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/2023-BD dated 22 July 2024). Rybelsus® is a registered trademark owned by Novo Nordisk A/S and registered in Denmark. Imported by: Novo Nordisk India Private Limited, Bangalore

*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.

This material is developed by Novo Nordisk India Private Limited NXT Tower -2, Floor 1 & 2 Embassy Manyata Business Park, Nagavara Village, Kasaba Hobli, Bangalore-560045.

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novo nordisk®

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RYBELSUS® semaglutide tablets

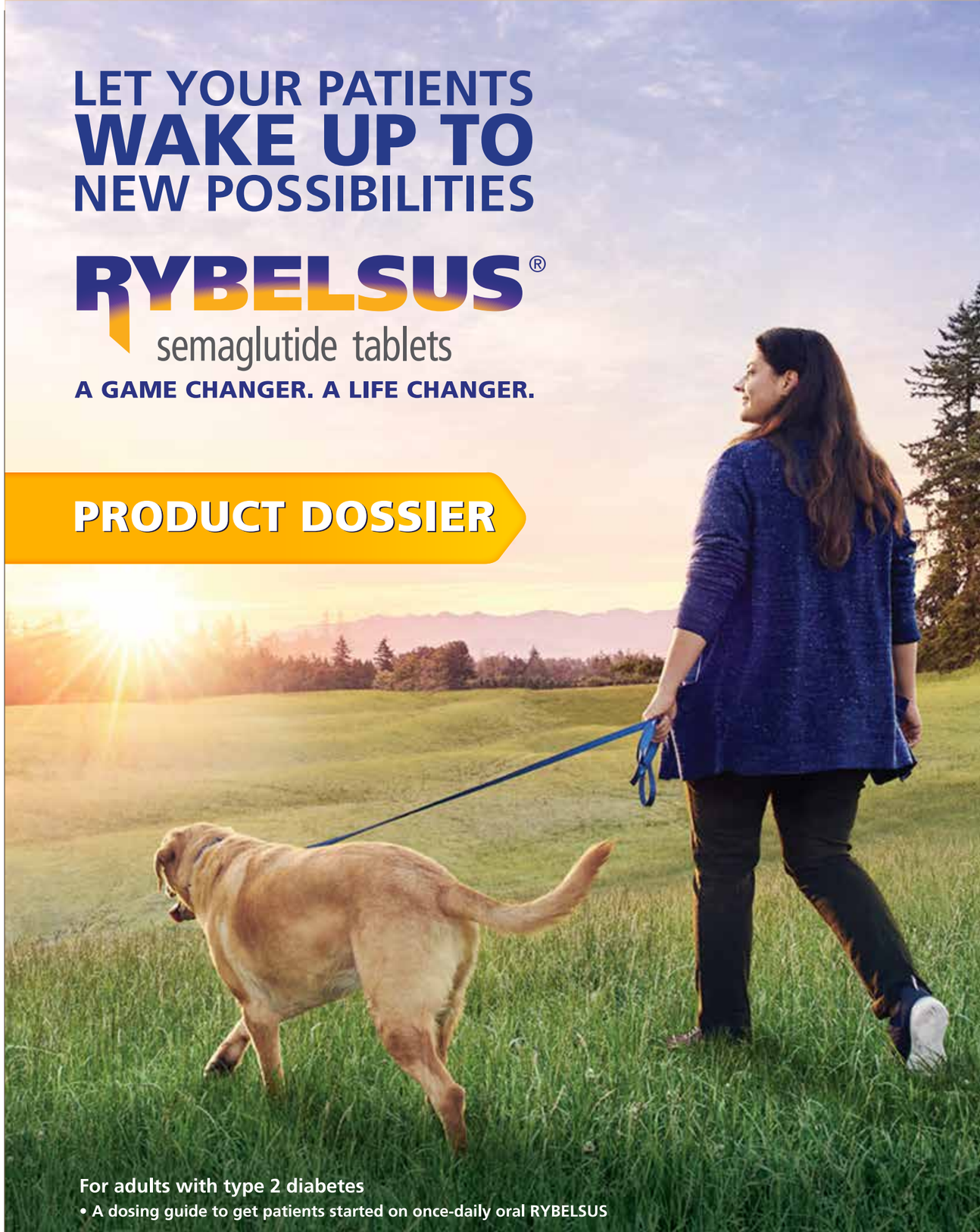
This content is strictly for healthcare professionals practicing in India.

