New Medicine Assessment

Semaglutide Oral Tablets (Rybelsus®▼)

For the Treatment of Adults with Insufficiently Controlled Type 2 Diabetes Mellitus to Improve Glycaemic Control as an Adjunct to Diet and Exercise

Recommendation: GREEN (restricted) as an alternative GLP-1 receptor agonist for patients who are unable to use subcutaneous formulations or patients who prefer oral administration. The effectiveness of semaglutide should be monitored 6 months after initiation in line with the targets below:

Semaglutide is an appropriate treatment option for initiation and ongoing prescribing in both primary and secondary care when prescribed in the following clinical circumstances:

- after second intensification of therapy fails to achieve targets*****:
    - has a BMI of ≥35 kg/m^2 and specific psychological or other medical problems associated with obesity (adjust accordingly for people from Black, Asian and other minority ethnic groups) or
    - has a BMI < 35 kg/m^2 and
        - if insulin therapy would have significant occupational implications or
        - if weight loss would benefit other significant obesity related comorbidities

Or, with specialist care advice and ongoing support from a consultant-led multidisciplinary team:

- combined with insulin at second intensification of treatment in patients who cannot take metformin

Semaglutide may only be continued if the person has a beneficial metabolic response, defined as follows:

- a reduction of HbA1c by at least 11 mmol/mol [1.0%] and
- a weight loss of at least 3% of initial body weight in 6 months

*** Wording consistent with LSCMMG antihyperglycaemics guideline**

Summary of supporting evidence:

- Rybelsus® is the first GLP-1 receptor agonist which can be taken orally preventing/delaying the need for subcutaneous injections for some patients.
- A clinical trials programme tested oral semaglutide against placebo, sitagliptin, liraglutide and empagliflozin.
- Oral semaglutide dose-dependently reduced HbA1c across all PIONEER trials by between 0.6 to 1.4 %.
- Body weight was reduced dose-dependently by 1.2 to 1.5 kg with oral semaglutide 3 mg, 2.2 to 2.4 kg with 7 mg and 3.1 to 4.4 kg with 14 mg in the key efficacy trials at week 26.
- The safety profile of oral semaglutide appears to be consistent with that of subcutaneous semaglutide and the other GLP-1 receptors agonists.
- Due to the high variability in the absorption of semaglutide, an important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy.

Date: September 2020

Details of Review

Name of medicine (generic & brand name)**:** Semaglutide (Rybelsus®▼)

Strength(s) and form(s): 3 mg, 7 mg and 14 mg oral tablets

Dose and administration:

The starting dose of semaglutide is 3 mg once daily for one month. After one month, the dose should be increased to a maintenance dose of 7 mg 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.

The maximum recommended single daily dose of semaglutide is 14 mg. Taking two 7 mg tablets to achieve the effect of a 14 mg dose has not been studied and is therefore not recommended. [1]

BNF therapeutic class / mode of action:

Other antidiabetic drugs / Glucagon-like peptide-1 (GLP-1) receptor agonists

Licensed indication(s):

Rybelsus is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise:

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in combination with other medicinal products for the treatment of diabetes.

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication.

Course and cost: 30 days treatment - £78.48, annual cost £954.82

Current standard of care/comparator therapies:

- Semaglutide (Ozempic®) injection – Four weeks treatment = £73.25, annual cost = £954.86
- Dulaglutide (Trulicity®) injection - Four weeks treatment = £73.25, annual cost = £954.86
- Exenatide (Bydureon®) injection – Four weeks treatment = £73.36, annual cost = £956.30
- Liraglutide (Victoza®) injection – 30 days treatment = £78.48 – £117.72, annual cost = £954.84 - £1,432.26
- Exenatide (Byetta®) injection – 30 days treatment = £81.89, annual cost = £996.33

- Lixisenatide (Lyxumia®) injection – 28 days treatment = £57.93, annual cost = £755.16

Relevant NICE guidance:

NICE guideline (NG28) – Type 2 diabetes in adults: management. [2]
1.6.28 If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults 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.

1.6.29 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).

1.6.31 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.

