First-in-Class Oral Semaglutide: Overcoming Barriers of Incretinisation in the Indian Context

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Abstract

Despite the availability of multiple therapeutic options and strategies, patients with type 2 diabetes mellitus (T2DM) the world over have inadequate glycaemic control and India is no exception. Patients with T2DM in India have benefitted from glucagon-like peptide-1 analogues similar to that of patients from other parts of the world. However, subcutaneous treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is limited by their injectable mode of administration. The present review highlights barriers to incretinisation with GLP-1RAs and the role of first-in-class oral semaglutide in the Indian context and provides guidance to physicians on its initiation and uses.

Keywords: First-in-class, glucagon-like peptide-1 receptor agonists, India, innovation, oral semaglutide, type 2 diabetes mellites

INTRODUCTION

Globally, more than 90% of the people with diabetes have type 2 diabetes mellitus (T2DM).[1] In India, there are 74.2 million adults living with diabetes (one in seven adults worldwide), which is predicted to rise to 124.9 million by 2045.[1] It is estimated, 53.1% of patients with diabetes are undiagnosed. Diabetes was responsible for 747,000 deaths in 2021 in South-East Asia.[1]

Despite the availability of multiple therapeutic options and strategies, patients with T2DM the world over have inadequate glycaemic control and India is no exception.[2] A significant decrease in life expectancy and reduced quality of life in patients with poorly managed glycaemia are observed. Such patients often have early complications, which significantly increases the cost of treating diabetes.[3] Appropriate glycaemic control may help in delaying the onset of complications and lower the cost of managing diabetes.[4]

An early implementation of appropriate pharmacotherapy may reduce the burden of uncontrolled glycaemia and subsequent complications. Evidence exists that T2DM can be prevented or delayed and there is accumulating evidence that reversal of T2DM is sometimes possible.[5]

The present review highlights barriers to incretinisation with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the role of first-in-class oral semaglutide (OS) in the Indian context and provides guidance to physicians on its initiation and uses.

MATERIALS AND METHODS

A literature review was performed from PubMed and Google Scholar to obtain available evidence on the efficacy and safety of OS and its recommendations. Systematic reviews, meta-analyses, randomised control trials, and key cited articles relating to OS were reviewed by doctors, and guidance relevant

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to the Indian scenario was framed. The recommendations were discussed at the 15th National Insulin and Incretin Summit (NIIS), held on 26 November 2021 by an expert panel of physicians, endocrinologists, and key opinion leaders. At this summit, a consensus was reached on the guidelines and general suggestions on the use of OS in the Indian context. The recommendations were based on experience, judgement, and expert opinions.

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) belong to the injectable drugs class for managing T2DM. In a glucose-dependent mechanism, GLP-1RAs act by stimulating insulin secretion and suppressing inappropriately elevated glucagon levels. These drugs are also observed to delay gastric emptying and promote satiety and are associated with a negligible risk of hypoglycaemia.[6]

Thus, GLP-1RAs can be viewed as either mimics or facilitators of calorie restriction. In addition, these treatments, unlike other antidiabetic therapies, can address several aspects of the metabolic syndrome, including obesity, hypertension, dyslipidaemia, polycystic ovarian syndrome, and fatty liver.[7,8]

With its well-established safety profile, GLP-1RAs can help lose weight, improve glycaemic control, and reduce the risk of developing hypoglycaemia.[9,10]

Both the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend GLP-1RA as a second-line treatment option in patients with inadequately controlled T2DM despite the use of metformin, especially in those with established atherosclerotic cardiovascular disease (CVD).[11,12] However, in patients who are intolerant to metformin or contraindicated, some GLP-1RAs are suggested as a first-line therapy.[12]

Barriers to Incretinisation in India: Hurdles in Starting and Sustaining with Injectable GLP-1RA

Until September 2019, six different GLP-1RA formulations were available with subcutaneous (SC) administration but with different dosing regimens (once daily, twice daily or once weekly).[13]

Patients with T2DM in India have also benefitted from GLP-1 analogues similar to that of patients from other parts of the world.[14] However, SC treatment with GLP-1 RAs is limited by their injectable mode of administration.[15] Patients' perception of injectable therapy includes perceived difficulty in use and fear of injections.[16,17] This can affect the acceptance of/or adherence to treatment by a patient with T2DM.[16,17] Injectable anti-diabetes drugs had the lowest persistence (28.7%) at 1 year among treatment-naïve patients in a previous study.[18]

Moreover, traditional insulin motivation strategies may not apply to non-insulin injectable therapies while counselling patients with T2DM due to different mechanisms of action, clinical effects, potential side effects, and contraindications and costs compared with insulin.[19]

Certain patients may prefer oral drugs over injectables[20,21] and studies have shown that patients are less likely to stick to treatment regimens that are difficult or inconvenient.[21]