LET YOUR PATIENTS WAKE UP TO NEW POSSIBILITIES

RYBELSUS® semaglutide tablets

A GAME CHANGER. A LIFE CHANGER.

PRODUCT DOSSIER

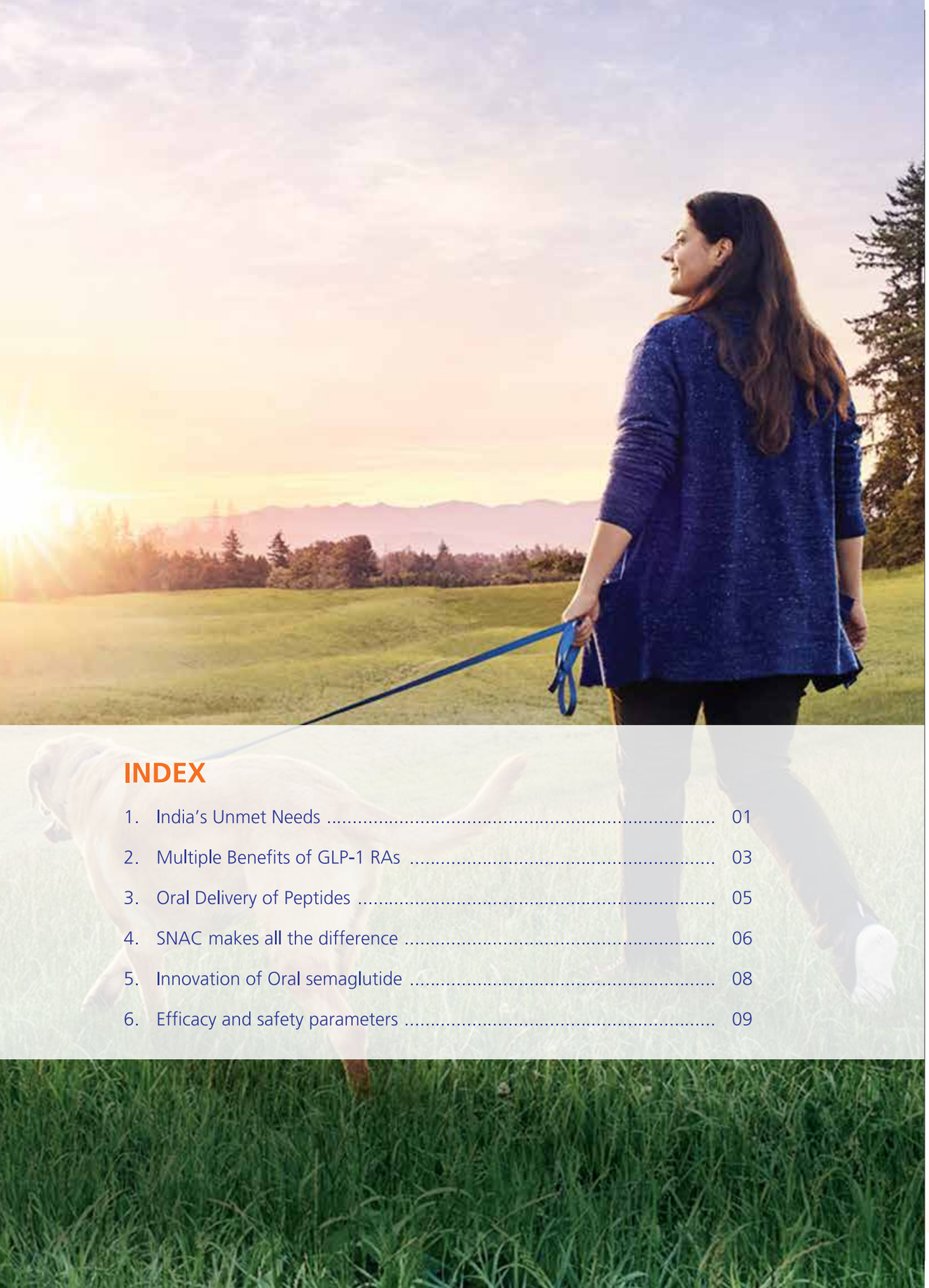


For adults with type 2 diabetes

• A dosing guide to get patients started on once-daily oral RYBELSUS

RYBELSUS® semaglutide tablets

novo nordisk®



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Summary

RYBELSUS® is used to treat adults with poorly controlled type 2 diabetes mellitus in adjust to diet and exercise.[24]

"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 et al., Prim Care Diabetes (2021)

RYBELSUS®
semaglutide tablets
A GAME CHANGER. A LIFE CHANGER.

