections / there are barriers to administration (e.g. needle phobia, limitations to manual dexterity etc.)

The needs of the community:

- The needs of the community may be low as the estimated patient numbers for treatment are low.
- There would currently be no increased costs if patients prescribed Rybelsus® instead of s.c. GLP1-RAs

Equity and Equality: No impact anticipated.
The pathway supports consistent, equitable access to treatment. Appropriateness of medicines for individual patients is a clinical decision by the prescribing clinician. There is no anticipated differential impact on people with protected characteristics

Policy drivers:

- **Scottish Medicines Consortium (SMC):**
  Issued the following advice following an abbreviated submission:
  Semaglutide (Rybelsus®) is accepted for restricted use within NHSScotland as an addition to other oral anti-diabetic medicines, or as an add-on to basal insulin, as an alternative glucagon-like peptide-1 receptor agonist option in T2DM.
  SMC has previously accepted semaglutide solution for subcutaneous injection (Ozempic) for restricted use. Oral semaglutide (Rybelsus) costs the same per day as subcutaneous semaglutide (Ozempic)
  The company's submission was only for use in addition to other medicinal products for the treatment of diabetes, therefore SMC cannot recommend semaglutide tablets as monotherapy
- **All Wales Medicines Strategy Group (AWMSG):**
  Semaglutide (Rybelsus®) was excluded from the appraisal process as it met the following exclusion criteria:
  Product is a new formulation or combination of an established medicine which is either:
  • an oral formulation intended for patients unable to swallow tablets or capsules, or;
  • an alternative formulation of an established medicine which costs the same or less than the existing established medicine.
  AWMSG had evaluated and published a restricted recommendation for s.c. semaglutide (Ozempic®) in 2018.
- **NICE guidelines for management of type 2 diabetes in adults recommends**
  - where TRIPLE therapy (metformin and 2 other oral antidiabetics) is not effective, not tolerated, or contraindicated, consider combination therapy with metformin, a sulfonylurea and a GLP-1 mimetic for adults with T2DM 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

    Only continue GLP-1 mimetic 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 in 6 months).

  - 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

EoE CCG decisions:

1. **Bedfordshire and Luton Joint Prescribing Committee, BLMK CCGs (Dec 2020):**
   Approved it for restricted use with shared care guidance:
   - In line with NICE recommendations on place in therapy for GLP1RA

- Second line choice after consideration of the s/c GLP1 agonist preparations noting that patient selection is key, given potential interactions
- Initiation (under any circumstances) only by the Specialist Service (as defined in the SCG) as patient selection is key. (Differs from Injectable GLP1 agonist criteria where GPs may initiate under certain circumstances)
- Passed to GPs for prescribing when patient stable. This would be after 3-6 months depending on co-morbidities/concurrent medication
- S.c. GLP1RAs are first line choice and oral semaglutide as an option if the s.c. preparations are unsuitable.

2. **Ipswich and Suffolk CCG (accessed June 2020)**:
   Approved for use in line with the SPC for Rybelsus®

Other decisions include:

1. **South East London Area Prescribing Committee (December 2020):**
   Approved for use for restricted use:

- Initiation and supply by specialist diabetes teams. GPs may be asked to take on prescribing after 3 months
- In line with NICE clinical guidelines for Type 2 diabetes in adults
- Oral semaglutide should only be offered in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team
- During COVID-19, oral semaglutide will be an option alongside the injectable GLP-1 agonists on the SEL formulary
- Patients who are already stabilised on injectable GLP-1 agonist therapy should not be switched over to oral semaglutide unless there is a robust clinical rationale to do so.

2. **Greater Manchester Medicines Management Group (GMMG) (January 2021):**
   Recommended for restricted use only for patients requiring a GLP1RA as per NICE NG28, and who are unable to tolerate injections / there are barriers to administration (e.g. needle phobia, limitations to manual dexterity etc.)

Implementability:

- Due to safety concerns about issues in bioavailability of switching from injectable GLP-1RA to oral Rybelsus® patients must be counselled on correct administration and dose titration schedule
- Prescribers should consult the summary of product characteristics and any MHRA safety advice when commencing treatment.

References:

- Scottish Medicines Consortium (Advice September 2020) https://www.scottishmedicines.org.uk/medicines-advice/semaglutide-rybelsus-abbreviated-smc2287/
- All Wales Medicines Strategy Group (AWMCG) Advice March 2020 https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/semaglutide-rybelsus/
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- Specialist Pharmacy Service. Accessed (Accessed June 2020): https://www.sps.nhs.uk/articles/cardiovascular-outcomes-with-glp-1-receptor-agonists/

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