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]

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1. Rybelsus® Prescribing Information. 2. Antza et al. Drug Design Development and Therapy. 2019:13:2985-2996.

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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)

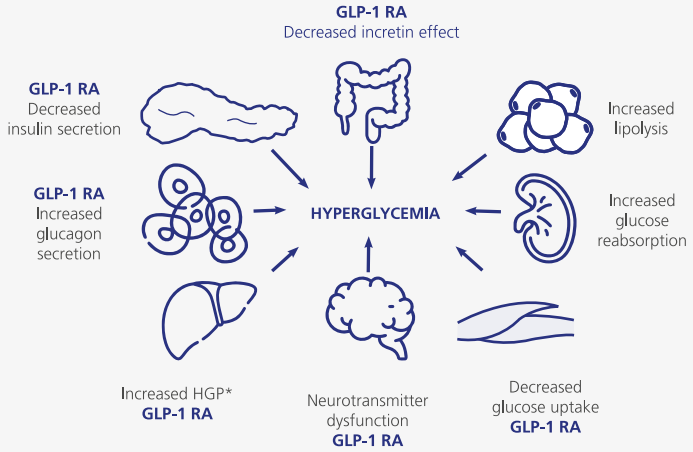

Fig 1: The Ominous Octet and Action of GLP-1

*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 BJ 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]

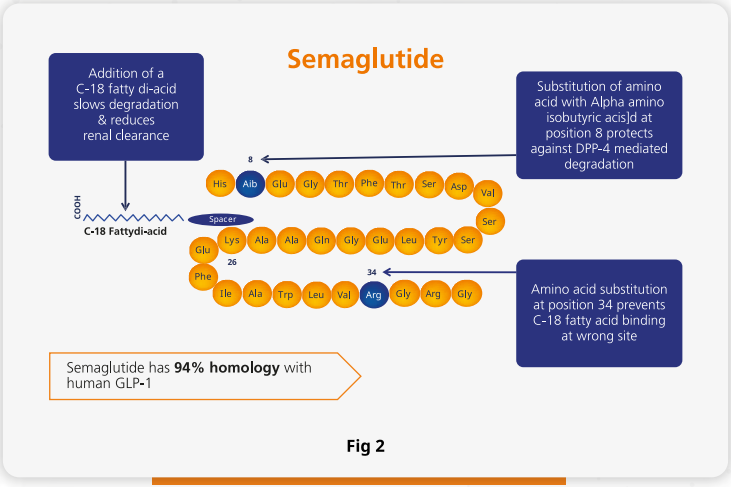

Fig 2

[$]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.

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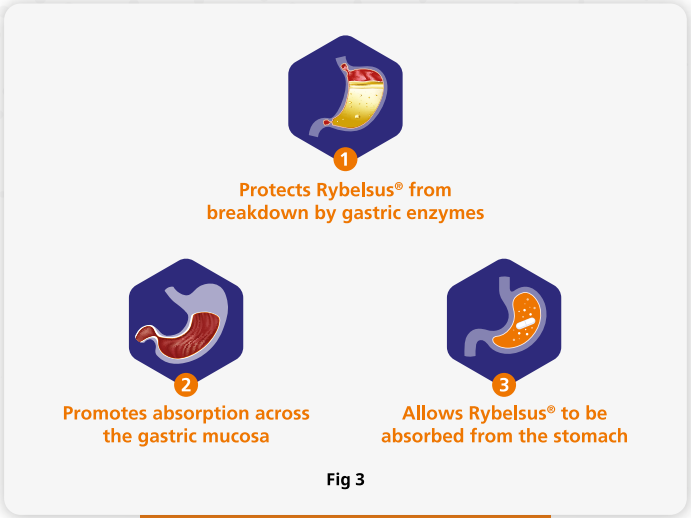


Fig 3

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]

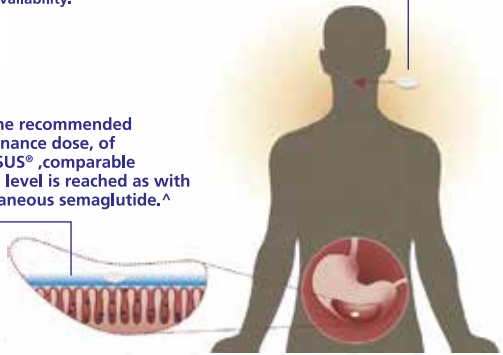
The pharmacological innovation: RYBELSUS®

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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Section 3

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 & 2 trials in Chinese population included 11,507 participants, 6,645 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 J 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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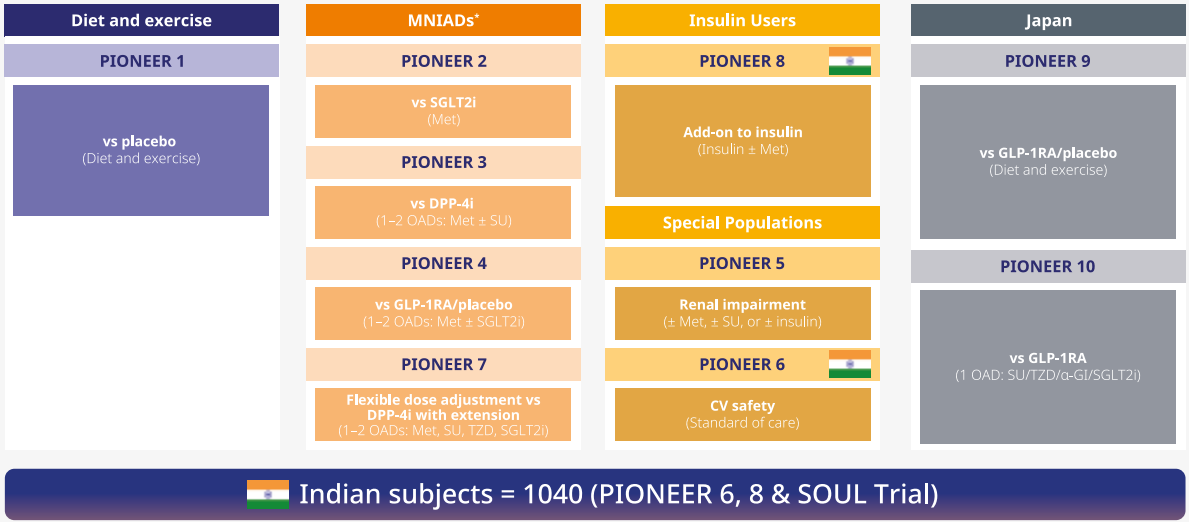
An overview of PIONEER program: Compared across diverse prevailing standards of care[11-20]



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 J 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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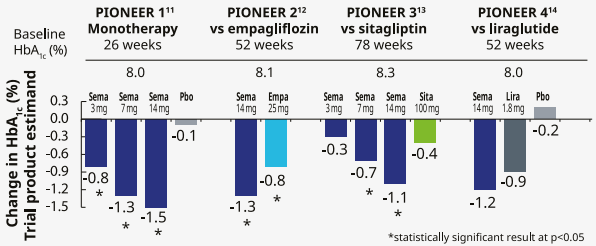
Section 3

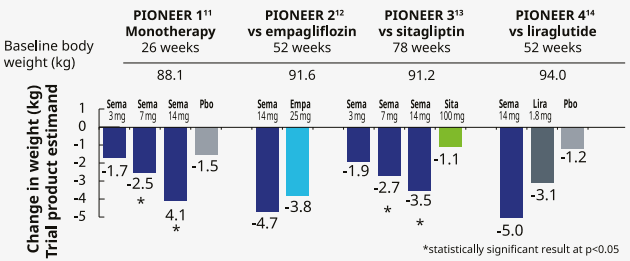
1. Change in HbA_{1c} and Body weight – end of treatment

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. Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. 13. Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. 15. 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 J 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) >8–≤9 (n=244) >9 (n=50)	-0.5 -1.1 -1.5	-1.1 -1.6 -1.8	-1.2 -1.8 **-2.6**	- - -	0.0 -0.1 -0.6	- - -
PIONEER 2 (vs empagliflozin 25 mg)	≤8 (n=457) >8–≤9 (n=211) >9 (n=153)	- - -	- - -	-1.0 -1.8 **-2.0**	- - -	- - -	-0.5 -1.1 -1.7
PIONEER 3 (vs sitagliptin 100 mg)	≤8 (n=850) >8–≤9 (n=593) >9 (n=420)	-0.3 -0.5 -1.0	-0.6 -1.1 -1.9	-0.9 -1.5 **-2.2**	- - -	- - -	-0.5 -0.8 -1.4
PIONEER 4 (vs liraglutide 1.8 mg and pbo)	≤8 (n=403) >8–≤9 (n=248) >9 (n=60)	- - -	- - -	-1.0 -1.6 **-2.2**	- - -	-0.0 -0.1 -0.1	-0.8 -1.4 -2.0
PIONEER 5 (renal impairment)	≤8 (n=188) >8–≤9 (n=108) >9 (n=28)	- - -	- - -	-0.8 -1.5 **-2.1**	- - -	0.1 -0.3 -0.4	- - -
PIONEER 7 (flex vs sitagliptin 100 mg)	≤8 (n=201) >8–≤9 (n=246) >9 (n=57)	- - -	- - -	- - -	-1.0 -1.5 -2.0	- - -	-0.5 -0.7 -1.5
PIONEER 8 (added-on to insulin)	≤8 (n=329) >8–≤9 (n=296) >9 (n=106)	-0.3 -0.7 -1.2	-0.6 -1.2 -1.8	-1.0 -1.6 **-2.3**	- - -	0.2 -0.2 -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.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. **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.** Husain M et al. N Engl J Med. 2019;381:841-851. **18.** 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].

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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 J 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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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 J Med. 2019;381:841-851. **18.** 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. Other undesirable effects being delayed gastric emptying, dysgeusia and dizziness

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.** Rodbard HW et al. Diabetes Care. 2019 Dec;42(12):2272-2281. **13.** Rosenstock J et al. JAMA. 2019 Apr 16;321(15):1466-1480. **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.** Husain M et al. N Engl J Med. 2019;381:841-851. **18.** 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 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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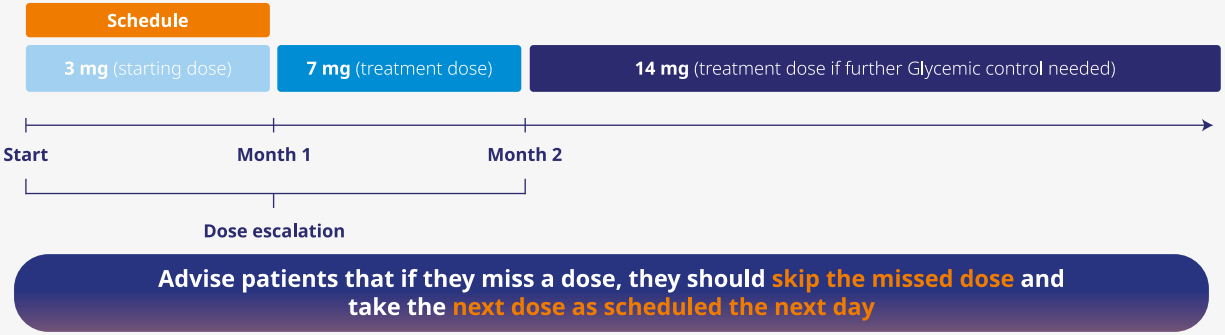
1. Rybelsus® Prescribing Information.

RYBELSUS® semaglutide tablets

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
Patients with renal impairment: No dose adjustment is required for patients with renal impairment. Experience with the use of semaglutide in patients with severe renal impairment is limited. Semaglutide is not recommended in patients with end stage renal disease.