LET YOUR PATIENTS WAKE UP TO NEW POSSIBILITIES

- **World's first Oral GLP-1 RA[1]**
- **Robust A1c reduction upto 1.5%**
- **Consistent CV outcomes with the GLP-1 RA class**
- **Clinically significant weight loss of up to 5 kg**

RYBELSUS®
EMA human medicines highlight 2020
Endocrinology

RYBELSUS®
Galien Award
Germany 2020
Primary Care

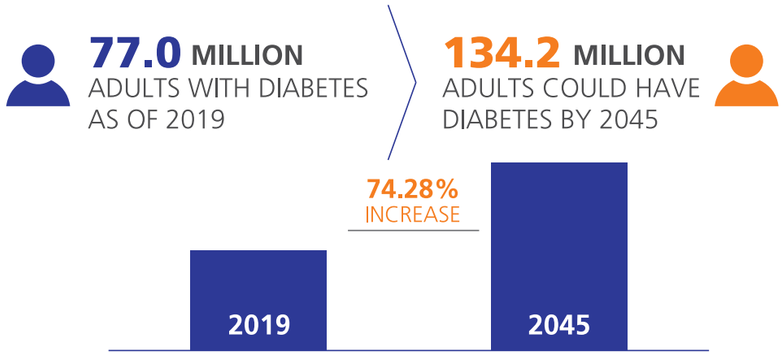
*EMA. HUMAN MEDICINES HIGHLIGHTS 2020. Stand: 21.1.2021. Verfugbar unter: https://www.ema. europa.eu/en/news/human-medicines-highlights-2020.

**ArzteZeitung. RYBELSUSR: Diabetes- Therapie mit oralem GLP-1-Analogon.
Verfugbar auf: https://www.aerztezeitung.de/Specials/Rybelsus-Diabetes-Therapie-mit-oralem-GLP-1-Analogon-413978.html, zuletzt abgerufen: 03/2021.

1

India’s Unmet Needs

India currently has a total adult population with diabetes of **over 101 million** with a prevalence of diabetes in adults at **8.9%**. **463 million people** have diabetes in the world and 88 million people in the SEA Region; by 2045 this will rise to 153 million. With such a high prevalence of diabetes in India[1], it is imperative that the healthcare sector is equipped to deliver quality care for people with diabetes and its management.



As per the rule of halves, only **18.22 million patients** are treated (~25% of people with diabetes). **70%** of the people with diabetes **do not achieve the recommended treatment target of an HbA_{1c} level below 7%**.[2] Diabetes is a progressive disease characterised by impaired beta cell function and reduced insulin sensitivity and secretion.

Moreover, obesity is a common co-morbidity in subjects with type-2 diabetes (60-90% of patients diagnosed). Additional weight gain as a consequence of treatment with SU’s or insulin for example, can reduce PwD's quality of life and hinder adherence to treatment. Obesity is also an independent risk factor for cardiovascular disease, further compromising outcomes.[5]

Over time, glycaemic control deteriorates and exacerbates the risk of PwD experiencing micro- and macrovascular complications.

The greatest challenge in treating people with type-2 diabetes is optimising therapy to address the current unmet needs: Improve glycaemic control without compromising safety i.e. Hypoglycaemia

Although there is an abundance of treatment options and guidelines available for the management of type-2 diabetes, they are unable to avert the natural progression of the disease and sustain glycaemic control in the long term. Furthermore, currently available treatment options are often associated with hypoglycaemia and weight gain.[3,4] Such adverse effects can have detrimental health implications for the person. For example, hypoglycaemia can be an unpleasant side-effect of anti-diabetic therapy which can compromise adherence to treatment, and serious hypoglycaemic events, left untreated, can lead to a loss of consciousness, brain damage or even death.

Multiple Benefits of GLP-1 RAs

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[6].