Oral Semaglutide

The United States Food and Drug Administration (FDA) approved oral semaglutide (OS), the first GLP-1RA designed for oral administration, to treat patients with T2DM in September 2019.[13] Sodium N-[8-(2-hydroxy-benzoyl) amino] caprylate (SNAC), an absorption enhancer, has been co-formulated with OS.[22,23] Previous reports have confirmed the safety of SNAC as a co-formulation.[23,24] Semaglutide is protected from degradation by pepsin and the acidic gastrointestinal pH by SNAC, which raises the pH around the tablet.[22]

Additionally, SNAC facilitates the production of semaglutide monomers, which are more readily absorbed.[22] SNAC also improves semaglutide absorption across the gastric epithelium that occurs via the transcellular pathway.[22] The development of a co-formulation of orally administered semaglutide with the absorption enhancer SNAC has overcome the barrier of poor absorption and degradation in the stomach, thereby increasing bioavailability.[22]

Multifaceted Management of T2DM: Role of Oral Semaglutide

The safety and efficacy of OS versus that of placebo and other oral and injectable antidiabetic agents were studied via the Peptide InnOvatioN for Early DiabEtes Treatment (PIONEER) programme. The major pioneer studies that evaluated the safety and efficacy of OS are depicted in Table 1. OS addresses glycaemic control and was effective even in subjects on multiple therapies.

Inadequate Glycaemic Control

There is inadequate glycaemic control with polytherapy in India despite multiple therapeutic options and strategies. A total of 77% of the people with diabetes in India have inadequate glycaemic control, with a mean HbA1c level of 8.6%.[2] Real-world evidence from Mumbai reported that 86% of people with uncontrolled diabetes are on > three antidiabetic agents.[25] In the absence of timely intervention, glycaemic control worsens with an increase in the duration of diabetes despite polytherapy (>3 drugs).[25]

Early intervention with OS can reduce the burden of uncontrolled glycaemia and subsequent complications.

PIONEER 1–8 studies[9,26-32] have addressed the problem of inadequate glycaemic control. Across global PIONEER trials,

OS has achieved HbA1c reduction up to 1.5% [Figure 1]. Nearly 7 out of 10 patients achieved the ADA-recommended HbA1c (<7%) with OS [Figure 2]. In a post hoc analysis where 14 mg of OS was administered, patients having baseline HbA1c >9% had HbA1c reduction up to 2.6% [Figure 3].[33] Hence, it can be concluded that OS offers benefits with reductions in HbA1c, and a greater proportion of people with diabetes can achieve HbA1c targets.

T2DM and Established Cardiovascular Disease

Worldwide, one person dies every 8 seconds from diabetes and its complications.[34] Half of these deaths are attributable to CVD.[35] At the age of 60 years, life expectancy is reduced by 12 years for a person with T2DM who has experienced a heart attack or stroke.[34] Among Indians, CVD is the leading cause of mortality and occurs 6 years earlier in Indian people than in people in other countries.[36] Moreover, many people already have macrovascular complications by the time they are diagnosed with diabetes.[37] Even after adjusting for age, sex, smoking status, hypertension, and obesity, T2DM appears to increase the risk of CVD by three to four times in Asian–Indian compared with White individuals. However, only a few people with T2DM receive diabetes medication with known cardiovascular (CV) benefits.[38]

The CAPTURE study provided a clue on therapeutic inertia, where 8 out of 10 patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) were not getting a glucose-lowering treatment with a proven CV benefit.[39] Clinical inertia can lead to progress in the chain of events in the CV continuum (from risk factors to CV death). A therapy that prevents or slows down the progression of the CV continuum must be initiated early. Treatment should be based on reversing
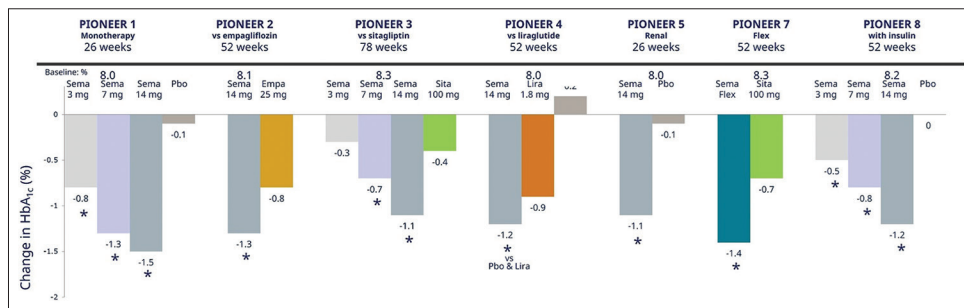

Figure 1: Change in HbA1c at the end of treatment in global PIONEER trials. A mean 1.5% reduction in HbA1c was achieved across global PIONEER trials with oral semaglutide. Empa, empagliflozin; Flex, flexible; HbA1c, glycated haemoglobin; Lira, liraglutide; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin. *Significant change ($p < 0.05$)