Background and context

Type 2 diabetes is a chronic metabolic condition characterised by insulin resistance (that is, the body's inability to effectively use insulin) and insufficient pancreatic insulin production, resulting in high blood glucose levels (hyperglycaemia). Type 2 diabetes is commonly associated with obesity, physical inactivity, raised blood pressure, disturbed blood lipid levels and a tendency to develop thrombosis, and therefore is recognised to have an increased cardiovascular risk. It is associated with long-term microvascular and macrovascular complications, together with reduced quality of life and life expectancy. [2]

In 2013, over 3.2 million adults were diagnosed with diabetes, with prevalence rates of 6% and 6.7% in England and Wales respectively. It is estimated that about 90% of adults currently diagnosed with diabetes have type 2 diabetes. Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family origin. It can occur in all age groups and is increasingly being diagnosed in children. [2]

GLP-1 receptor agonists are used in type 2 patients whose HbA1c remains uncontrolled despite the use of triple therapy oral antihyperglycaemic agents. A drawback of GLP-1 receptor agonists has been the need for injections, but semaglutide is now available in a formulation that can be administered orally as a tablet. Oral semaglutide was prioritised for review following requests by specialist diabetologists from Blackpool Teaching Hospitals Trust and Lancashire Teaching Hospitals Trust.

Summary of evidence

Summary of efficacy data in proposed use:

Pioneer Clinical trials programme

Ten phase IIIa trials (PIONEER 1–10) were performed with oral semaglutide. PIONEER 9 and 10 were conducted in Japan only, according to Japanese requirements, and have not been included in this review. The phase IIIa trials included a total of 9543 randomised subjects, of whom 5707 were exposed to oral semaglutide. Baseline demographics and disease characteristics of the trial populations studied represented a broad type 2 diabetes (T2D) population as seen in clinical practice. [3] In all the key clinical efficacy trials, the primary endpoint evaluated the effect of the oral semaglutide on glycaemic control estimated based on the average blood glucose concentration (HbA1c) at about three months. Weight-loss was pre-defined as a confirmatory, secondary endpoint.

In three of the pivotal trials, placebo was used as the only comparator, and in four of the pivotal trials active comparators were used at relevant doses (empagliflozin 25 mg, liraglutide 1.8 mg, and sitagliptin 100 mg). Five of the seven pivotal studies were double-blinded of which two were additionally double-dummy trials. Study duration ranged from 12 to 72 weeks.

PIONEER 1 (Monotherapy) [4]

In drug naïve T2D subjects, semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (semaglutide 3 mg -0.6% [CI95% −0.8; −0.4] ; 7 mg -0.9% [CI95% −1.1; −0.6], and 14 mg -1.1% [CI95% −1.3; −0.9]) compared to placebo. In addition, there were changes in body weight (semaglutide 3 mg -0.1 kg; 7 mg -0.9 kg; 14 mg -2.3 kg versus placebo).

PIONEER 2 (vs Empagliflozin) [5]

The study was performed in T2DM subjects who had not achieved adequate control on metformin. Compared to empagliflozin 25 mg, semaglutide 14 mg was associated with a clinically relevant decrease in HbA1c after 52 weeks (-0.4% [CI95% -0.6; -0.3]). Superiority of oral

semaglutide 14 mg vs empagliflozin 25 mg in reducing body weight was not confirmed.

PIONEER 3 (vs Sitagliptin) [6]

PIONEER 3 compared three doses of semaglutide to sitagliptin in T2DM subjects who had not achieved adequate control on metformin or sulfonylurea treatment. Superiority of oral semaglutide 7 mg and 14 mg vs sitagliptin 100 mg was confirmed (semaglutide 7 mg: -0.3% [CI95% −0.4; −0.1]; semaglutide 14 mg: -0.5% [CI95% −0.6; −0.4] vs sitagliptin) at week 26. For oral semaglutide 3 mg, non-inferiority vs sitagliptin 100 mg could not be confirmed and the decrease in HbA1c was statistically significantly smaller with oral semaglutide 3 mg than with sitagliptin 100 mg. The decrease in body weight from baseline at week 26 was statistically significantly greater with oral semaglutide 3 mg, 7 mg and 14 mg than with sitagliptin 100 mg.

PIONEER 4 (vs Liraglutide) [7]

In PIONEER 4 T2DM subjects on background anti-diabetic medication (metformin alone or in combination with a SGLT-2 inhibitor) were randomised to once daily treatment with a dose-escalation regimen to semaglutide 14 mg, liraglutide 1.8 mg or placebo, respectively. Superiority of oral semaglutide 14 mg vs placebo and non-inferiority of oral semaglutide 14 mg vs liraglutide 1.8 mg in reducing HbA1c were both confirmed; superiority of oral semaglutide 14 mg vs liraglutide 1.8 mg could not be confirmed (Hba1c: -0.1% [CI95% -0.3; – 0.0]). Body weight was significantly reduced in semaglutide vs liraglutide (-1.2 kg [CI95% -1.9; -0.6]). There were more premature treatment discontinuations with semaglutide than liraglutide (12.6% vs 9.2%) with a higher incidence of gastro-intestinal disorders.