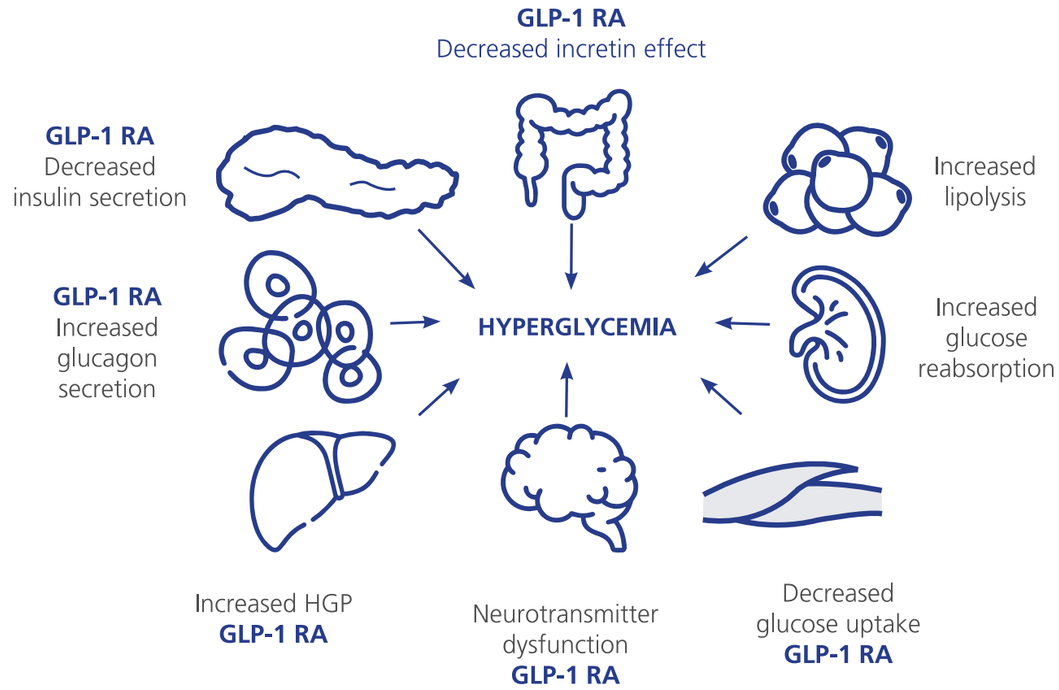
In addition, GLP-1 promotes satiety and reduces energy intake by virtue of its neurotransmitter role in brainstem-hypothalamus pathways signalling satiety and some long-acting GLP-1RAs including semaglutide have shown cardiovascular risk reduction[6].

Effects of GLP-1 RAs on various tissues

Source: Andersen A, Lund A, Knop FK, et al. Nat Rev Endocrinol 2018;14:390–403.

GLP-1 RAs target multiple pathophysiological defects of T2DM

GLP-1 RAs directly or indirectly target nearly all of the eight core pathophysiological defects of T2DM (ominous octet), more than any other class of antihyperglycemic medication



Source: Brunton SA, Wysham CH. Postgrad Med. 2020;132(sup2):3-14.

3

Oral Delivery of Peptides

Medicines like peptides are effective but until recently could only be delivered by injection. Many patients prefer pills over injections, hence posing a challenge to patients, in initiating and adherence to therapy.

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.[7]

This is mainly because the 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 tripeptides before absorption in the small intestine.

Thus, subtherapeutic exposure and high inter- and intraindividual variability have resulted. In addition, many peptides obtain protraction from the subcutaneous administration site while having a shorter intravenous t½, making the duration of action unsuitably short if given orally.

GI-tract degrades and digests peptides[8,25,26,27]

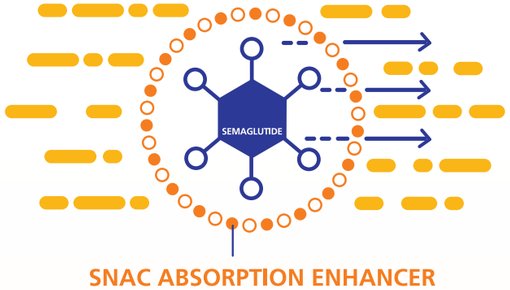
Low permeability through the intestinal cell wall[25-26]

Pairing the right molecule with the right absorption enhancer[8]

In line with this, 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 analogue with a t½ of ~1 week in humans.[8]

The need of the hour was to find a way to make GLP-1 protein withstand the digestive functions, preventing GLP-1 molecule from breaking down in the stomach required right pairing with the right absorption enhancer.

After a significant effort, there was a breakthrough with an enhancer called SNAC, which protects semaglutide from breaking down in the stomach.



SNAC ABSORPTION ENHANCER
protects semaglutide from breaking down in the stomach

8. Knudsen and Lau. Front Endocrinol. 2019;10:155;doi: 10.3389/fendo.2019.00155. 25. Antza et al. Drug Design Development and Therapy. 2019:13:2985-2996. 26. Brayden and Alonso. Adv Drug Deliv Rev. 2016 Nov 15;106(Pt B):193-195. 27. Buckley et al. Sci Transl Med. 2018:10; eaar7047.

4

SNAC makes all the difference

SNAC is Sodium N-[8-(2-hydroxybenzoyl) aminocaprylate]

Semaglutide has a high degree of homology (~94%) with the human GLP-1 molecule with the three key changes in the molecule.[9]

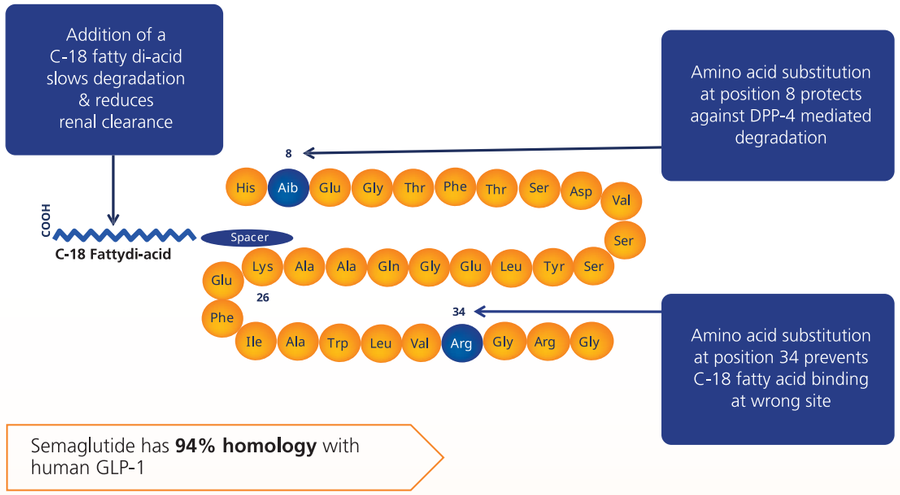
SNAC is an absorption enhancer with the ability to increase the absorption of semaglutide across the GI epithelium. SNAC interacts with the gastric cell membraneand secures transcellular absorption of semaglutide.[10]

Unlike most drugs, the co-formulation of semaglutide & SNAC is absorbed in the stomach rather than in the intestine. SNAC buffers the local pH of the stomach to protect against enzymatic degradation and facilitate transepithelial absorption via the transcellular route. Thus, SNAC protects against enzymatic degradation via local buffering actions and only transiently enhances absorption.

Co-formulation of semaglutide with an absorption enhancer is necessary to achieve adequate bioavailability of oral administration.[11]

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.

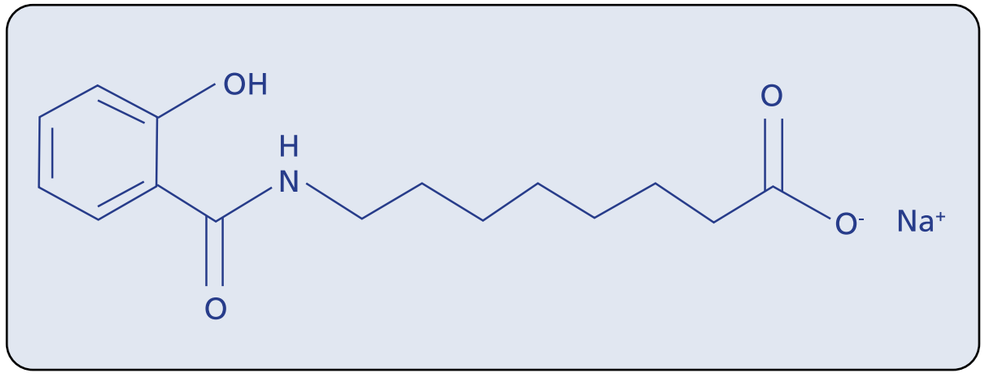
Semaglutide



Semaglutide has **94% homology** with human GLP-1

Sources: 1. Kalra S, Sahay R. Diabetes Ther. 2020;11(9):1965-1982.
2. Bucheit JD, Pamulapati LG, Carter N, et al. Diabetes Technol Ther. 2020;22(1):10-18.