Table 1: Characteristics of the PIONEER studies that evaluated the safety and efficacy of oral semaglutide

PIONEER trial	n	Trial type	Treatment period	Patient's characteristics; age (years), DD (years), BMI (kg/m²), HbA1c (%)	Baseline treatment	Comparator	Semaglutide dose
1	703	Placebo (monotherapy)	26	55, 3.5, 31.8, 8.0	Diet and exercise alone	Placebo	3, 7 or 14 mg/day
2	822	Active (empagliflozin)	52	58, 7.4, 32.8, 8.1	Metformin	Empagliflozin 25 mg/day	14 mg/day
3	1864	Active (sitagliptin)	78	58, 8.6, 32.5, 8.3	Metformin with or without SU	Sitagliptin 100 mg/day	3, 7 or 14 mg/day
4	711	Active (liraglutide)	52	56, 7.6, 33, 8.0	Metformin with or without an SGLT-2i	Liraglutide (dose escalated to 1.8 mg/day)	Up to 14 mg/day
5	324	Placebo (moderate renal impairment)	26	70, 14, 32.4, 8.0	Metformin or SU, or both or basal insulin with or without metformin	Placebo	Up to 14 mg/day
6	3183	Placebo (high-risk group)*	~80	66, 14.9, 32.3, 8.2	Any SOC except GLP1-RAs, DPP-4i or pramlintide	Placebo	14 mg/day
7	504	Active (sitagliptin)	52	57, 8.8, 31.5, 8.3	1–2 oral antidiabetic agents	Sitagliptin 100 mg/day	3, 7 or 14 mg/day
8	731	Placebo (add-on to insulin)	52	61, 15, 31, 8.2	Insulin with or without metformin	Placebo	3, 7 or 14 mg/day

BMI, body mass index; DD, diabetes duration; DPP4-I, dipeptidyl peptidase-4 inhibitors; HbA1c, glycated haemoglobin; GLP1-RA, glucagon-like peptide 1-receptor agonist; *n*, trial population; SGLT-2i, sodium/glucose cotransporter-2 inhibitors; SU, sulfonylurea; SOC, standard of care. *Established cardiovascular disease or chronic kidney disease or 60 years of age or older and had cardiovascular risk factors only
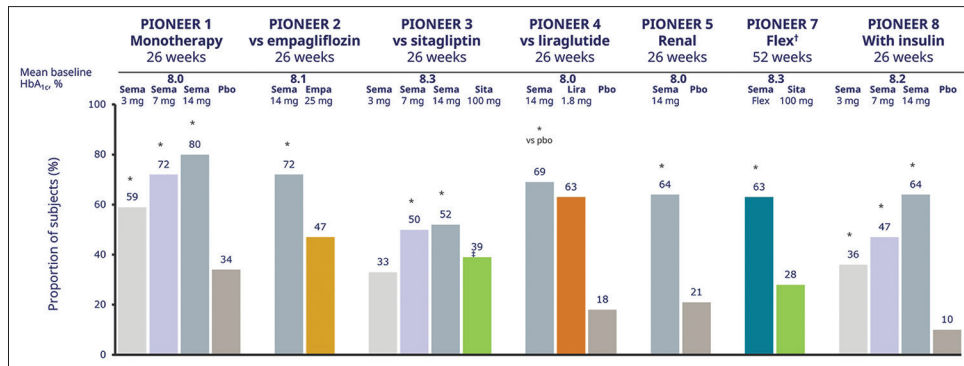
Figure 2: Proportion of subjects achieving HbA1c < 7% in global PIONEER trials at the end of treatment. Across PIONEER trials, approximately 7 out of 10 patients achieved HbA1c < 7% with Oral semaglutide. Empa, empagliflozin; Flex, flexible; HbA1c, glycated haemoglobin; Lira, liraglutide; Met, metformin; OAD, oral anti-diabetes drug; Pbo, placebo; Sema, semaglutide; SGLT2i, sodium-glucose co-transporter 2 inhibitor; Sita, sitagliptin. *$p < 0.05$ for odds of achieving HbA$_{1c}$ < 7.0% with oral semaglutide vs. placebo or active comparator. †Primary endpoint in PIONEER 7, subjects achieving HbA$_{1c}$ < 7.0%. ‡$p < 0.05$ for odds of achieving HbA$_{1c}$ < 7.0% with sitagliptin 100 mg vs. oral semaglutide 3 mg
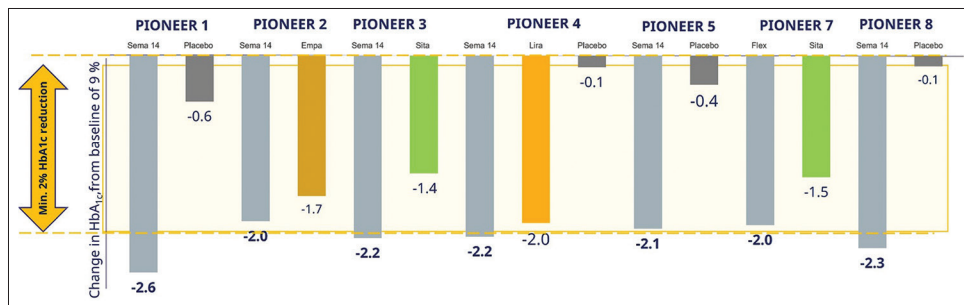