PIONEER 5 (Patients with Moderate Renal Impairment) [8]

PIONEER 5 subjects with T2DM and moderate renal impairment were randomised to oral semaglutide 14 mg or placebo on a background of metformin and/or SU, basal insulin alone, or metformin in combination with basal insulin. A clinically relevant change in HbA1c after 26-weeks was demonstrated with semaglutide 14 mg: HbA1c -0.8% [CI95% -0.1; -0.6], compared to placebo. The difference in body weight was -2.5 kg in favour of semaglutide.

PIONEER 7 (Flexible dose adjustment semaglutide vs sitagliptin) [9]

PIONEER 7 subjects with T2DM were randomised to flexible dosing (3, 7 or 14 mg) of oral semaglutide once-daily or 100 mg sitagliptin once-daily as an add-on to their anti-diabetic background medication. More patients in the flexible dosing semaglutide group achieved an HbA1c < 7% compared to subjects receiving sitagliptin (58.3% vs 25.2%). A clinically relevant difference in weight loss was observed in favour of semaglutide (-1.9 [CI95% -2.6; -1.2 kg]. More subjects in the semaglutide flexible dosing arm discontinued treatment prematurely compared to sitagliptin (11.9% vs 6.8%). This difference was mainly driven by more gastrointestinal adverse events in the oral semaglutide flexible dosing group.

PIONEER 8 (Add-on to Insulin vs Placebo) [10]

In PIONEER 8, subjects with T2DM on basal and/or bolus insulin with or without metformin were randomised to semaglutide or placebo. Semaglutide was associated with a clinically relevant decrease in HbA1c after 26 weeks (semaglutide 3 mg –0.5%[CI95% −0.7; −0.3] ; semaglutide 7 mg -0.9%[CI95% −1.1; −0.7] ; semaglutide 14mg -1.2%[CI95% −1.4; −1.0]) compared to placebo. In addition, compared to placebo, semaglutide was associated with a clinically relevant decrease in body weight after 26 weeks (semaglutide 3 mg -0.9 kg; semaglutide 7 mg -2.0 kg; semaglutide 14mg -3.3kg). From a mean baseline insulin dose of 58 IU across the 4 groups, significant reductions of insulin doses of 8 IU, 16 IU and 17 IU were seen at week 26 with semaglutide 3 mg, 7 mg and 14 mg, respectively, when compared to placebo. There was a dose-related higher number of premature discontinuations, gastrointestinal adverse events and other adverse events with semaglutide compared to placebo.

Other efficacy data:

Meta-Analysis of RCTs for Oral Semaglutide [11]

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 T2D. 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.

Summary of safety data:

The description of the safety profile in the EMA public assessment report of oral semaglutide is primarily based on the pooled analysis of Phase IIIa trials, including 4116 subjects treated with oral semaglutide and 2236 subjects treated with active comparator or placebo. The mean, individual observation time was slightly above one year in both groups; therefore, the experience corresponds to 4379 and 2335 patient-years exposure. [3]

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, non-serious 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). Below is the list of AEs documented in the SPC for oral semaglutide [1]:

MedDRA system organ class	Very common	Common	Uncommon	Rare
Immune system disorders				Anaphylactic reaction
Metabolism and nutrition disorders	Hypoglycaemia when used with insulin or sulfonylurea	Hypoglycaemia when used with other oral antidiabetic products Decreased appetite		
Eye disorders		Diabetic retinopathy complications		
Cardiac disorders			Increased heart rate	
Gastrointestinal disorders	Nausea Diarrhoea	Vomiting Abdominal pain Abdominal distension Constipation Dyspepsia Gastritis Gastro-oesophageal reflux disease Flatulence	Eructation	Acute pancreatitis
Hepatobiliary disorders			Cholelithiasis	
General disorders and administration site conditions		Fatigue		
Investigations		Increased lipase Increased amylase	Weight decreased	