1. Rybelsus® Prescribing information.

Section 5

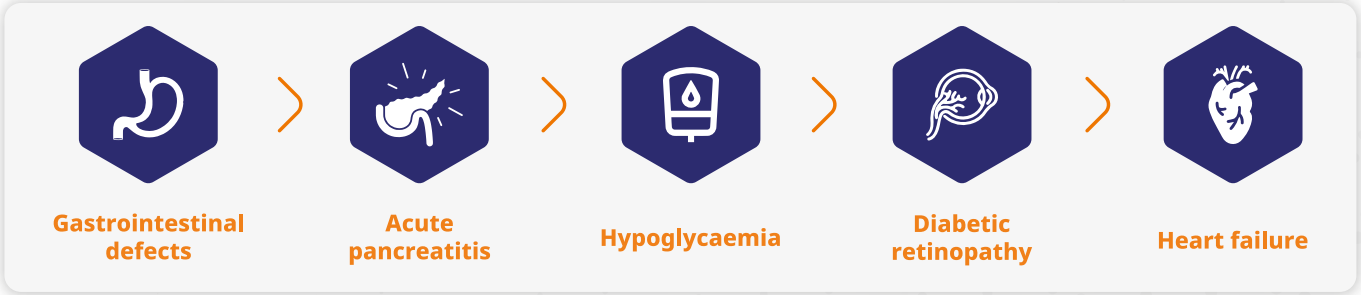
Contraindications & Drug Interactions[1]

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. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines.



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 J 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. J 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. J 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 J 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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RYBELSUS® semaglutide tablets

Abbreviated prescribing information (and not full package insert)
Generic Name: Semaglutide Tablets

Brand Name: Rybelsus® 3 mg tablets, Rybelsus® 7 mg tablets and Rybelsus®14 mg tablets.
Presentation: Rybelsus® 3 mg, 7 mg and 14 mg tablets for once-daily oral use. Each tablet contains 3, 7 or 14 mg semaglutide. Tablet for once daily oral use. **Indication:** RYBELSUS® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • RYBELSUS® has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis. [see section 4.4 Special Warnings and Precautions] •RYBELSUS® is not indicated for use in patients with type 1 diabetes mellitus. **Description:** The semaglutide drug products are white to light yellow oval shaped tablets. The primary packaging is a blister card composed of coloured forming foil and non-coloured lid foil. The colour of the forming foil is unique for each tablet strength: green for 3 mg tablets, red for 7 mg tablets and blue for 14 mg tablets. The blister card contains 10 identical cavities, each containing 1 tablet. Batch specific information is printed on each blister card. The secondary packaging consists of an outer sales carton. **Dosing and administration: Posology** The starting dose of Rybelsus® is 3 mg once daily. After 1 month, the dose should be increased to a maintenance dose of 7 mg once daily. If additional benefits are needed after at least one month on the 7 mg dose, the dose can be increased to a maintenance dose of 14 mg once daily. Rybelsus® can be used as monotherapy or in combination with one or more glucose-lowering medicinal products. When Rybelsus® is used in combination with metformin and/or a sodium-glucose co-transporter 2 inhibitor (SGLT2i) or thiazolidinedione, the current dose of metformin and/or SGLT2i/thiazolidinedione can be continued. When Rybelsus® is used in combination with a sulfonylurea or insulin, a reduction in the dose of sulfonylurea or insulin should be considered to reduce the risk of hypoglycaemia. Missed dose: If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day. **Method of administration:** Rybelsus® is a tablet for once-daily oral use. Rybelsus® should be taken on an empty stomach. Rybelsus® should be swallowed whole with up to half a glass of water equivalent to 120 ml. Do not split, crush or chew the tablet. Wait at least 30 minutes before the first meal or drink of the day or taking other oral medicinal products. Waiting less than 30 minutes may decrease the absorption of semaglutide. **Special Population:** Elderly (≥65 years old): No dose adjustment is required based on age. Gender: No dose adjustment is required based on gender. Race and ethnicity: No dose adjustment is required based on race and ethnicity. Patients with hepatic impairment: No dose adjustment is required for patients with hepatic impairment. Patients with renal impairment: No dose adjustment is required for patients with renal impairment. Children and adolescents: The safety and efficacy of Rybelsus® in children and adolescents below 18 years have not been studied. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** Rybelsus® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Gastrointestinal effects: Use of GLP-1 receptor agonists may be associated with gastrointestinal adverse reactions that can cause dehydration, which in rare cases can lead to a deterioration of renal function. Acute pancreatitis: Acute pancreatitis has been observed with the use of GLP-1 receptor agonists. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Rybelsus® should be discontinued; if confirmed, Rybelsus® should not be restarted. Caution should be exercised in patients with a history of pancreatitis. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis. Hypoglycaemia: Insulin and sulfonylurea are known to cause hypoglycaemia. When it is used in combination with a sulfonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Rybelsus®. Diabetic retinopathy: Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Long-term glycaemic control decreases the risk of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for worsening and treated according to clinical guidelines. Heart failure: There is no therapeutic experience in patients with congestive heart failure New York Heart Association (NYHA) class IV. **Pregnancy and lactation:** Studies in animals have shown reproductive toxicity. There are limited data from the use of semaglutide in pregnant women. Therefore, Rybelsus® should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with Rybelsus®. If a patient wishes to become pregnant, or pregnancy occurs, Rybelsus® should be discontinued. Rybelsus® should be discontinued at least 2 months before a planned pregnancy due to the long half-life. In lactating rats, semaglutide, salcaprozate sodium and/or its metabolites were excreted in milk. As a risk to a breast-fed child cannot be excluded, Rybelsus® should not be used during breast-feeding. **Drug Interaction:** Interaction with other medicines: In vitro studies have shown very low potential for semaglutide to inhibit or induce CYP enzymes, and to inhibit drug transporters. Semaglutide delays gastric emptying which may influence the absorption of other oral medicinal products. No clinically relevant drug-drug interaction with semaglutide was observed based on the evaluated medicinal products. Therefore, no dose adjustment is required for medicinal products when taken with Rybelsus®. Effects of Rybelsus® on other medicinal products: Total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33% following administration of a single dose of levothyroxine. Maximum exposure (Cmax) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with semaglutide at the same time as levothyroxine. No clinically relevant change in AUC or Cmax of warfarin, digoxin, oral contraceptives (containing ethinylestradiol and levonorgestrel), metformin, furosemide or rosuvastatin was observed when concurrently administered with semaglutide. Effects of other medicinal products on semaglutide: No clinically relevant change in AUC or Cmax of semaglutide was observed when taken with omeprazole. Interaction with food: Concomitant intake of food reduces the exposure of semaglutide. **Undesirable Effects:** In 10 phase 3a trials, 5,707 patients were exposed to Rybelsus® 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 reactions 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. Other undesirable effects being delayed gastric emptying, dysgeusia and dizziness **Shelf life:** 3 mg: 24 months; 7 mg: 30 months; 14 mg: 30 months. **Storage** Keep this medicine out of the sight and reach of children. Do not use this medicine after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month. Do not store above 30°C. Store in the original package to protect from moisture and light. Keep the tablet in the blister until you are ready to take it. Removing it too soon can prevent it from working as planned. Do not use this medicine if you notice that the package is damaged or shows signs of being open.
Disclaimer: The abbreviated package insert is updated from the CDSCO approved package insert (F. No.-4-40/Novo Nordisk/PAC-R-Semaglutide/2021-PRD dated 20 July 2021).

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*The full prescribing information can be obtained at no cost from Novo Nordisk. For full prescribing information please contact +91-080-40303200 or write to us at INAgree@novonordisk.com or reach us at Novo Nordisk India Private Limited, NXT Tower -2, Floor 1 & 2, Embassy Manyata Business Park, Nagavara Village, Kasaba Hobli, Bangalore-560045).

Note: For detailed information on this product, please refer to full package insert*. RYBELSUS® and the Apis bull logo are registered trademarks of Novo Nordisk A/S. Please refer latest summary of product characteristics for more details.
To get information on the updated package insert please contact +91 80 4030 3200 or write to us at inagree@novonordisk.com.
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