Meeting the Challenge of Virtual Diabetes Care: A Consensus Viewpoint on the Positioning and Value of Oral Semaglutide in Routine Clinical Practice

Marc Evans · Angharad R. Morgan · Stephen C. Bain ·

Sarah Davies · Debbie Hicks · Pam Brown · Zaheer Yousef ·

Umesh Dashora · Adie Viljoen · Hannah Beba · W. David Strain

ABSTRACT

While glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, are among the most effective drugs for treating people with type 2 diabetes (T2D), they are clinically under-utilised. Until recently, the only route for semaglutide administration was via subcutaneous injection. However, an oral formulation of semaglutide was recently licensed, with the potential to address therapy inertia and increase patient adherence to treatment, which is essential in controlling blood glucose and reducing complications. The availability of oral semaglutide provides a new option for both clinicians and patients who are reluctant to use an injectable agent. This has been of particular importance in addressing the challenge of virtual diabetes care during the COVID-19 pandemic, circumventing the logistical problems that are often associated with subcutaneous medication administration. However, there remains limited awareness of the clinical and economic value of oral semaglutide in routine

M. Evans (✉)
Diabetes Resource Centre, University Hospital Llandough, Penlan Road, Llandough, Cardiff CF64 2XX, UK
e-mail: marclyndon1@hotmail.com

A. R. Morgan
Health Economics and Outcomes Research Ltd., Cardiff, UK

S. C. Bain
Diabetes Research Unit, Swansea University Medical School, Swansea, UK

S. Davies
Woodlands Medical Centre, Cardiff, UK

D. Hicks
Medicus Health Partners, Enfield, London, UK

P. Brown
SA1 Medical Centre, Swansea, UK

Z. Yousef
Wales Heart Research Institute, Cardiff University, Cardiff, UK

U. Dashora
East Sussex Healthcare NHS Trust, Seaford, UK

A. Viljoen
East and North Hertfordshire NHS Trust, Stevenage, UK

H. Beba
County Durham and Darlington NHS Foundation Trust, Durham, UK

W. D. Strain
Diabetes and Vascular Research Centre, University of Exeter Medical School, Exeter, UK

W. D. Strain
The Academic Department of Healthcare for Older Adults, Royal Devon and Exeter Hospital, Exeter, UK

clinical practice. In this article, we present our consensus opinion on the role of oral semaglutide in routine clinical practice and discuss its value in reducing the burden of delivering diabetes care in the post-COVID-19 pandemic period of chronic disease management.

Keywords: Glucagon-like peptide-1 receptor agonists; Oral semaglutide; Type 2 diabetes

Key Summary Points

The need for subcutaneous injection of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has been a barrier to the use of these drugs for some people with type 2 diabetes (T2D) and the healthcare professionals involved in their care.

Oral semaglutide presents an additional option for the management of T2D, which, by removing the injectable barrier, will enable access to the therapeutic benefits of GLP-1RAs to many more people with T2D.

Oral semaglutide could help to address delays in treatment intensification, improve patient adherence and help individuals reach their treatment goals.

The availability of oral semaglutide has been of particular importance in addressing the challenge of virtual diabetes care during the COVID-19 pandemic, circumventing the logistical problems that are often associated with subcutaneous medication administration.

INTRODUCTION

Type 2 diabetes (T2D) is a major public health crisis, with an estimated 463 million adults currently affected worldwide and a projected increase to 578 million by 2030, and 700 million by 2045 [1]. Poorly controlled glycaemia

and delays in treatment intensification increase the risk of related microvascular complications and elevate the risk of cardiovascular (CV) disease in people with T2D [2, 3]. Only 50% of adults with T2D in the UK achieved their glycated haemoglobin (HbA1c) target in 2020, and only 36% achieved all HbA1c, cholesterol and blood pressure targets [4]. Consequently, a large proportion of the T2D population are at increased risk of diabetes-related complications, despite the number of treatments currently available.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are among the most effective drugs for treating people with T2D, providing good glycaemic control with a low risk of hypoglycaemia in those for whom other oral anti-diabetic drugs (OADs), such as metformin, have failed to adequately control their condition [5, 6]. However, despite a wealth of evidence in relation to the efficacy, safety and potential CV outcome benefits, GLP-1 RAs are under-utilised [7]. While perceived high acquisition cost (albeit at a cheaper cost per unit HbA1c reduction than dipeptidyl peptidase-4 [DPP-4] inhibitors) and positioning in clinical guidelines are contributory factors, reluctance to use subcutaneous injectable medications may also play a significant role, with as many as 49% of general practitioners in the UK reporting that the injectable route of administration is a barrier to prescribing a GLP-1 RA [8]. There is also the consideration of time and resources spent by healthcare personnel in educating people with T2D about initiating injectable therapies, which has become more apparent with virtual clinics replacing traditional face-to-face diabetes clinics as a consequence of the COVID-19 pandemic in order to minimise inter-individual contact within surgeries [9].

Virtual clinics for remote consultations present multiple clinical and therapeutic challenges, including ensuring an equitable access to necessary technologies, difficulties in performing key health checks (such as testing blood pressure, HbA1c or urine sampling) [10], maintenance of patient relationships and difficulties in patient education about injectable therapies [11]. These issues have likely led to significant delays in treatment

intensification, lack of patient adherence and fewer people reaching their treatment goals.

It is well recognised that therapy adherence tends to be greater with oral as opposed to injectable therapies in people living with diabetes [12]. Oral semaglutide, the first oral GLP-1 RA, has demonstrated superior glycaemic control compared with other oral therapies and equivalent metabolic effects compared to once-daily liraglutide (a comparator GLP-1 RA), along with the benefit of weight loss with a once-daily pill [13–15]. Oral semaglutide was approved for the treatment of T2D in adults by the European Medicines Agency (EMA) in June 2020 and consequently was made available across all 27 European Union member states and the UK. As such, patients and clinicians who may be reluctant to initiate an injectable drug for T2D may benefit from the ease of drug initiation with oral semaglutide. This is especially important during the COVID-19 pandemic as healthcare providers can prescribe the drug virtually without worrying about the logistics of starting a person with T2D on a new route of medication administration, such as attempting to teach the injection technique virtually or requiring a clinic visit for that purpose. However, there remains limited awareness of the clinical and economic value of oral semaglutide to healthcare system stakeholders involved in the management of T2D. In this article we develop a consensus opinion on the role of semaglutide in routine clinical practice and discuss the value of oral semaglutide with respect to the holistic healthcare system in terms of providing a potential solution to the burden of diabetes care in a post-COVID-19 pandemic period of chronic disease management.

This article is based on previously published studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE ROLE OF ORAL SEMAGLUTIDE IN THE MANAGEMENT OF T2D

The GLP-1 RAs are effective glucose-lowering agents that are a standard feature in T2D treatment guidelines, including the National Institute for Health and Care Excellence (NICE) guidelines which recommend that GLP-1 RAs are only prescribed after oral treatment failure and if weight loss is a desirable outcome [16]. The current NICE guidelines are considered by many to be restrictive and out of alignment with contemporary practice as they fail to take into account the full benefits of GLP-1 RAs. This is a consequence of these guidelines being published prior to CV benefit being demonstrated with liraglutide, dulaglutide and semaglutide. However, it should be noted that these guidelines are presently being updated, with planned publication in 2022, and that this update is expected to better align with international consensus on GLP-1 RA positioning.

The Cardiology Renal and Metabolic (CaReMeUK) group recommends GLP-1 RAs as a second-line therapy following metformin treatment failure in people with T2D who have atherosclerotic cardiovascular disease (ASCVD), including cardiac, peripheral artery and cerebrovascular disease; chronic kidney disease (CKD); and insufficiently controlled HbA1c targets [17]. The European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes (EASD), recommends GLP-1 RAs, including oral semaglutide, as a first-line treatment in persons with T2D and CV disease at high risk of CV events—they are otherwise recommended after failure of metformin monotherapy to adequately control blood glucose levels [18]. The American Diabetes Association (ADA), also in collaboration with EASD, recommends GLP-1 RAs in people with T2D with a compelling need to minimise weight gain/promote weight loss or to minimise hypoglycaemia or with established CV disease, as a second-line therapy following metformin monotherapy [19].

Semaglutide improves hyperglycaemia by stimulating beta-cell insulin secretion and reducing alpha-cell production of glucagon secretion in both the fasting and post-fed state [20, 21]. Lower glucagon levels result in a reduction in post-hepatic glucose production. Additionally, the drug slows gastric emptying and improves satiety, thereby favouring weight loss [20, 21]. Furthermore, semaglutide also

demonstrates a beneficial effect on plasma lipids, lowering systolic blood pressure and reducing inflammation [22, 23].

Co-formulation of semaglutide with the absorption enhancer sodium N-(8-[2-hydroxy-benzoyl] amino) caprylate (SNAC) increases gastric pH at the site of adherence on the gastric mucosa, allowing the peptide to safely exit the pill and be absorbed into the capillaries of the gastric mucosa [24]. This formulation offers people with T2D the option of an oral GLP-1 RA treatment with similar efficacy in reducing HbA1c and body weight, and with similar tolerability, as most injectable GLP-1 RAs [25].

The PIONEER (Peptide Innovation for Early Diabetes Treatment) trials, a global trial programme that enrolled approximately 9500 people with T2D on various background therapies across eight global clinical trials and two centres in Japan, demonstrated that oral semaglutide reduced HbA1c more than placebo, empagliflozin (a sodium-glucose transport protein 2 [SGLT2] inhibitor) or sitagliptin (a DPP-4 inhibitor), and showed similar HbA1c reductions to liraglutide. It also demonstrated greater reductions in body weight than placebo, sitagliptin or liraglutide, and a similar reduction to empagliflozin (Table 1) [13–15, 23, 26–30]. Furthermore, oral semaglutide had a safety profile consistent with that of subcutaneously injected GLP-1 RAs, with the most common adverse reactions being nausea, diarrhoea and, when used with insulin and/or sulfonylurea (SU), hypoglycaemia [31]. Additionally, a recent network meta-analysis demonstrated that orally administered semaglutide had an efficacy similar to or better than semaglutide adminstered by subcutaneous injection, as well as similar tolerability [25].

With regards to CV outcomes, there are no completed CV outcomes trials (CVOTs) for oral semaglutide at present. The event-driven, double-blind PIONEER 6 trial, for which data analysis was halted as soon as it accumulated the necessary number of events to demonstrate noninferiority, was powered to determine excess CV risk associated with oral semaglutide and demonstrated noninferiority of oral semaglutide to placebo, ruling out an excess CV risk [27]. Post hoc analysis of PIONEER 6 and

SUSTAIN 6 showed that semaglutide consistently improved major adverse cardiovascular event (MACE) outcomes versus placebo, irrespective of the mode of administration [22]. In addition, a post hoc analysis of the LEADER, SUSTAIN 6 and PIONEER 6 trials demonstrated that semaglutide was particularly effective in reducing stroke incidence in patients with T2D and high CV risk [32], a complication that is considered by people with T2D to be a particular concern [33]. PIONEER 6 was not powered to prove superiority and, thus, CV benefit. However, the ongoing SOUL CVOT (A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes; NCT03914326) will further inform on CV outcomes with oral semaglutide over a longer period of time and assess a larger population than PIONEER 6 [34]. The primary endpoint is time to the first occurrence of MACE, and this trial is powered for an assessment of superiority compared to placebo.

The findings highlighted in the clinical trial data indicate that oral semaglutide presents a valuable option for managing T2D, with the potential to expand the number of people with T2D benefiting from GLP-1 RAs. As such, oral semaglutide should be considered alongside other recommended OADs as second-line treatment in place of injectable GLP-1 RAs. While both GLP-1 RAs and SGLT2 inhibitors have demonstrated efficacy as a second-line treatment for people with T2D with heart failure (HF) and/or CKD comorbidities [35], SGLT2 inhibitors should be the preferred option for this group of people with T2D, since they provide a greater benefit, but at a significantly lower cost [36]. As a consensus group, we recommend that oral semaglutide should be considered for metabolic control over alternative options, such as DPP-4 inhibitors, SUs and thiazolidinediones (TZDs). Furthermore, in patients with T2D and HF/CKD, for whom SGLT2 inhibitors may be considered a preferential therapy, when additional glucose-lowering effects are required, such as in patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, oral semaglutide should be considered as the preferred add-on OAD therapy.

Table 1 Summary of result from the global PIONEER trials

Trial	Intervention	Comparator	Population	Primary endpoint(s)[a]	Secondary endpoint(s)[a]	Results summary
PIONEER 1 (Aroda et al. [26])	Semaglutide (3, 7 or 14 mg); monotherapy	Placebo	HbA1c 7.0–9.5%; management by diet and exercise (n = 703)	HbA1c change (%), week 26 ETD: 3 mg: −0.6%* 7 mg: −0.9%* 14 mg: −1.1%*	Body weight change, week 26 ETD: 3 mg: −0.1 kg 7 mg: −0.9 kg 14 mg: −2.3 kg*	Semaglutide (7 mg, 14 mg) resulted in significant reductions in HbA1c and body weight
PIONEER 2 (Rodbard et al. [14])	Semaglutide (14 mg) + metformin	Empagliflozin (25 mg) + metformin	HbA1c 7.0–10.5%; uncontrolled on metformin (n = 787)	HbA1c change (%), week 26 ETD: −1.3 vs. −0.9%*	Body weight change, week 26 ETD: −3.8 vs. 3.7 kg	Semaglutide was superior to empagliflozin with meaningful reductions in HbA1c at 26 weeks Superior weight loss not confirmed at week 26, significantly better than empagliflozin at week 52
PIONEER 3 (Rosenstock et al. [15])	Semaglutide (3, 7, or 14 mg) + metformin ± SU	Sitagliptin (100 mg) + metformin ± SU	HbA1c 7.0–10.5%; uncontrolled on metformin (n = 1864)	HbA1c change (%), week 26 ETD: 3 mg: +0.13% 7 mg: −0.3%* 14 mg: −0.5%*	Body weight change, week 26 ETD: 3 mg: −0.6 kg 7 mg: −1.6 kg* 14 mg: −2.5 kg*	Semaglutide (7 mg, 14 mg) resulted in significantly greater reductions in HbA1c and body weight

Table 1 continued

Trial	Intervention	Comparator	Population	Primary endpoint(s)[a]	Secondary endpoint(s)[a]	Results summary
PIONEER 4 (Pratley et al. [13])	Semaglutide (14 mg) + metformin ± SGLT2 inhibitor	Liraglutide (1.8 mg) + metformin ± SGLT2 inhibitor Placebo + metformin ± SGLT2 inhibitor	HbA1c 7.0–9.5%; uncontrolled on metformin (n = 711)	HbA1c change (%), week 26; − 1.2 vs. − 1.1* vs. − 0.2%*	Body weight change, week 26; − 4.4 vs. − 3.1 vs. − 0.5 kg*	Semaglutide was non-inferior to daily injections of liraglutide and superior to placebo in decreasing HbA1c, and superior in decreasing bodyweight over both comparators at week 26
PIONEER 5 (Mosenzon et al. [28])	Semaglutide (14 mg) ± metformin ± SU; semaglutide (14 mg) ± basal insulin ± metformin	Placebo ± metformin ± SU; Placebo ± basal insulin ± metformin	HbA1c 7.0–9.5%; eGFR 30–59 mL/min per 1.73 m² (n = 324)	HbA1c change (%), week 26; − 1.0 vs. − 0.2%*	Body weight change, week 26; − 3.4 vs. − 0.9 kg*	Semaglutide (14 mg) was superior to placebo in decreasing HbA1c and bodyweight
PIONEER 6 (Husain et al. [27])	Semaglutide (target dose: 14 mg)	Placebo	Age ≥ 50 years, established CV/CKD; Age ≥ 60 years, CV risk factors only (n = 3183)	First occurrence of a MACE; 3.8 vs. 4.8% HR: 0.79*	MACE + unstable angina or hHF; 5.2 vs. 6.3% HR: 0.82	Noninferiority of oral semaglutide to placebo, ruling out an 80% excess cardiovascular risk
PIONEER 7 (Pieber et al. [29])	Semaglutide (flexible dose adjustment: 3, 7, or 14 mg) + metformin, SGLT2 inhibitor, SU or thiazolidinediones	Sitagliptin (100 mg) + metformin, SGLT2 inhibitor, SU or thiazolidinediones	HbA1c 7.5–9.5% (n = 504)	HbA1c change (< 7%), week 52; 58 vs. 25% OR: 4.40*	Body weight change, week 52; − 2.6 vs. − 0.7 kg*	Semaglutide provided superior glycaemic control and weight loss compared with sitagliptin

Table 1 continued

Trial	Intervention	Comparator	Population	Primary endpoint(s)[a]		Secondary endpoint(s)[a]		Results summary
				HbA1c change (%), week 26	ETD:	Body weight change, week 52	ETD:	Semaglutide was superior to placebo in reducing HbA1c and body weight
PIONEER 8 (Zinman et al. [30])	Semaglutide (3, 7 or 14 mg) + insulin ± metformin	Placebo + insulin ± metformin	HbA1c 7.0–9.5% (n = 731)		3 mg: – 0.5%*		3 mg: – 0.9 kg	
					7 mg: – 0.9%*		7 mg: – 2.0 kg*	
					14 mg: – 1.2%*		14 mg: – 3.3 kg*	

ACM all-cause mortality, *CKD* chronic kidney disease, *CV* cardiovascular, *eGFR* estimated glomerular rate *ETD* estimated treatment difference, *HbA1c* haemoglobin A1c, *bHF* hospitalisation for heart failure, *HR* hazard ratio, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *OR* odds ratio, *SGLT2* sodium-glucose cotransporter-2, *SU* sulfonylurea

*Statistically significant result

[a]Efficacy assessed according to the treatment policy estimand, defined as the difference between treatments in change in HbA1c and body weight regardless of trial product discontinuation and/or addition of rescue medication

THE ECONOMIC VALUE OF ORAL SEMAGLUTIDE FOR MANAGING T2D

Based on 52-week data from the PIONEER 2, 3 and 4 randomised controlled trials, oral semaglutide was assessed for long-term cost effectiveness versus empagliflozin, sitagliptin and liraglutide in the UK setting, for people with diabetes who require blood glucose control and weight control [37]. Oral semaglutide was demonstrated to have superior cost effectiveness over sitagliptin and empagliflozin, with incremental cost-effectiveness ratios (ICERs) of £4930 and £11,006 per quality-adjusted life year (QALY) gained, respectively, as well as dominance over liraglutide (cost saving with greater health gain).

Analysis based on a network meta-analysis of PIONEER 2 (oral semaglutide vs. empagliflozin) with the SUSTAIN trials comparing once-weekly semaglutide with sitagliptin, exenatide and canagliflozin (SUSTAIN 2, 3 and 8 respectively) [14, 38–40] demonstrated that oral semaglutide was strongly cost effective versus empagliflozin as an add-on to other OADs (including metformin) in people with inadequate glycaemic control, with a base-case ICER of £4439 per QALY gained [41]. Conversely, another cost-effective analysis demonstrated empagliflozin was dominant versus oral semaglutide, in addition to metformin in people with T2D who had experienced hospitalisation for HF, using data from the PIONEER 2 trial [42]. Given the benefits of SGLT2 inhibitors in people with HF and CKD, the presence of these comorbidities should be considered when evaluating cost-effective options for glycaemic control.

While treatment costs of oral semaglutide may be greater than those of other oral agents, such as DPP-4 inhibitors, the additional prescription costs may be offset by cost savings due to the avoidance of both diabetes-related morbidity and excess service utilisation consequent upon the superior efficacy of oral semaglutide. The oral formulation of semaglutide may also reduce the need to utilise specialist services for GLP-1 RA treatment initiation. This has obvious implications for healthcare service efficiencies,

cost savings and capacity issues, whilst also addressing the burden of therapy inertia in people with T2D which has been further exacerbated during the COVID-19 pandemic.

Based on the above discussion, oral semaglutide can be considered as representing good value for money. There is, however, the wider value of oral semaglutide to the healthcare system, and associated stakeholders, beyond price and cost-effectiveness analyses to consider.

THE VALUE OF ORAL SEMAGLUTIDE TO HEALTHCARE BEYOND PRICE

While GLP-1RAs are among the most effective drugs for treating people with T2D, the reluctance of some patients to accept subcutaneous injections and the use of healthcare resources associated with injectables has resulted in low uptake of GLP-1RAs in clinical practice. Oral semaglutide may circumvent these issues and provide a new avenue for clinicians to enrol people with T2D on effective new therapies.

Being able to offer people with T2D the option of an oral GLP-1 RA can make it easier and quicker for people with T2D to be initiated on a GLP-1 RA, without the burden of considering an injectable route of administration. This has been of particular importance during the COVID-19 pandemic, as healthcare providers now have the option of an oral treatment without having to consider the logistical issues associated with initiating a person with T2D on an injectable therapy, whether by providing education virtually or by a physical visit for that purpose. As the simpler method of treatment administration can be explained more easily through virtual communications to people with diabetes compared with injection technique instruction, oral semaglutide facilitates the reduction of unnecessary attendance at clinics, reducing the risk of COVID-19 transmission from face-to-face appointments, including the visits of district nurse for those who are unable to self-inject.

Patient preference should also be taken into account when considering oral daily treatments versus weekly subcutaneous injections. Many people may struggle with the concept of using needles independently, and some may refuse to escalate treatment to injectables despite consultations explaining the benefits of GLP-1 RA over insulin, such as those with a severe phobia of needles. Furthermore, dexterity issues and hand osteoarthritis may also impede implementation of an injection technique, particularly in attaching a needle and sustaining the thumb pressure required to inject. Oral treatment in these instances may be more likely to be accepted and reduce the inertia surrounding the uptake of GLP-1 RAs.

Oral semaglutide may circumvent all of the issues described above and help to deliver value in the context of diabetes care not only to the healthcare system, but also to patients and their families.

APPROPRIATE PRESCRIBING OF ORAL SEMAGLUTIDE IN T2D

The selection of appropriate people with T2D for oral semaglutide treatment is critical for maximising both the risk–benefit profile and value associated with this treatment. Based on the PIONEER clinical trial data, as well as the label indication, and our expert consensus opinion, we have developed a checklist that serves as a tool to advise on the appropriate prescribing of oral semaglutide in people with T2D (Table 2). The checklist follows a traffic light system which recommends that people in the green section should be considered for treatment with oral semaglutide. This group includes adults (aged 18–74 years of age) with T2D without HF/CKD who require second-line treatment after metformin to control glycaemia. Oral semaglutide could also be considered in those individuals who do not have HF/CKD but do have a history of stroke or transient ischemic attack (TIA), or have ASCVD or are at high CV risk.

In the PIONEER trials, there were no overall differences in the safety or efficacy of oral semaglutide between older adults aged > 75 years with T2D and younger people with T2D [28]. However, the overall therapeutic experience of oral semaglutide in older adults is

Table 2 Appropriate prescribing of oral semaglutide in patients with type 2 diabetes

	Consider prescribing oral semaglutide for people with T2D without HF/CKD with any of the following:
🟢	• Age 18-74 years and insufficiently controlled T2D, after first line therapy with metformin • ASCVD, or at high risk of ASCVD • Past history of stroke or TIA
	Consider prescribing WITH CAUTION oral semaglutide for people with T2D with any of the following:
🟡	• Age ≥ 75 years old • Diabetic retinopathy • History of pancreatitis • History of bariatric surgery • Personal or family history of medullary thyroid carcinoma • Severe kidney disease (eGFR <30 ml/min/1.73 m^2) • Acute kidney injury
	DO NOT consider prescribing oral semaglutide in people with T2D with any of the following:
🔴	• Age < 18 years old • Multiple Endocrine Neoplasia syndrome type 2 • End-stage kidney disease (eGFR <15 ml/min/1.73 m^2) • Congestive heart failure (NYHA) class IV • Previous DKA • Gastroparesis • Type 1 diabetes mellitus • Women who are pregnant • Women who are breastfeeding

ASCVD atherosclerotic cardiovascular disease, *CVD* cardiovascular disease, *DKA* diabetic ketoacidosis, *eGFR* estimated glomerular filtration rate, *NYHA* New York Heart Association, *TIA* transient ischemic attack, *T2D* type 2 diabetes

relatively limited, and, as such, prescribing in this population should be considered with caution (amber section of the checklist).

The SUSTAIN 6 CVOT reported an increased incidence of diabetic retinopathy complications in patients randomised to semaglutide compared to placebo [43]. The majority of these adverse outcomes were attributed to a large and rapid fall in HbA1c during the first 16 weeks of the trial in individuals with pre-existing retinopathy who had a high HbA1c at baseline and were already receiving insulin [44]. This finding is supported by data from the LEADER and REWIND trials that demonstrated an increase in retinopathy events associated with a large, sudden fall in HbA1c in participants who were randomised to liraglutide and dulaglutide, respectively [45, 46]. Therefore, in alignment with other published guidance [47], we recommended that oral semaglutide should be prescribed with caution in people with T2D with a history of diabetic retinopathy requiring active ophthalmology follow-up, receiving insulin treatment and with poor glycaemic control (HbA1c > 91 mmol/mol [0.5%]), and monitored closely, particularly if there has been no recent retinal screening.