Cardiovascular safety

The PIONEER 6 is a preapproval cardiovascular outcomes trial specifically designed to rule out an excess in cardiovascular risk with oral semaglutide among patients with type 2 diabetes. [12] A total of 3183 subjects were randomised. The trial reached its primary objective and demonstrated non-inferiority of semaglutide versus placebo in terms of major adverse cardiovascular events (MACE). The composite primary outcome occurred in 61 of 1591 patients (4.1%) in the semaglutide group and 76 of 1592 (4.8%) in the placebo group (hazard ratio, 0.79; [95%CI 0.57;1.11, P<0.001 for noninferiority]. Superiority was not confirmed with the upper bound of the 95% CI being below 1.0 (p=0.1749). [3]

Contraindications

Oral semaglutide is contraindicated in pregnancy and breast feeding, and for patients with hypersensitivity to the active substance or to any of the excipients in the preparation. Women of childbearing potential are recommended to use contraceptives while being treated with semaglutide. [1]

Cautions

General

No dose adjustment is necessary in elderly patients, patients with renal impairment or patients with hepatic impairment. However, caution should be exercised when treating patients with severe renal or hepatic impairment. Use of GLP-1 receptor agonists may be associated with GI AEs that can cause dehydration, which in rare cases can lead to a deterioration of renal function. Patients treated with semaglutide should be advised of the potential risk of dehydration in relation to GI side effects and take precautions to avoid fluid depletion.

Semaglutide should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. 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.

There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV and semaglutide is therefore not recommended in these patients. There is also no therapeutic experience with semaglutide in patients with bariatric surgery. [1]

Acute pancreatitis

Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, semaglutide should be discontinued; if confirmed, semaglutide should not be restarted. Caution should be exercised in patients with a history of pancreatitis. [1]

Hypoglycaemia

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. [1]

Diabetic retinopathy

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. These patients should be monitored closely and treated according to clinical guidelines. 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. [1]

Interactions

Thyroxine and warfarin

Monitoring of thyroid parameters should be considered when treating patients with semaglutide at the same time as levothyroxine. Upon initiation of semaglutide treatment in patients on warfarin or other coumarin derivatives, frequent monitoring of INR is recommended. [1]

Administration with other medicines

The presence of multiple tablets in the stomach influences the absorption of semaglutide if co-administered at the same time. After administering semaglutide, the patients should wait 30 minutes before taking other oral medicinal products. It is also recommended that patients do not eat or drink within 30 minutes of taking oral semaglutide. [1]

Strengths and limitations of the evidence:

Strengths

- Rybelsus® is the first GLP-1 receptor agonist which can be taken orally preventing/delaying the need for subcutaneous injections for some patients.
- A clinical trials programme tested oral semaglutide against placebo, sitagliptin, liraglutide and empagliflozin.
- Oral semaglutide dose-dependently reduced HbA1c across all PIONEER trials by between 0.6 to 1.4 %.
- Body weight was reduced dose-dependently by 1.2 to 1.5 kg with oral semaglutide 3 mg, 2.2 to 2.4 kg with 7 mg and 3.1 to 4.4 kg with 14 mg in the key efficacy trials at week 26.
- The safety profile of oral semaglutide appears to be consistent with that of subcutaneous semaglutide and the other GLP-1 receptors agonists.

Limitations

- 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 semaglutide, an important concern identified in the pharmacokinetic evaluation of oral semaglutide is the risk of low exposure and resulting negative impact on efficacy. [3]
- 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. A further long term cardiovascular outcomes study is in progress to clarify the cardiometabolic benefits of oral semaglutide.
- 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.

Summary of evidence on cost effectiveness:

A cost-effectiveness analysis has been published, funded by the manufacturing company, comparing oral semaglutide to empagliflozin, sitagliptin and liraglutide. [13] Baseline cohort characteristics and treatment effects were based on 52-week data from the PIONEER 2, 3 and 4

randomised controlled trials, comparing oral semaglutide with empagliflozin, sitagliptin and liraglutide, respectively.

Oral semaglutide was associated with improvements in quality-adjusted life expectancy of 0.09 quality-adjusted life years (QALYs) versus empagliflozin, 0.20 QALYs versus sitagliptin and 0.07 QALYs versus liraglutide. Direct costs over a patient's lifetime were GBP 971 and GBP 963 higher with oral semaglutide than with empagliflozin and sitagliptin, respectively, but GBP 1551 lower versus liraglutide. Oral semaglutide was associated with a reduced incidence of diabetes-related complications versus all comparators. Therefore, oral semaglutide 14 mg was associated with incremental cost-effectiveness ratios of £11,006 and £4,930 per QALY gained versus empagliflozin 25 mg and sitagliptin 100 mg, respectively, and was more effective and less costly (dominant) versus liraglutide 1.8 mg.