SNAC is Sodium N-[8-(2-hydroxybenzoyl) aminocaprylate]



Orally administered semaglutide is co-formulated with an absorption enhancer, SNAC (Sodium N-[8-(2-hydroxybenzoyl) Amino] Caprylate):

- Allows Rybelsus® to be absorbed from the stomach
- Promotes absorption across the gastric mucosa
- Protects Rybelsus® from breakdown by gastric enzymes

Source: Kalra S, Sahay R. Diabetes Ther. 2020;11(9):1965-1982

5

Innovation of Oral semaglutide

Oral semaglutide developed by Novo Nordisk, is the first oral Glucagon Like Peptide-1 Receptor Agonist (GLP-1 RA) for the treatment of type 2 diabetes mellitus. It is a result of 15 long years of ceaseless efforts to make semaglutide available in a pill. Strong beliefs, collaborations and sheer dedication of the scientists, to help improve the management of type 2 diabetes led to this breakthrough achievement.

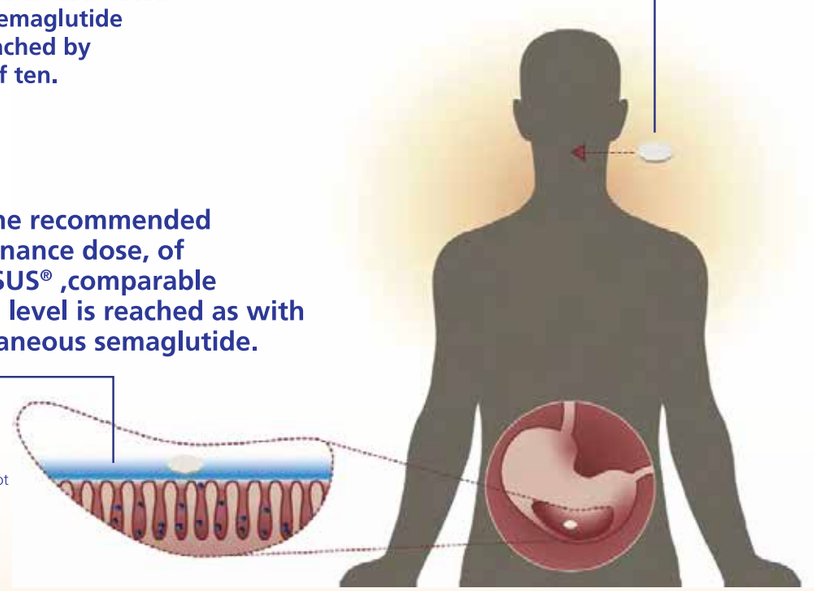
The pharmacological innovation by RYBELSUS®

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

- **SNAC protects against semaglutide gastrointestinal degradation, by increasing the pH locally.**
- **SNAC promotes the transcellular Absorption of Semaglutide via the gastric epithelium.**
- **With SNAC there is an estimated increase in Oral Semaglutide Bioavailability reached by almost a power of ten.**

- White oval tablet for oral use Administration. (All dosages have the same size of 13.5 × 7.5 mm).[24]
- Active ingredient: Semaglutidum (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.



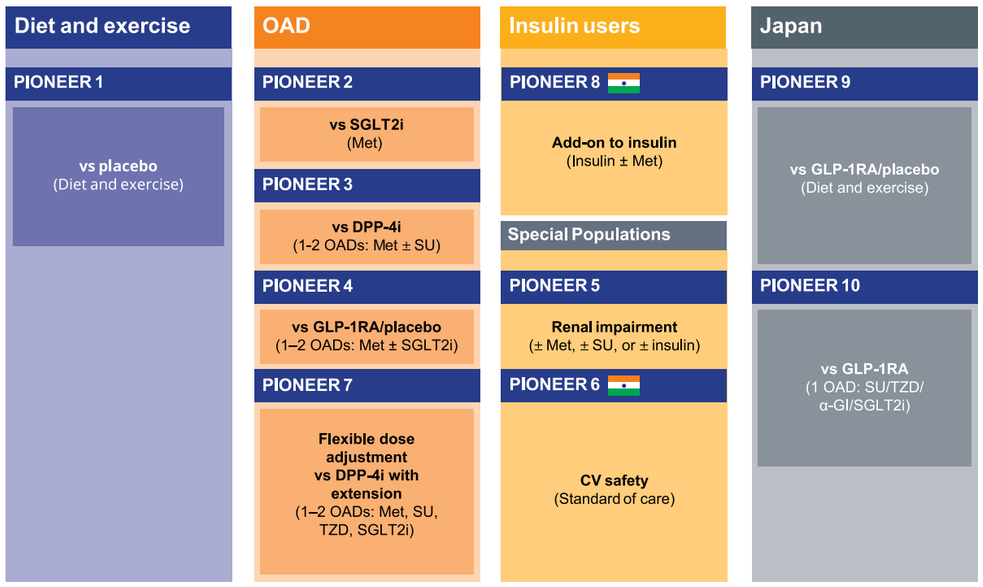
"Subcutaneous semaglutide is not approved in India"