Figure 3: Change in HbA1c from baseline (>9%) with 14 mg oral semaglutide in *post hoc* analysis. In *post hoc* analysis with baseline HbA1c > 9%, oral semaglutide resulted in HbA1c reduction up to 2.6%. Empa, empagliflozin; Flex, flexible; HbA1c, glycated haemoglobin; Lira, liraglutide; Min., minimum; Sema, semaglutide; Sita, sitagliptin

known pathogenic abnormalities and not simply reducing the HbA1c.[40]

Glucagon-like peptide-1 receptor agonists act in multiple stages of the CV continuum. Recent international and local guidelines have been updated, given the favourable CV profile of GLP-1RAs. According to the Research Society for the Study of Diabetes in India (RSSDI), in patients with established CVD, GLP-1 analogues and sodium-glucose cotransporter 2 inhibitors (SGLT2i) with proven efficacy may be, and in patients with heart failure and chronic kidney disease (CKD), SGLT2i or GLP-1RAs may be preferred unless contraindicated.[16]

Oral semaglutide demonstrated a favourable CV profile in PIONEER 6, a randomised, double-blind, event-driven trial comparing the CV safety of OS 14 mg vs. placebo (both in combination with standard of care) in 3,183 adults with T2DM at a high risk of CV events. The first occurrence of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke as a composite major adverse cardiovascular event (MACE) outcome was the primary endpoint. OS was non-inferior to placebo in terms of MACE when both were added to standard-of-care treatment (hazard ratio [HR] = 0.79; 95% confidence interval [CI] = 0.57–1.11; $P < 0.001$). There was reduction in CV-related death with OS (0.9%) compared with

placebo (1.9%) (HR = 0.49; 95% CI = 0.27–0.92). All-cause mortality was reduced by 51% with OS compared with placebo (HR = 0.51; 95% CI = 0.31–0.84).[30]

A systematic review and meta-analysis of seven CV outcome trials (CVOTs) conducted with GLP-1RAs demonstrated a significant reduction in MACE compared with placebo in Asian patients (HR = 0.71; 95% CI = 0.59–0.86; $P < 0.001$). Additionally, despite lesser number of Asians were represented in GLP-1RAs CVOTs ($n = 4298$), a significant reduction in MACE was observed, whereas SGLT-2 studied with a relatively larger number ($n = 4987$) (compared with GLP-1RAs CVOTs) neither showed a significant decrease in MACE (HR = 0.88; 95% CI = 0.67–1.15; $P = 0.35$) nor reduced the composite of hospitalisation for heart failure or CV death (HR = 0.86; 95% CI = 0.55–1.36; $P = 0.53$).[41] In SUSTAIN 6 ($n = 3297$) and PIONEER 6 ($n = 3183$), the pooled analysis demonstrated that a GLP-1 analogue-based treatment strategy reduced the risk of a stroke, irrespective of subtype, in high-risk individuals with T2DM. Pooled semaglutide data showed (24%) consistent reduction in MACE compared with placebo (HR for overall MACE = 0.76; 95% CI = 0.62–0.92).[42]

Hence, based on the previously mentioned trials, it can be concluded that semaglutide provides effective glucose control with a possible favourable effect on CV profile. Early initiation

of semaglutide in the CV continuum may offer better patient outcomes. OS has proven to be CV safe and reduce the incidence of stroke.

DIABETES AND OBESITY – PARTNERS IN CRIME!

TIGHT[25] and urban Puducherry reports[43] have shown that about 20% and 67%, respectively, of people with T2DM in India, are overweight and obese. Overweight and obesity in people with T2DM are associated with an increased risk of several comorbidities such as cancer (34% and 31% increased risk in men and women, respectively),[44] albuminuria,[45] renal disease (five times higher than those with normal weight),[46] depression (three times higher odds with body mass index [BMI] $\geq$30 kg/m^2),[47] retinopathy (64% higher risk compared with those with normal weight),[48] obstructive sleep apnoea (a 1-cm increase in waist circumference [WC] increases the likelihood of developing obstructive sleep apnoea by 10%),[49] and mobility difficulties (6–7 times increased risk of mobility difficulty compared with people without diabetes and normal weight).[50]

Comprehensive clinical practice guidelines of the AACE and ACE advocate that to improve the overall health and quality of life, management should target weight-related complications and adiposity.[51]

A 5% weight loss from baseline is generally accepted as 'clinically meaningful.'[52] However, the greater the weight loss, the greater the improvement in the overall health and complications of patients with T2DM. A weight loss of up to 5% has been shown to improve hyperglyceamia and hypertension,[51] 5% to 10% weight loss can prevent the progression of T2DM, improve polycystic ovarian syndrome-related signs and symptoms, non-alcoholic fatty liver disease and dyslipidemia,[51] a weight loss between 10% and 15% can improve CV diseases, urinary stress incontinence, non-alcoholic steatohepatitis, obstructive sleep apnoea syndrome, gastro-oesophageal reflux disease and knee osteoarthritis,[51,53] and a weight loss of >15% can lead to remission of T2DM and decrease the risk of CV mortality and heart failure with preserved ejection fraction.[54-56]

Semaglutide directly activates GLP-1 receptors in the hindbrain and hypothalamus and induces an area prostrema (AP)/nucleus tractus solitarius (NTS)-directed secondary response in the parabrachial nucleus (PB). This induction is hypothesised to occur directly through GLP-1R stimulation of AP to PB projections or indirectly through the AP-NTS-PB pathway.

To simplify this, direct activation of various GLP-1R populations and affecting neural pathways of food intake, reward and energy expenditure by semaglutide is the mechanism behind lowering body weight.[57]

Oral semaglutide offers >5% weight loss, thereby reducing the cost of diabetes and complications.[26,27] In global PIONEER trials, one in two patients achieved >5% weight loss, and one in every five patients achieved >10% weight loss.[26,27] PIONEER 2 reported a 24% greater weight reduction than empagliflozin at 52 weeks.[26] OS also provides a significantly greater weight loss compared with sitagliptin, as evident from the PIONEER 3 trial, where the mean decrease in body weight at week 26 was 1.2 kg, 2.2 kg and 3.1 kg for 3, 7 and 14 mg/day, respectively, compared with baseline. The mean decrease in body weight in the OS arm was 0.6 kg only. The PIONEER 3 arm also demonstrated superiority of 7 mg/day and 14 mg/day OS dosages to sitagliptin with respect to body weight reduction at week 26 ($\Delta = -1.6$ kg; 95% CI $= -2.0$ to -1.1; $P < 0.001$ and $\Delta = -2.5$ kg; 95% CI $= -3.0$ to -2.0; $P < 0.001$, respectively). Also, the body weight reductions at week 78 were statistically significantly greater with all OS dosages than sitagliptin.[27] This highlights that OS was significantly superior in weight reduction across all doses of 3 mg, 7 mg and 14 mg compared with sitagliptin 100 mg.

Central adiposity and WC are also associated with increased CV risk in patients with T2DM. OS also leads to a reduction of 4.2 cm WC. Additionally, reductions in WC were significantly greater with OS (45% greater reduction in WC) than with empagliflozin at week 26 (both estimands) and week 52 (trial product estimand) in the PIONEER 2 trial.[26] Both PIONEER 2 and 3 trials highlight a sustained change in weight and WC with OS compared with empagliflozin.[26,27]

To summarise, OS has been shown to reduce weight by up to 5 kg and WC by about 4.2 cm. The effect of OS on weight is significantly better than active comparators such as SGLT2i and dipeptidyl peptidase-4 inhibitors. A total of 39.5%, 40.6%, 26.7%, 40.9%, 33.6%, and 34.8% of the patients achieved HbA1c reduction of 1% with body weight loss of $\geq$5% compared to 7.5% with placebo (PIONEER 1),[9] 20.3% with empagliflozin (PIONEER 2),[26] 10.8% with sitagliptin (PIONEER 3)[27] and 17.8% with liraglutide (PIONEER 4),[28] respectively.

DIABETES AND CHRONIC KIDNEY DISEASE

Out of the total Indian population, 8.8% have T2DM,[5] of which, 40% of people with diabetes had CKD.[58] Most (84%) patients with CKD belonged to stages 3 and 4. Also, globally, India has the second-highest CKD-related deaths of patients with T2DM.[5] This highlights that T2DM is the most common cause of the end-stage renal disease (ESRD) and the only solution is to prevent the progression to ESRD.[59]

Moreover, diabetes, hypertension, kidney failure and CVD are highly linked. A vast majority (70–80%) of patients with T2DM are affected by hypertension and are at an increased risk of MI, stroke and all-cause mortality.[60] Hypertension is present in 80% to 85% of adult patients with CKD.[61] More than 80% of ESRD cases are caused by diabetes, hypertension or both.[61] The majority of people with CKD die because of CV problems or eventually advance to ESRD.

Major determinants associated with CKD in patients with T2DM are HbA1c, systolic blood pressure (SBP) and BMI.

A subgroup analysis of the US National Health and Nutrition Examination Survey (NHANES) datasets developed during 2007 and 2012 revealed that higher HbA1c (odds ratio [OR] =1.18 per 1% increase, $P = 0.0001$), higher SBP (OR = 1.22 per 10 mmHg increase, $P < 0.0001$) and higher BMI (OR = 1.14 per 5 kg/m^2 increase, $P = 0.0266$) conferred significantly greater odds for CKD in patients with T2DM.[62]

Glucagon-like peptide-1 receptor agonists have been demonstrated to prevent the onset of macroalbuminuria and reduce the decline of GFR in patients with diabetes. These drugs may benefit the kidneys through blood glucose and blood pressure (BP), lowering effects, reducing insulin levels and decreasing weight.[63] In the PIONEER 6 trial, greater HbA1c reduction was observed with OS than placebo at the end of the trial compared with baseline (–1.0 vs. –0.3 percentage points, respectively). Body weight (–4.2 kg vs. –0.8 kg percentage points, respectively) and SBP (data not provided here) also decreased more in the OS group than in the placebo group.[30] Semaglutide also had lower estimated HRs than placebo in a pooled analysis of 6480 participants (SUSTAIN 6 [$n = 3297$] and PIONEER 6 [$n = 3183$]) evaluating yearly change in estimated glomerular filtration rate (eGFR). Results showed a reduced risk of persistent lower eGFR with semaglutide compared with placebo ($P = 0.03$). This analysis supports the possibility of a smaller magnitude of eGFR decline with semaglutide vs. placebo and suggests a potential kidney disease benefit of semaglutide in people with T2DM and established CKD.[64]

Hence, it is evident from the above-mentioned data that GLP-1RAs have been shown to be beneficial in controlling CKD progression with added improvements in patient's HbA1c, SBP and BMI. Moreover, no dose adjustments are required with OS, which makes it more suitable for patients with CKD.

Similarly, no dose adjustment is warranted in patients with hepatic impairment. This was proved by Baekdal *et al.*[65] where once daily OS (5 mg for 5 days followed by 10 mg for 5 days) was evaluated in subjects with (mild = 12, moderate = 12 and severe = 8) and without ($n = 24$) hepatic impairment. No difference in the area under the semaglutide plasma concentration-time curve (0–24 hours) and the maximum semaglutide concentrations were observed post the 10th dose across the hepatic function groups. No apparent effect of hepatic impairment on time to maximum semaglutide concentration (median range 1.0–1.5 h) or half-life (geometric mean range 142–156 h) was observed.

ADVERSE EVENTS WITH ORAL SEMAGLUTIDE

The overall number of adverse events (AEs) and proportion of patients reporting AEs were similar with OS and placebo (PIONEER 1),[9] empagliflozin (PIONEER 2)[26] and sitagliptin (PIONEER 3).[27] The most frequent AEs were nausea and diarrhoea, generally mild to moderate and transient. Table 2 shows the proportion of patients across the global PIONEER trials for the occurrence of nausea with OS and its comparators. Discontinuation of OS was uncommon and mainly occurred during the initial dose escalation. The safety of OS was also compared with injectable GLP-1 RAs in a systematic review of seven RCTs. Once-daily OS (14 mg) was associated with similar odds of experiencing nausea, vomiting, or diarrhea compared to injectable GLP-1 RAs.[66]

CURRENT INDIAN GUIDELINE AND PLACEMENT OF ORAL SEMAGLUTIDE

Multiple Indian Diabetes Management Guidelines/Consensus Statements are available to guide physicians in managing patients with T2DM.[67] The RSSDI recommends that the choice of any antidiabetic agent should consider the patient's general health status and associated medical disorders. This approach may be referred to as the ABCD (EFGH) approach for diabetes management because the patient's age (A), BMI (B), the status of CKD (C), duration of diabetes (D), established CVD (E), financial concerns (F), glycaemic status (G) and risk of hypoglycaemia (H) should be considered while deciding the treatment.[67]

ORAL SEMAGLUTIDE: BEST SUITED FOR INDIAN PATIENTS WITH TYPE 2 DIABETES MELLITUS
Glycaemic status
Glucagon-like peptide-1 receptor agonists are second only to insulin in the glucose-lowering ability. OS has shown superior

Table 2: Proportion of patients with nausea

	The proportion of nausea in percentage			
Trial (comparator)	Comparator (%)	Oral semaglutide (%)		
		3 mg	7 mg	14 mg
PIONEER 1 (placebo)	5.6	8	5.1	16
PIONEER 2 (Empagliflozin 25 mg)	2.4	NA	NA	19.8
PIONEER 3 (Sitagliptin 100 mg)	6.9	7.3	13.4	15.1
PIONEER 4 (liraglutide 1.8 mg)	18	NA	NA	20
PIONEER 5 (placebo)	7	NA	NA	19
PIONEER 7 (sitagliptin 100 mg)	2	NA	NA	21
PIONEER 8 (placebo)	7.1	11.4	16.6	23.2

NA, not applicable

efficacy in terms of HbA1c reduction. The observed proportion of patients achieving HbA1c <7.0% without hypoglycaemia and body weight gain was greater with OS. OS achieved a statistically significant outcome vs. placebo in the PIONEER 1 and 8 trials.[9,32]

Duration of diabetes

Long-standing diabetes reduces β-cell mass and requires frequent insulin therapy.[68] GLP-1Ras bring about improved β-cell function[69] and reduced β-cell death[70] with significant HbA1c reduction[71] and reduced risk of hypoglycaemia.[71] Efficacy of OS by the duration of diabetes was established in the PIONEER 1, 4, 5 and 8 trials.[9,28,29,32]

Age and body mass index

Oral semaglutide can be prescribed to any age group of patients with T2DM due to its proven efficacy and established safety profile. GLP-1Ras are associated with clinically significant weight loss, especially in obese and overweight patients, and match the best for the Indian patients with T2DM due to the unique thin–fat phenotype.[72] The PIONEER trial results have shown significant and sustained weight reduction and optimal glycaemic control with OS.[9,26-29,31,32]

Established cardiovascular disease

The American Diabetes Association–European Association for the Study of Diabetes (EASD) consensus report 2019 recommends GLP-1RAs as the first-line drug in patients with high, very high CVD risk or established CVD.[11] PIONEER 6 assessed the CV safety of once-daily OS in T2DM patients at high CV risk (age of ≥50 years with established CV or CKD, or the age of ≥60 years with CV risk factors only). It was not powered to prove superiority and, thus, CV benefits. Additionally, MACE was measured by the number of events without any minimum duration. Ongoing Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL) is a large (*n* = 9,640) and longer trial (3.5–5 years) than PIONEER 6. SOUL is designed to evaluate the first occurrence of MACE in patients with T2DM and CVD, cerebrovascular disease, symptomatic peripheral artery disease, or CKD with once-daily OS (up to 14 mg) and was powered for superiority over placebo.[10] Post-hoc pooled analysis of the SUSTAIN 6 and PIONEER 6 trials indicates that semaglutide reduces MACE across the spectrum of the CVD risk continuum.[42]

Risk of hypoglycaemia

Glucagon-like peptide-1 receptor agonists should be considered a first-line therapeutic option for patients at high risk of hypoglycaemia. A meta-analysis of seven randomised controlled trials evaluating the efficacy of GLP-1RAs in combination with insulin in patients with type 1 diabetes mellitus reported no significant increase in the risk of hypoglycaemia but showed improved HbA1c control versus monotherapy.[73] OS does not increase the risk of hypoglycaemia[9,26,29] unless combined with sulfonylureas or insulin[32] as revealed by the PIONEER trials.

Box 1: Factors decreasing semaglutide exposure

Food intake before dosing, increased water volume (more than 120 mL) and decreased post-dosing fasting time (shorter than 30 min) can affect semaglutide absorption.

Box 2: Switching from another GLP-1RA to OS

For patients tolerating the maximal dose of existing GLP-1RA therapy, initiate OD semaglutide.[79,81,82]

One day (if switching from a OD/BID GLP-1RA therapy) after the last dose (or when GI symptoms have resolved if not tolerating the maximal dose), or

One week (if switching from OW GLP-1RA) after the last dose (or when GI symptoms have resolved if not tolerating the maximal dose)

Initiate at 3 mg OD (initiation dose), increasing to 7 mg OD after 30 days and, if needed, 14 mg OD after a further 30 days (maintenance doses).

Box 3: Patients' management strategy for nausea (if needed)

Pause the treatment until AEs resolve.

Encourage to resume once AE ceases.

If the pause is for >21 days, re-escalate from a lower dose of OS.

Box 4: Reasons for early initiation in the continuum of T2DM

Effective in reducing HbA1c and weight when given early or late in therapy.[93]

Well-tolerated, with nausea being the most common AEs.[94]

Superior in reducing HbA1c when compared with sitagliptin, empagliflozin, and liraglutide.[26-28]

Chronic kidney disease status

Glucagon-like peptide-1 receptor agonists (liraglutide and dulaglutide) can be used in eGFR for up to 15 mL/min.[74] The renal function does not alter OS exposure in the early phase and haemodialysis does not affect drug exposure. The PIONEER 5 trial results indicate that in patients with moderate renal impairment, OS has superior efficacy in HbA1c reduction and more significant weight loss and was well tolerated.[29]

Physician guidance on oral semaglutide initiation

According to the ADA 2022 guidelines, patients with high-risk indicators (age ≥55 with coronary, carotid or lower extremity artery stenosis >50% or left ventricular hypertrophy) or established ASCVD, CKD or heart failure (HF) can be started on GLP-1RA or SGLT2i with proven CVD benefits, independent of metformin or baseline HbA1c or individualised HbA1c target.[75]

If further intensification is required or the patient cannot tolerate GLP-1RAs and/or SGLT2i, agents demonstrating CV benefit and/or safety should be chosen. For patients on GLP-1RAs, adding SGLT2i with proven CVD benefits and vice versa should be considered.[75] However, oral GLP-1RAs score high compared with SGLT2i, as discussed in previous sections of this review.

Successful diabetes management includes educating patients regarding their specific treatment plan to know what to expect from the treatment and how to use it correctly.

Ideal Indian patients for initiation

• For patients taking one or more oral antihyperglycaemic agents (including metformin) with inadequate glycaemic control, OS seems to be an appropriate agent for the second-line setting after the failure of metformin.

• For patients for whom weight loss would be beneficial, OS provides superior weight reduction than comparators; hence it is reasonable to consider it for patients who would benefit from weight loss.

• For patients in whom hypoglycaemia is a concern, OS has demonstrated an overall low risk of hypoglycaemia in the PIONEER trials.

• Before starting OS, there is a need to explore challenges related to adherence with injectables. If a patient is non-adherent due to injection fear, consider switching to a tablet formulation.

• For patients with established CVD or at high CV risk, patient preference for oral therapy can be higher than SC injection.

• No dose adjustments are recommended for patients with established renal or hepatic dysfunction.

• For older patients with T2DM, OS can be an ideal choice as patient age does not appear to affect the efficacy or safety of OS.

Dosing rationale

• Based on the Phase 2 trial results, three once-daily dose levels were expected to have optimal benefit–risk profiles: 3 mg, 7 mg and 14 mg.

• OS should be initiated with the lowest dose and a 4-week dose escalation to reduce the risk of gastrointestinal AEs.

Oral semaglutide dosing instructions are designed to optimise absorption and provide more convenience to patients.

Dosage and administration

Oral semaglutide is recommended to be taken in a fasting state in the morning with half a glass of water (120 mL). To achieve relevant therapeutic exposure, patients should be advised to wait for at least 30 min before taking any meal, further liquid or concomitant medications.[76] For patients taking comedication (thyroid hormone replacement therapy) with the same dosing instruction as with OS, comedication should be administered at a different time of the day to ensure compliance with OS.[76]

Oral semaglutide should be started with 3 mg once daily and titrated to 7 mg/day after 30 days; 14 mg/day can be initiated after 30 days of the previous dose for further glycaemic control. As per the OS prescribing information, patients taking 0.5 mg once weekly semaglutide can be switched to either 7 or 14 mg once daily up to 7 days after the last semaglutide injection. However, a 14 mg/day dose is equivalent to 0.5 mg once weekly SC dose.[76]

STRATEGY OF SWITCHING FROM OTHER GLP-1RA TO ORAL SEMAGLUTIDE

Between 4 and 24% of patients with T2DM switch from their initial GLP-1RA therapy to another in their first year of treatment.[77-79] Improved glycaemic control and weight loss, CV benefits, improved safety and tolerability, patient preference, and adherence are the reasons to switch between GLP-1RAs in T2DM patients.[79,80]

When switching from another GLP-1RA to OS, the recommended posology in the labels should be adhered to, including the need for gradual dose titration where applicable.[79,81-88]

MEANS OF MANAGING ADVERSE DRUG EFFECTS

Nausea (25–60%) followed by vomiting (5–15%) and diarrhoea (10–20%) are the most frequently reported treatment-related adverse effects occurring with GLP-1 RAs in previous clinical trials.[89]

In the global PIONEER trials, 80% to 90% of the subjects tolerated treatment with the OS and did not experience any nausea.[9,26-29,31,32]

Before beginning therapy with OS, patients should be informed of potential gastrointestinal AEs and any tips for mitigating them if they occur. Patients should be advised to seek medical advice for severe or persistent symptoms.

BENEFITS OF EARLY INITIATION OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor agonists provide adequate glycaemic control, reduce weight and lower the risk of hypoglycaemia.[90,91] OS is the first oral formulation of a GLP-1RA developed to treat T2DM. GLP-1RAs as a class have numerous direct and indirect positive effects on various organs, including the brain, heart, liver and pancreas [Box 1-4].[92]

CONCLUSION

Oral semaglutide represents the first oral GLP-1RA for the treatment of T2DM. Across the global PIONEER trial, OS demonstrated significantly greater HbA_{1c} and weight reductions than sitagliptin, empagliflozin and liraglutide. CV safety with OS (greater reduction in MACE than with placebo) is also established in the PIONEER 6 trial. The safety and tolerability of OS are also consistent with GLP-1RA class. Mild-to-moderate nausea was the most common AE, which was transient in nature. To conclude, the efficacy of OS is established; it can be given early in therapy, late in treatment and regardless of renal or hepatic impairment in Indian patients with T2DM.

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There are no conflicts of interest.

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