Prescribing and risk management issues:

Compliance with the dosing regimen is recommended for optimal effect of semaglutide. If the treatment response with semaglutide is lower than expected, the treating physician should be aware that the absorption of semaglutide is highly variable and may be minimal (2-4% of patients will not have any exposure), and that the absolute bioavailability of semaglutide is low. [1]

The licensed indications for oral semaglutide are much wider than the relatively restrictive settings in the LSCMMG antihyperglycaemics guideline. If oral semaglutide was approved for use across Lancashire and South Cumbria, its place would need to be defined in the LSCMMG antihyperglycaemics pathway.

Commissioning considerations:

Comparative unit costs:

Drug	Example 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 MIMS list prices August.
This table does not imply therapeutic equivalence of drugs or doses.

Innovation, need and equity implications of the intervention:
Rybelsus® is the first GLP-1 receptor agonist available as an oral tablet. This provides an additional treatment option for patients who are unable to use subcutaneous formulations or patients who prefer oral administration.
Financial implications of the intervention:
The acquisition cost of oral semaglutide is identical to the acquisitional cost of subcutaneous semaglutide and dulaglutide and similar to the remaining GLP-1 receptor agonists. Consequently, there is not expected to be any significant cost burden or saving associated with the use of oral semaglutide. **Please note – if semaglutide was used earlier in the treatment pathway due to the availability of an oral formulation this would result in a significant cost burden to the Lancashire and South Cumbria health economy, as GLP-1 receptor agonists have the highest acquisition cost of all the antihyperglycaemic agents.**
Service Impact Issues Identified:
Use of oral semaglutide would not be expected to generate additional workload for clinicians managing patients with type 2 diabetes mellitus.
Equality and Inclusion Issues Identified:
None identified
Cross Border Issues Identified:
Both Pan Mersey and GMMMG APCs are in the process of assessing the place of semaglutide in the treatment pathway.
Legal Issues Identified:
N/A
Media/ Public Interest:
N/A

References

[1] Electronics Medicines Compendium, "Summary of Product Characteristics Rybelsus," Novo Nordisk Limited, 03 April 2020. [Online]. Available: https://www.medicines.org.uk/emc/product/11507. [Accessed 20 August 2020].

[2] National Institute for Health and Care Excellence, "Type 2 diabetes in adults: management," December 2015. [Online]. Available: https://www.nice.org.uk/guidance/ng28. [Accessed October 2018].

[3] European Medicines Agency, "Public Assessment Report Rybelsus EMA/95374/2020," 30 January 2020. [Online]. Available: https://www.ema.europa.eu/en/documents/assessment-report/rybelsus-epar-public-assessment-report_en.pdf. [Accessed 21 August 2020].

[4] VR Aroda et al, "PIONEER 1: Randomized Clinical Trial Comparing the Efficacy and Safety of Oral Semaglutide Monotherapy with Placebo in Patients with Type 2 Diabetes," *Diabetes Care,* p. dc190749, 2019.

[5] HW Rodbard et al, "Oral Semaglutide Versus Empagliflozin in Patients with Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial," *Diabetes Care,* vol. 42, pp. 2272-2281, 2019.

[6] J Rosenstock et al, "Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea," *JAMA,* vol. 321, no. 15, pp. 1466-1480.

[7] R Pratley et al, "Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial," *Lancet,* vol. 394, pp. 39-50, 2019.

[8] O Mosenzon et al, "Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial," *The Lancet,* vol. 7, no. 7, pp. 515-527, 2019.

[9] TR Pieber et al, "Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial," *The Lancet,* vol. 7, no. 7, pp. 528-539, 2019.

[10] B Zinman et al, "Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial," *Diabetes Care,* vol. 42, p. 2262–2271, 2019.

[11] I Avgerinos et al, "Oral semaglutide for type 2 diabetes: A systematic review and meta-analysis," *Diabetes Obes Metab,* vol. 22, pp. 335-345, 2020.

[12] M Husain et al, "Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes,"

NEJM, vol. 381, pp. 841-51, 2019.

[13] SC Bain et al, "Oral Semaglutide Versus Empagliflozin, Sitagliptin and Liraglutide in the UK: Long-Term Cost-Effectiveness Analyses Based on the PIONEER Clinical Trial Programme," *Diabetes Therapy,* vol. 11, pp. 459-277, 2020.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality