

## ORAL SEMAGLUTIDE: A STRATEGIC CHOICE FOR PRIMARY CARE

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### ABSTRACT

**Type 2 diabetes has been a long-standing concern worldwide and in Singapore. Having one of the highest diabetes prevalence rates in Southeast Asia, Singapore has explored various ways of enhancing the management of chronic illnesses, one of which is to treat diabetic patients in primary care settings rather than speciality facilities. Primary care physicians are tasked to manage their diabetic patients' glycated haemoglobin levels, along with a myriad of related complications including hypoglycaemia, cardiovascular risk, and body weight issues. With the ever-increasing complexity of population health demands, oral semaglutide can be a strategic weapon utilised by primary care doctors to treat type 2 diabetic patients. In terms of glycaemic control and body weight reduction, oral semaglutide has outperformed several other oral anti-diabetic medicines. Moreover, oral semaglutide has a proven cardiovascular safety profile with potential benefits. The development of oral semaglutide, rather than the injectable type, has made it simpler for patients to benefit from semaglutide treatment. Oral semaglutide is a feasible and effective strategy in type 2 diabetes management, for both initiation and intensification needs, and is well positioned to be a game changer in primary care.**

**Keywords:** Type 2 diabetes, semaglutide, oral, primary care

**SFP2022; 48(3):**

### INTRODUCTION

Type 2 diabetes (T2D) is a severe public health concern, affecting about 463 million adults globally, with numbers expected to rise to 578 and 700 million by 2030 and 2045 respectively. Singapore has one of the highest diabetes prevalence rates in Southeast Asia of 14.9 percent; one in three Singaporeans is predicted to be diabetic in their lifetime and the overall number of diabetics is expected to exceed one million by 2050.<sup>1,2</sup>

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In Singapore, the term “right-siting” was coined in 2004 to reflect the idea that patients with stable chronic illnesses should be handled by primary care physicians, in order to mitigate the rise in healthcare costs and to free up resources in tertiary care. Since then, the public and private sectors have joined forces to deliver comprehensive and integrated treatment to patients afflicted with diabetes.<sup>3,4</sup> At present, the Primary Care Network (PCN) – a multidisciplinary team consisting of general practitioners (GPs), nurses, care coordinators, and administrative assistants – offers team-based primary health services. Diabetic foot screening, eye screening, and counselling by nurses are some services that patients can benefit from. Concurrently, these services are supported administratively through the use of the chronic disease registry, care coordination, and monitoring of clinical outcomes.<sup>5</sup> Hence, GPs can effectively track their patients' diabetic conditions and treatment progress, with clinical outcomes recorded in compliance with local clinical practice guidelines. This approach has allowed patients to have better glycaemic control over time.<sup>6,7</sup>

Between 2013 to 2019, only 51.5 percent of patients with T2D in the SingHealth Diabetes Registry achieved their personalised glycated haemoglobin (HbA1c) targets.<sup>8</sup> Additionally, from 2019 to 2020, 26 percent of known diabetics still had poor glycaemic control.<sup>9</sup> For such patients, further delays in treatment intensification raise the risk of microvascular problems and cardiovascular disease (CVD).<sup>10-12</sup> This places many diabetic patients in Singapore at a higher risk of diabetes-related complications.

GLP-1 receptor agonists (GLP-1 RAs) are one of the most successful medications for managing patients with T2D, enabling good glycaemic control with minimal risk of hypoglycaemia among those who have failed to manage their disease with other oral anti-diabetic drugs (OADs), like metformin.<sup>13-15</sup> A plethora of evidence has been published in support of their effectiveness, safety, and potential CV benefits.<sup>16,17</sup> However, due to the perceived high price and aversion to using subcutaneous injectable drugs, GLP-1RAs have been underutilised. With the approval of the first oral GLP-1 RA, oral semaglutide can now be a strategic weapon for the primary care settings for uncontrolled diabetic patients.

### RATIONALE AND CLINICAL REASONING FOR THE USE OF GLP-1 RAS IN PRIMARY CARE

#### Challenges Faced in the Healthcare Setting

Global primary care systems have been burdened by extensive need for primary care, increasingly complex

population health demands and difficulties in organising health care resources.<sup>18</sup> In a bid to meet the needs of the population, Singapore's Ministry of Health (MOH) has encouraged the implementation of shared care programmes that involve both the specialists and primary care providers (PCPs) facilitating optimal patient management in primary care for chronic disease.<sup>5,19</sup> Although private GP clinics make up the majority of PCPs in Singapore, only 55 percent of patients with chronic patients are seen by these clinics.<sup>20</sup> This may be due to the challenges PCPs face in T2D management: they need to address concerns such as risk of hypoglycaemia, high body weight, and cardiovascular and renal issues, beyond the mere monitoring of HbA1c levels, but may not be sufficiently equipped to do so.<sup>21</sup> The role of PCPs is undeniably crucial, thus they should be well supported through the use of robust treatment options that can simplify clinical treatment and enhance patients' adherence to anti-diabetic treatment. A strong candidate for consideration would definitely be semaglutide.

### Role of Semaglutide in the Management of T2D

Several guidelines have delineated the usefulness of semaglutide in T2D management. For the majority of T2D patients, metformin is the first-line therapy; however, if patients do not reach their personalised HbA1c targets within 3-6 months, additional glucose-lowering medicine should be introduced.<sup>22-25</sup>

The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) new consensus guidelines for the management of high blood sugar in T2D were introduced in 2018, and the 2019 update recommend that patient-specific comorbidities should be evaluated and certain favourable classes of glucose-lowering medications should be used.<sup>25,26</sup>

GLP-1 RAs are a class of efficacious glucose-lowering class of medication in T2D. GLP-1 RAs, including oral semaglutide, are recommended as first-line therapies in T2D patients with CVD or patients who are at greater risk of cardiovascular events, according to the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD).<sup>18</sup> They are also recommended after metformin monotherapy fails to control blood sugar levels sufficiently.<sup>25,27,28</sup> In patients with T2D who need to lose weight or need to reduce the risk of hypoglycaemia, or those who have developed ASCVD or are at high risk, the ADA recommends GLP-1 RAs.<sup>25</sup>

In patients with T2D who have atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and uncontrolled HbA1c, the Cardiology Renal and Metabolic (CaReMeUK) group recommends GLP-1 RAs as second-line after metformin treatment.<sup>29</sup>

The abovementioned recommendations made in favour of semaglutide underscore the multitude of benefits it confers. In both the fasted and post-fed states, semaglutide lowers blood glucose levels by increasing insulin secretion and lowering glucagon secretion, which results in reduced post-hepatic glucose synthesis.<sup>30-34</sup> Furthermore, it promotes weight reduction by slowing stomach emptying and increasing satiety.<sup>35</sup> Semaglutide also has a positive effect on plasma lipids and decreases inflammation and systolic blood pressure.<sup>30,33,36,37</sup> This is accompanied by a significant improvement in the major adverse cardiovascular event (MACE) outcomes with semaglutide treatment compared to placebo, according to a post-hoc analysis of the cardiovascular outcome trials for semaglutide.<sup>39</sup> In these trials, semaglutide demonstrated particular effectiveness in reducing the risk of non-fatal stroke in T2D patients with high cardiovascular risk.<sup>40</sup> Semaglutide is available in both the injectable and oral formulations, presenting physicians with opportunities for personalising treatment. Oral semaglutide represents the first oral formulation of the GLP-1RA class and was developed through co-formulation with an absorption enhancer. Exhibiting greater HbA1c and weight-lowering effect with a comparable safety profile as most injectable GLP-1RAs, oral semaglutide may confer great value to primary care.<sup>38</sup>

### Value of Oral Semaglutide in the Primary Care Setting

Although GLP-1RAs are one of the most efficacious medications for managing T2D, poor adoption of GLP-1RAs in primary care can be attributed to certain patients' aversion to needles.<sup>29</sup> The availability of oral semaglutide eradicates one barrier to treatment and offers patients a convenient GLP-1RA option that promotes early adoption and enhances treatment adherence. This is especially important in times of the COVID-19 pandemic, which has made telemedicine services commonplace: PCPs can prescribe a GLP-1RA easily without going through the inconveniences associated with injectable treatments.<sup>41</sup> By simplifying diabetes treatment, oral semaglutide brings about greater convenience and ease of administration compared to injections. Ultimately, it adds substantial value to healthcare providers, patients, and their families.<sup>29</sup>

### Patients With T2D Who are Suited for Oral Semaglutide

There are various considerations to be undertaken by a PCP when prescribing medication for their patients with T2D. Oral semaglutide can be used in diverse patient populations and its usage is summarised in Table 1.

**Table 1: Patient groups suitable for oral semaglutide**

Patient groups	Usage of oral semaglutide
Patients who are not suitable for metformin	Oral semaglutide as monotherapy.
Patients whose HbA1c is still uncontrolled by metformin or insulin	Oral semaglutide as second-line treatment or with insulin.
Patients where weight loss is favourable	Oral semaglutide promotes weight loss.
Patients where hypoglycaemia is of concern	Oral semaglutide has low risk of hypoglycaemia.
Patients with renal impairment	No dose adjustments with oral semaglutide.
Patients with hepatic impairment	No dose adjustments with oral semaglutide.
Elderly patients	No dose adjustments with oral semaglutide.

**Oral Semaglutide as Monotherapy or as Second-Line Treatment or With Insulin**

Oral semaglutide is suitable as a monotherapy in T2D patients if metformin is not suitable. If patients are uncontrolled on metformin, the choice of second-line therapy includes GLP-1 RAs, sodium-glucose cotransporter 2 inhibitors (SGLT2i), dipeptidyl peptidase IV inhibitors (DPP-4i), sulfonylureas (SU), and thiazolidinediones (TZD).<sup>42,43</sup> Several studies have proved that oral semaglutide may be a better choice than other OADs and the findings are summarised in Table 2.<sup>44,45</sup> Furthermore, oral semaglutide can be considered as an add-on for patients with T2D on insulin who require further intensification to achieve their glycaemic and body weight targets.<sup>46</sup>

**Table 2: Summary of oral semaglutide versus other OAD**

Study	Findings
PIONEER 2	Lower HbA1c after 26 weeks with oral semaglutide vs empagliflozin (SGLT2-i) in uncontrolled patients with T2D on metformin
PIONEER 3	Lower HbA1c after 26 weeks with oral semaglutide vs sitagliptin (DPP4-i) in uncontrolled patients with T2D on metformin with/without SU

**Oral Semaglutide for Patients With T2D Where Weight Loss Is Favourable**

Fifty percent of the diabetes disease burden is caused by patients being overweight.<sup>47</sup> Hence, an OAD that promotes weight loss like oral semaglutide is a favourable option. Both GLP-1 RAs and SGLT2i have been linked to weight

reduction. DPP-4 inhibitors, on the other hand, had no impact, whilst TZD, SU, and insulin can cause weight gain.<sup>43</sup>

**Oral Semaglutide for Patients With T2D Where Hypoglycaemia Risk Is of Concern**

GLP-1 RAs, metformin, DPP-4i, SGLT2i, and TZD are thought to have a neutral impact on the risk of hypoglycaemia; however, SU and insulin are linked to an increased risk.<sup>42,48</sup> Oral semaglutide, similar to the subcutaneous injection of GLP-1 RAs, has been shown to be associated with a low risk of hypoglycaemia reported across the PIONEER studies.<sup>44,45,49-53</sup>

**Oral Semaglutide for Patients With T2D With Renal Impairment**

Several OADs need to be dosed differently in patients with renal impairment.<sup>19,20</sup> For semaglutide, renal impairment has no clinically significant influence on semaglutide pharmacokinetics, and no dose adjustments are indicated for glomerular filtration rate (GFR)  $\geq 15$  mL/min per  $1.73m^2$ .<sup>54,55</sup> Oral semaglutide has demonstrated its efficacy and safety in patients with T2D and moderate renal impairment.<sup>50</sup>

**Oral Semaglutide for Patients With T2D With Hepatic Impairment**

Dose adjustment is not needed for patients with hepatic impairment. In a study of patients with mild, moderate, or severe hepatic impairment, there was no observed clinically significant change in the pharmacokinetics.<sup>54</sup>

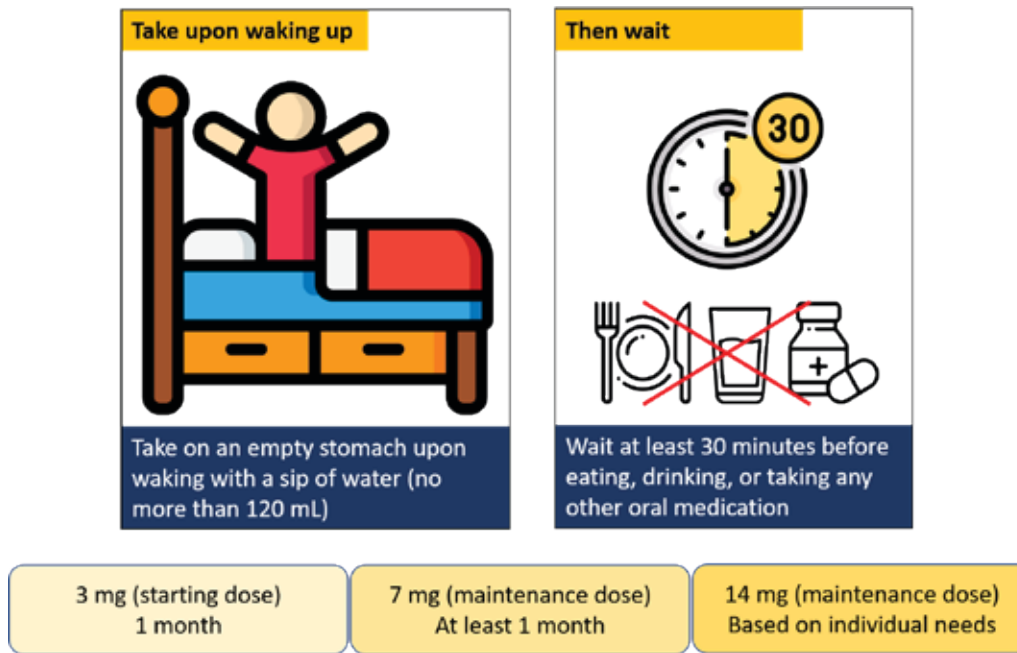
**Oral Semaglutide for Elderly Patients With T2D**

The efficacy and safety of oral semaglutide were shown to be not impacted by age, and no dose adjustment is needed.<sup>54</sup>

**Ease of Dosing**

Patients with T2D are required to take oral semaglutide in a fasted state, with a sip of water ( $\leq 120$  mL) in the morning when they wake up and wait at least 30 minutes before ingestion of any other food, drinks, or oral medication (refer to Figure 1).<sup>56</sup> This guarantees that semaglutide is properly absorbed to produce clinically meaningful effects.<sup>57</sup> Patients with T2D initiate with a starting dose of 3 mg once daily for a month, before moving to the maintenance dose of 7 mg for at least one month (refer to Figure 1). If further reduction in HbA1c is required, the maintenance dose can be increased to 14 mg once daily.<sup>54,56</sup>

**Figure 1: Administration and initiation of oral semaglutide**



**Side Effects of Oral Semaglutide and How to Manage It**

As observed in clinical trials, gastrointestinal side effects were dose-dependent, with <25 percent of patients experiencing nausea at 14 mg dose, and diarrhoea and vomiting occurring at rates of <15 percent.<sup>44,45,49-53</sup> Such side effects were more common during treatment initiation and dose escalation of oral semaglutide. Hence, PCPs can manage patients’ expectations by informing them on the probability of these events and by reassuring them that the symptoms are transient and mild to moderate in severity. Patients can be further advised to minimise consumption of fatty or fried foods or to decrease the amount of food they consume in one sitting. If symptoms worsen and occur for a prolonged period, physicians can consider a temporary dose modification until symptoms subside.

**CONCLUSION**

Oral semaglutide has proven superior efficacy compared to other OADs in terms of lowering HbA1c and body weight, which makes it easier for patients to access the benefits of semaglutide. It has enabled PCPs to overcome challenges faced in primary care and has facilitated prescription as dose adjustments are not required. Overall, it is a realistic and successful way to manage patients with T2D who require both treatment initiation and intensification alike, potentially shifting the paradigm of care in the primary care setting.

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## LEARNING POINTS

- **The need for subcutaneous injection of glucagon-like peptide-1 receptor agonists (GLP-IRAs) has been a barrier to the use of these drugs for 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-IRAs to a greater number of people with T2D.**
  - **Oral semaglutide is the first oral GLP-IRA approved for the treatment of T2D, and demonstrates glucose lowering, body weight loss, a low risk of hypoglycaemia, and favourable CV risk profile.**
  - **To ensure optimal efficacy and to improve compliance with oral semaglutide, it is important for primary care providers to discuss practical issues with patients, such as dosing instructions and gastrointestinal-adverse events.**
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