Treatment with oral semaglutide is not recommended in people with end-stage kidney disease (eGFR < 15 ml/min/1.73 m^2); however, pharmacokinetic–pharmacodynamic studies have demonstrated no significant effect of declining eGFR on the pharmacological profile [48]. The PIONEER clinical trial programme largely excluded patients with eGFR < 30 ml/min/1.73 m^2; hence experience in this group is limited. While semaglutide may be prescribed in patients with eGFR of 15–30 ml/min/1.73 m^2, due to limited experience in this group we would suggest proceeding with caution in such

patients. Similarly, in patients with acute kidney injury, the use of oral semaglutide should be used with caution, largely from the perspective that should significant gastrointestinal effects occur, these could potentiate dehydration and exacerbate kidney injury.

While there is no definitive evidence of a causal association between semaglutide and acute pancreatitis, we would advocate the use of oral semaglutide with caution in patients with prior history of pancreatitis, be that idiopathic or precipitated by a specific aetiological factor, such as, for example, gallstone pancreatitis.

Patients with T2D and with prior bariatric surgery may be considered as appealing candidates for a GLP-1 RA. A study assessing the safety and efficacy of liraglutide in people with persistent or recurrent T2D after bariatric surgery demonstrated that liraglutide treatment was associated with a difference of − 1.22% (95% confidence interval − 19.7 to − 7.0; $p = 0.0001$) in HbA1c change from baseline to 26 weeks and no difference in the frequency of adverse events, compared with placebo [49]. The effects of bariatric surgery and in particular the different surgical modalities on the absorption, and thus clinical efficacy, of oral semaglutide have not been studied, as such we would recommend the use of oral semaglutide with caution in patients with T2D and prior bariatric surgery.

Oral semaglutide increases the incidence of thyroid C-cell tumours in certain settings. A meta-analysis of once-weekly GLP-1 RAs in people with T2D showed no increased risk in comparison with other treatments [50]; however, there are documented cases of medullary thyroid carcinoma in people with T2D treated with the GLP-1 RA liraglutide, although a causal relationship is not established. We therefore recommend caution in the use of oral semaglutide in patients with a personal or family history of medullary thyroid carcinoma. However, we do not recommend prescribing oral semaglutide in people with T2D with multiple endocrine neoplasia syndrome type 2, guidance which is in accordance with the licence.

Oral semaglutide is not indicated as a treatment in people with type 1 diabetes, for the treatment of diabetic ketoacidosis (DKA), or in those with a history of DKA [51]. DKA has been documented in insulin-dependent people with T2D that initiate GLP-1 RAs, who rapidly discontinue insulin therapy ahead of initiation.

The safety and efficacy of oral semaglutide has also not been established in the paediatric setting and is therefore not indicated for those aged < 18 years. There is also no documented experience of treating people with congestive HF, NHYA (New York Heart Association) class VI, and as such treatment in this population should not be considered.

Oral semaglutide is contraindicated in pregnant women due to the potential risk to the foetus; treatment should only be considered in instances where treatment benefit justifies the risk to the foetus. Oral semaglutide should be discontinued at least 2 months before planned pregnancy due to the long washout period associated with this drug [52]. Improved glycaemic control and weight loss afforded by oral semaglutide has the potential to improve fertility, and patients should be informed of this benefit if they are planning a pregnancy in the future, although they should be warned to avoid conception whilst taking the drug. Oral semaglutide is not recommended in women who are lactating. There are no data regarding the presence of semaglutide in breast milk, although in animal studies it was demonstrated that semaglutide and its excipients or associated metabolites were present.

GLP-1 RAs have a well-recognised effect on gastric emptying. Consequently, we would not advocate the use of oral semaglutide in people with T2D and established gastroparesis.

PRACTICAL CONSIDERATIONS FOR OPTIMAL USE OF ORAL SEMAGLUTIDE

Due to the formulation of oral semaglutide, clinicians need to be aware of specific considerations in its administration. As absorption of oral semaglutide is reduced if taken with food and large volumes of fluid, with higher levels of absorption from longer post-dose fasting period [24, 52], individuals prescribed oral semaglutide

should be informed that once-daily dosing is required at least 30 min before eating, drinking or taking other oral medicinal products. They should additionally be advised that the tablet should be swallowed whole (and should not be split, crushed or chewed) with up to half a glass of tap water (approximately 120 mL/4 fluid oz) [52] to ensure it traverses the oesophagus (avoiding irritancy) and reaches the stomach to be absorbed. It is also possible that consuming more than the recommended 120 mL water may also adversely impact absorption [24]. Thus, to ensure adherence to this instruction, it is imperative that the pack label includes the volume of water in the administration instructions. Furthermore, given the importance of adhering to the administration directions in achieving an effective bioavailability, it is vital that healthcare professionals, including pharmacists, effectively communicate these instructions and their importance to those initiating treatment with oral semaglutide.

Gradual dose escalation is recommended (and if a dose is missed, the missed dose should be skipped and the next dose should be taken the following day), with 3 mg tablets taken daily in the first month, increasing to a maintenance daily dose of 7 mg tablets in the second month and thereafter. After at least 1 month of 7 mg tablets once daily, the dose can be increased to a maintenance daily dose of 14 mg tablets to further improve glycaemic control if required (taking two 7 mg tablets to achieve the effect of one 14 mg dose has not been studied, but would increase the cost, and so is not recommended). This escalation will minimise gastrointestinal adverse reactions during the initial stages of treatment [21]. While these reactions are typically mild to moderate and abate over time [20, 21], monitoring of renal function in people with T2D experiencing severe gastrointestinal reactions is recommended in case of potential dehydration.

Treatment response should be assessed initially at 3 months to identify those with weaker response than expected, although full response will not be observed until 6 months after first dose. Absorption may vary between individuals, and in those achieving insufficient response adherence should be examined and treatment

discontinuation considered. No dose adjustments are necessary in those with severe renal impairment (eGFR < 15 ml/min/1.73 m^2), upper gastrointestinal disease or hepatic impairment, as the presence of these comorbidities does not affect the pharmacokinetics of oral semaglutide [28].

Medication management strategies to mitigate potential adverse events and to support treatment continuation are important and could include the incorporation of treatment pauses or dose reduction when tolerability issues arise, alongside patient education [53]. The most frequent side-effects from using GLP-1 RAs are gastrointestinal (GI). Individuals need to be warned of the possibility of nausea and vomiting but should also be reassured that these are usually mild to moderate in intensity and dissipate with time. The importance of continuing with treatment should be reiterated, and slowed titration may be considered in severe cases until GI side effects have resolved. Individuals should also be provided with education regarding smaller meal sizes and reduced carbohydrate and fat content in their diets, as well as to generally reinforce healthy eating to achieve best outcomes with this drug, thereby reducing the incidence of nausea, vomiting and other GI side effects.

Oral semaglutide alone is not associated with an increased risk of hypoglycaemia. However, when it is used in combination with agents that may cause hypoglycaemia, such as, for example, SUs or exogenous insulin, the potential improvement in glucose control may be associated with hypoglycaemia, and patients should be educated accordingly. In order to reduce potential hypoglycaemia risk, our consensus viewpoint is that in patients with Hb1Ac < 7.5%, a dose reduction of insulin and SU insulin of up to 50% may be considered, while in those with HbA1c < 8%, up to 20% dose reduction may be considered.

Further consideration should be given when prescribing oral semaglutide to people already taking oral medications that require ingestion on an empty stomach, such as bisphosphonates and levothyroxine. Oral bisphosphonates should not be taken with oral semaglutide, and instead annual intravenous infusions should be

considered as an alternative. As administration of oral semaglutide in people taking thyroxine can result in excess thyroxine absorption [54], monitoring of thyroid parameters should be undertaken when treating people with T2D with semaglutide if they are also prescribed levothyroxine. In addition, dosing schedules should be altered, such as administrating levothyroxine at night, in order to minimise any potential impact on thyroid hormone levels that may occur if oral semaglutide and levothyroxine are administered at the same time of day. It is important that these issues are discussed with the individual to ensure that appropriate dosing of both medications is compatible with lifestyle, thus optimising the potential for therapy adherence. The REVISE study demonstrated the importance of educating people with diabetes on the relative merits of the available options to ensure that they are able to initiate new therapies that fit their lifestyle [55].

SUMMARY

In the PIONEER clinical development programme, oral semaglutide demonstrated significant HbA1c and weight reductions, and as such may be considered as the most efficacious oral therapy with respect to metabolic control in people with T2D. The evolution of GLP-1 RA therapy into an oral formulation will enable many more people with T2D to access the therapeutic benefits of this treatment class and help address the well-described issue of therapy inertia in this population. The COVID-19 pandemic has only served to further exacerbate the problems of therapy inertia in the management of people with T2D, and the availability of oral semaglutide at this time further enhances the clinical and economic value of this treatment in the management of people with T2D.

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Compliance with Ethics Guidelines. This article is based on previously published studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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