SCIENTIFIC SYNOPSIS

LET YOUR PATIENTS WAKE UP TO NEW POSSIBILITIES

FOR PEOPLE WITH UNCONTROLLED DIABETES

RYBELSUS® semaglutide tablets

A GAME CHANGER. A LIFE CHANGER

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Indexing

Section 1

What is Oral Semaglutide

RYBELSUS® is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).[1]

> Oral semaglutide may offer a practical and effective means of managing people living with T2D who require treatment intensification, and may change the paradigm of care in the primary care setting.
>
> -Seidu S et al. Prim Care Diabetes. 2021 Feb;15(1):59-68.

THE WORLD'S FIRST
ORAL GLP-1 RA[2]

Section 1

How do GLP-1 RAs work in the body?

- Pharmacologically, long-acting GLP-1 receptor agonists (GLP-1RAs) exhibit glucoregulatory functions via multiple mechanisms, **namely, stimulation of insulin release in a glucose-dependent manner,** suppression of glucagon activity during hyperglycemia, and a minor delay of gastric emptying resulting in slower glucose absorption.[3]

- In addition, GLP-1 promotes satiety and reduces energy intake by virtue of its neurotransmitter role in brainstem-hypothalamus pathways signalling satiety and some long-acting GLP-1RAs including injectable semaglutide have shown cardiovascular risk reduction.[3]

GLP-1 RAs target multiple pathophysiological defects of T2DM[4]

- GLP-1 RAs directly or indirectly target 6 out of 8 pathophysiological defects of T2DM (ominous octet), more than any other class of antihyperglycemic medication[4]. (Fig 1)

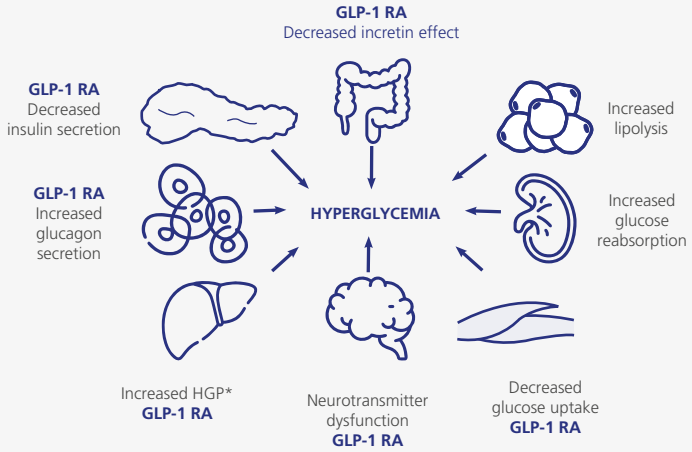

Fig 1: The Ominous Octet and Action of GLP-1

*HGP - Hepatic Glucose Production

3. Zhao X et al. Front Endocrinol (Lausanne). 2021 Aug 23;12:721135. 4. DeFronzo RA. Diabetes Obes Metab. 2017 Oct;19(10):1353-1362.

Section 2

Innovation of Oral Semaglutide

Oral Delivery of Peptides

Oral administration of therapeutic peptides is hindered by poor absorption across the gastrointestinal barrier and extensive degradation by proteolytic enzymes. The inherent physicochemical properties of peptides (high molecular weight, enzymatically labile, hydrophilicity, and low permeability) have hampered attempts to deliver peptides such as GLP-1 via the oral route.[5]

Recent advancements in fatty acid acylation–based protraction technology have provided the possibility of achieving extended plasma half-lives (t½) without increasing molecular size, leading to the discovery of semaglutide, a GLP-1 receptor agonist with a t½ of ~1 week in humans.[6]

***GI-tract degrades and digests Peptides**

Low permeability through the intestinal cell wall

$SNAC ABSORPTION ENHANCER protects semaglutide from breaking down in the stomach

Pairing the right molecule with the right absorption enhancer

This is mainly because vast majority of peptides evaluated for oral delivery have been ill-equipped to surmount the challenges presented by the hostile environment of the GIT, which is designed to degrade proteins and peptides ingested in food to di- and tri-peptides before absorption in the small intestine.

The need of the hour was to find a way to make GLP-1 peptides withstand the digestive functions, preventing GLP-1 peptide from breaking down in the stomach. This required right pairing with the absorption enhancer SNAC$. After a significant effort, there was a breakthrough with an absorption enhancer called $SNAC which protects semaglutide from breaking down in the stomach.

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***SNAC -** Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate **GIT -** Gastrointestinal tract

5. Bruno EJ et al. Ther Deliv. 2013 Nov;4(11):1443-67. **6.** Knudsen LB et al. Front Endocrinol (Lausanne). 2019 Apr 12;10:155.

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Structural changes in the Semaglutide molecule and their consequences

Semaglutide has a high degree of homology (~94%) with the human GLP-1 molecule with the three key changes in the molecule.[7]

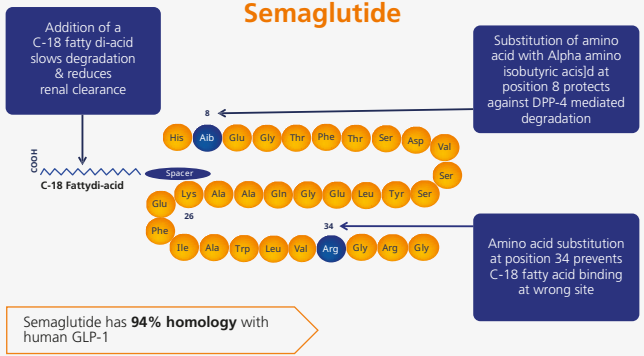


Fig 2

[$]SNAC is an absorption enhancer with the ability to increase the absorption of semaglutide across the GI epithelium.[8]

The co-formulation of semaglutide & SNAC is absorbed in the stomach rather than in the intestine. SNAC buffers the local pH of the stomach, protects against enzymatic degradation and facilitate absorption via the transcellular route.

[$]**SNAC** - Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate **DPP-4:** Dipeptidyl Peptidase-4

7. Kapitza C et al. J Clin Pharmacol. 2015 May;55(5):497-504. **8.** Kalra S et al. Diabetes Ther. 2020;11(9):1965-1982.

Section 2

Protects Rybelsus® from breakdown by gastric enzymes

Promotes absorption across the gastric mucosa

Allows Rybelsus® to be absorbed from the stomach

Fig 3

The mechanism of absorption is shown to be compound specific, transcellular, and without any evidence of effect on tight junctions. This might be the game changer in management of T2DM.[9]

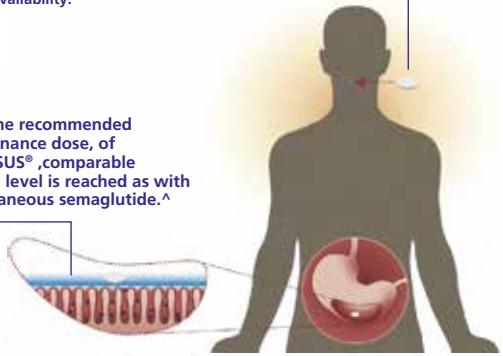
The pharmacological innovation: RYBELSUS®

The co-formulation with the absorption enhancer SNAC enables the gastrointestinal absorption of semaglutide

- **Protects semaglutide from gastrointestinal degradation, by increasing the pH locally.**
- **SNAC promotes the transcellular absorption of Semaglutide via the gastric epithelium.**
- **With SNAC there is an estimated 100-fold increase in Oral Semaglutide bioavailability.[10]**

- White oval tablet for oral use Administration. (All dosages have the same size of 13.5 × 7.5 mm).[1]
- Active Ingredient: Semaglutide (3 mg, 7 mg or 14 mg per tablet).

With the recommended maintenance dose, of RYBELSUS® ,comparable plasma level is reached as with subcutaneous semaglutide.^



^ Seidu S et al. Prim Care Diabetes. 2021 Feb;15(1):59-68

9. Buckley ST et al. Sci Transl Med. 2018 Nov 14;10(467):eaar7047. **10.** Seidu S et al. Prim Care Diabetes.2021 Feb;15(1):59-68.

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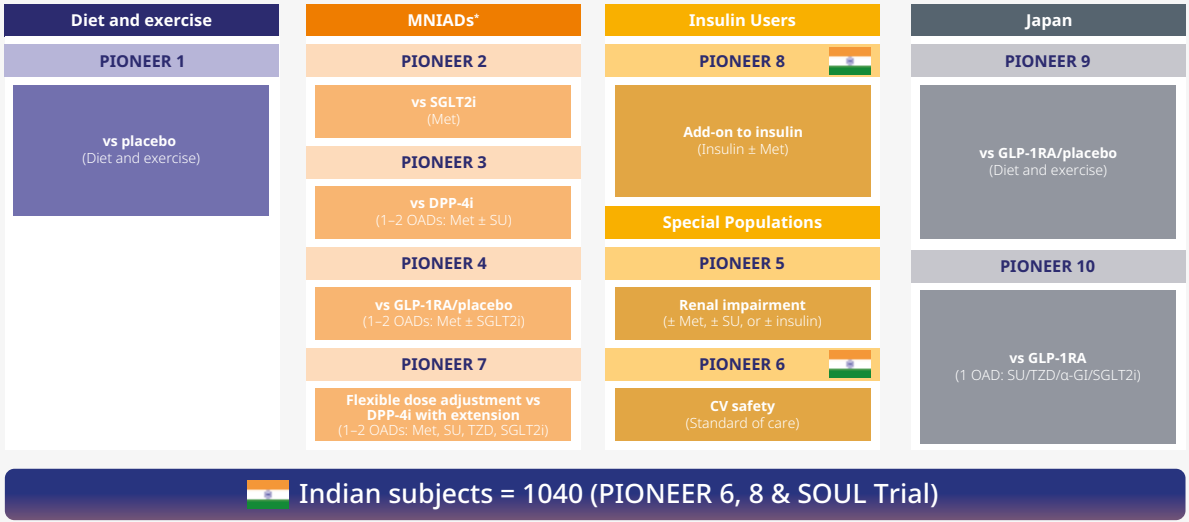
PIONEERing Oral Semaglutide

PIONEER (Peptide Innovation for Early Diabetes Treatment) – the Phase 3a clinical trials were initiated in 2016, with 8 global trials and 2 trials in Japanese population and included 9,543 participants, 5707 of whom were exposed to oral semaglutide.[11-20]

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

An overview of PIONEER program: Compared across diverse prevailing standards of care[11-20]



SOUL Trial: Available at https://clinicaltrials.gov/ct2/show/NCT03914326. Accessed on 19 Jan 2022

*MNIADs - Modern Non Insulin Anti-diabetic Drugs

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

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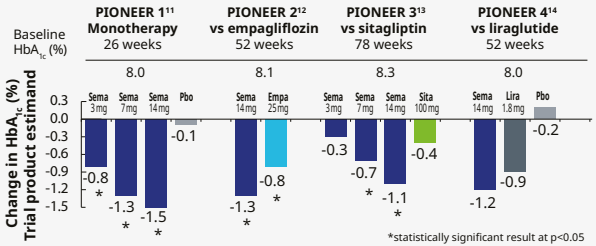
Section 3

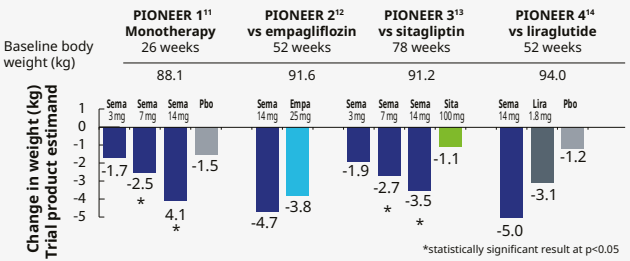
1. Change in HbA_{1c} and Body weight – end of treatment

Oral semaglutide reduced HbA1c in a clinically relevant and dose-dependent manner; the reductions were up to 1.5% and sustained weight loss of up to 5 kg[11-20]

Upto **1.5%** HbA_{1c}



Upto **5 kg** Weight Loss



11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

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2. Efficacy of oral semaglutide according to baseline HbA1c[11-15,17,18]

Oral Semaglutide provides unsurpassed HbA1c reduction in T2D patients with baseline HbA1c >9%

Change from baseline in HbA_{1c} by baseline HbA_{1c} subgroup in 7 of the global Phase 3a PIONEER trials

Trial	HbA_{1c} (%) at baseline	Estimated mean change from baseline in HbA_{1c} (%-points)					
		Oral semaglutide				Comparator(s)	
		3 mg	7 mg	14 mg	Flex	Pbo	Active
PIONEER 1 (diet and exercise)	≤8 (n=409)	-0.5	-1.1	-1.2	-	0.0	-
	>8-≤9 (n=244)	-1.1	-1.6	-1.8	-	-0.1	-
	>9 (n=50)	-1.5	-1.8	**-2.6**	-	-0.6	-
PIONEER 2 (vs empagliflozin 25 mg)	≤8 (n=457)	-	-	-1.0	-	-	-0.5
	>8-≤9 (n=211)	-	-	-1.8	-	-	-1.1
	>9 (n=153)	-	-	**-2.0**	-	-	-1.7
PIONEER 3 (vs sitagliptin 100 mg)	≤8 (n=850)	-0.3	-0.6	-0.9	-	-	-0.5
	>8-≤9 (n=593)	-0.5	-1.1	-1.5	-	-	-0.8
	>9 (n=420)	-1.0	-1.9	**-2.2**	-	-	-1.4
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	≤8 (n=403)	-	-	-1.0	-	-0.0	-0.8
	>8-≤9 (n=248)	-	-	-1.6	-	-0.1	-1.4
	>9 (n=60)	-	-	**-2.2**	-	-0.1	-2.0
PIONEER 5 (renal impairment)	≤8 (n=188)	-	-	-0.8	-	0.1	-
	>8-≤9 (n=108)	-	-	-1.5	-	-0.3	-
	>9 (n=28)	-	-	**-2.1**	-	-0.4	-
PIONEER 7 (flex vs sitagliptin 100 mg)	≤8 (n=201)	-	-	-	-1.0	-	-0.5
	>8-≤9 (n=246)	-	-	-	-1.5	-	-0.7
	>9 (n=57)	-	-	-	-2.0	-	-1.5
PIONEER 8 (added-on to insulin)	≤8 (n=329)	-0.3	-0.6	-1.0	-	0.2	-
	>8-≤9 (n=296)	-0.7	-1.2	-1.6	-	-0.2	-
	>9 (n=106)	-1.2	-1.8	**-2.3**	-	-0.1	-

Mixed model for repeated measures analysis with treatment, region, stratification factors and interaction between them, as well as baseline HbA_{1c} group and interaction between treatment and baseline HbA_{1c} groups as factors, and baseline value of dependent variable as covariate. -, not investigated in trial; flex, flexible dose adjustment: pbo, placebo.

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271.

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3. Patients reaching target with Oral Semalgutide[11-18]

7 out of 10
patients achieving the targets of HbA1c <7% with Oral Semaglutide

4. Cardiovascular safety[16]

Consistent cardiovascular safety was shown in PIONEER 6 which resulted in a 21% risk reduction for MACE (non-inferior) and a 49% risk reduction in all-cause death with a 51% risk reduction in CV Death*[16]

Patients treated with semaglutide had a significant 24% lower risk of the first occurrence of MACE compared to placebo[16].

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271.

Section 3

5. Multiple cardio-metabolic risk factor reduction

Systolic blood pressure[16]

-5 mmHg

Lipid parameters[17,n.s]

LDL#, TG#, TC#

Waist circumference[18]

-4.7 cm*

*Estimated Treatment difference between Oral semaglutide 14 mg (Baseline - 104 cm and Placebo (104 cm)

ns - non-significant
Baseline SBP - 135+- 18 mmHg
#**LDL** – Low Density Lipoprotein | **TC** – Total cholesterol | **TG** – Triglyceride

6. Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271.

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Section 3

Summary of safety profile[11-20]

In 10 phase 3a trials, 5,707 patients were exposed to oral semaglutide alone or in combination with other glucose-lowering medicinal products. The duration of the treatment ranged from 26 weeks to 78 weeks. The most frequently reported adverse events in clinical trials were gastrointestinal disorders, including nausea, diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

Across PIONEER Trials[11-20]

~ 80-95% of patients **did not experience any nausea**

Pancreatitis incidence were comparable to placebo and active comparators

Retinopathy incidence were comparable to placebo and active comparators

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

Section 4

Dosing & Administration[1]

Therapeutic Indication

Oral Semaglutide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

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

Method of Administration[1]

Take on an empty stomach upon waking

Swallow the whole tablet with a sip of water (up to 120 mL)

Wait at least 30 minutes before eating, drinking, or taking any other oral medication

Oral semaglutide is a tablet for once-daily oral use. It should be taken on an empty stomach upon waking up. It should be swallowed whole with up to half a glass of water upto 120 ml.

- *Do not split, crush or chew the tablet.*
- *Wait at least 30 minutes before the first meal - Waiting less than 30 minute may decrease the absorption of semaglutide.*

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1. Rybelsus® Prescribing information.

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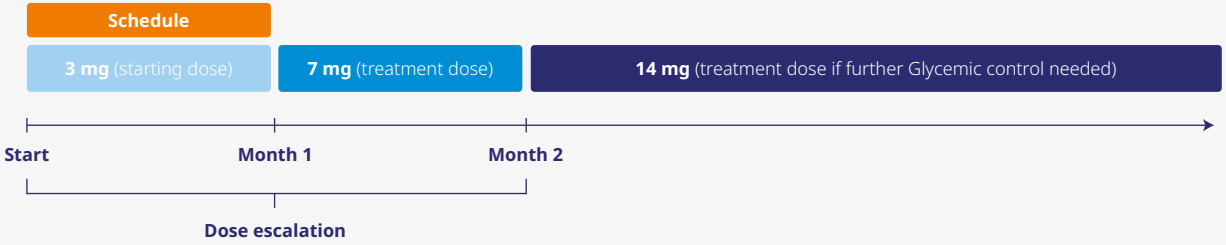
Section 4

Dosing[1]

The starting dose of oral semaglutide is 3 mg once daily. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily.

The dose can be further increased to a maintenance dose of 14 mg once daily.



Advise patients that if they miss a dose, they should skip the missed dose and take the next dose as scheduled the next day

1. Rybelsus® Prescribing information.

Section 4

Special Population[1]

Age & Gender
No dose adjustment is recommended in the elderly (≥65 years old) or based on gender.

Race & ethnicity
No dose adjustment is required based on race and ethnicity.

Pregnancy & Breastfeeding
There is limited data on the use of oral semaglutide in pregnant or breastfeeding women.

Children & adolescents
The safety and efficacy of Oral semaglutide in children and adolescents below 18 years have not been studied.

Renal and hepatic impairment
Renal and hepatic impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner.

1. Rybelsus® Prescribing information.

Section 5

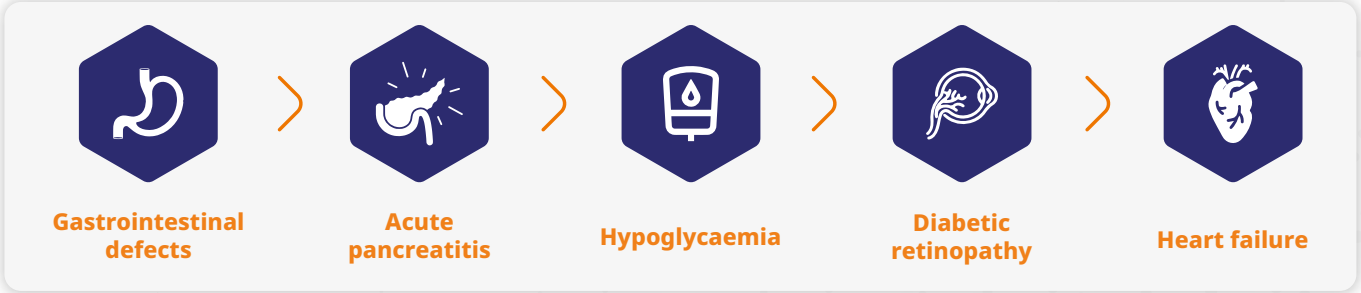
Contraindications & Drug Interactions[1]

Contraindications[1]

- Hypersensitivity to the active substance or to any of the excipients
- In patients with personal or family history of medullary Thyroid cancers (MTCs)
- In patients with Mention Multiple Endocrine Neoplasia (MEN) Type 2.

Special warnings and precautions for use[1]

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



Section 6

Summary[11-20]

- Oral semaglutide reduces HbA1c in a clinically relevant and dose-dependent manner
- No dose adjustment recommended regardless of renal or hepatic impairment
- The risk of hypoglycaemia is low with oral semaglutide when used as monotherapy
- No dose adjustment recommended in elderly patients
- Clinical inertia and non-adherence seen with injectables pose significant obstacles in reaching glycemic targets in T2DM, this is overcome with oral semaglutide due to patient convenience and ease of administration
- Additional effects of oral semaglutide beyond glycemic control can provide benefits in the multifactorial approach to type 2 diabetes management.

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

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Section 6

Summary[11-20]

A GAME CHANGER IN T2DM

HBA1c (%): 8.0 +– 0.7
^Aroda VR et al. Diabetes Care. 2019 Sep;42(9):1724-1732.
Weight (kg): 92·9 (20·6) Pratley R et al. Lancet. 2019 Jul 6;394(10192):39-50.
n.s. - not significant
#Husain M et al. N Engl .1 Med. 2019;381:841-851. 18.
^Dahl K et al. Diabetes Obes Metab. 2021 Jul;23(7):1594-1603 Husain M et al. N Engl .1 Med. 2019;381:841-851. 18.
*Pratley R et al. Lancet. 2019 Jul 6;394(10192):39-50.

11. Aroda VR et al. Diabetes. Diabetes Care. 2019 Sep;42(9):1724-1732. 12. **12.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. **14.** Pratley R et al. Lancet. Lancet. 2019 Jul 6;394(10192):39-50 **15.** Mosenzon O et al. Lancet Diabetes Endocrinol. 2019;7:515-527. 17. **16.** Husain M et al. N Engl .1 Med. 2019;381:841-851. 18. **17.** Pieber TR et al. Lancet Diabetes Endocrinol. 2019 Jul;7(7):528-539. **18.** Zinman B et al. Diabetes Care. 2019 Dec;42(12):2262-2271. **19.** Yamada Y et al. Lancet Diabetes Endocrinol. 2020 May;8(5):377-391. **20.** Yabe D et al Lancet Diabetes Endocrinol. 2020 May;8(5):392-406.

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