Adapted from Seidu et al. 2021

Efficacy and safety parameters

Clinical trials[12-19]

- PIONEER – the largest ever phase 3 clinical trials were initiated in 2016, with 9,543 participants.
- 9543 subjects enrolled into the study and 5907 were exposed to oral semaglutide 8 global trials and 2 trials in Japanese population. Overall, ten PIONEER efficacy and safety trials as well as cardiovascular safety trial were completed with encouraging results.



CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; Met, metformin; OAD, oral anti-diabetes drug; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

HbA_{1c} reduction[12-19]

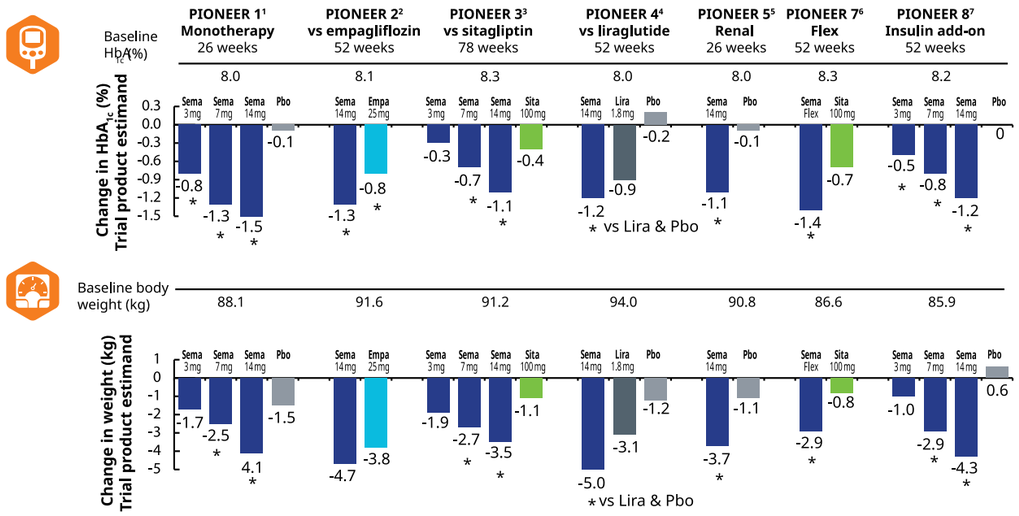
- HbA_{1c} reduction of 1.3 and 1.5 % was seen in 7 mg and 14 mg Oral semaglutide doses respectively at the end of 26 weeks as compared to placebo which was statistically significant.

Proportion of patients achieving HbA_{1c} targets[12-19]

- Up to 80% of the patients achieved HbA_{1c} <7.0%12. The odds of achieving HbA_{1c} <7.0% were statistically significantly greater with oral semaglutide than with sitagliptin, empagliflozin and placebo. Up to 68% of the patients achieved HbA_{1c} ≤6.5%. The odds of achieving HbA_{1c} ≤6.5% were statistically significantly greater with oral semaglutide than with sitagliptin, empagliflozin, liraglutide and placebo.
- Up to 73% of the patients achieved HbA_{1c} <7.0% (7 out of 10 patients) without severe or blood glucose confirmed symptomatic hypoglycaemia and without weight gain. The odds of achieving the target were statistically significantly greater with oral semaglutide than with placebo, sitagliptin, empagliflozin and liraglutide.

Body weight[12-19]

- Oral semaglutide 14 mg was associated with sustained weight reduction over the duration of the trials (up to –5.0 kg from baseline to final time point). Oral semaglutide 14 mg used as monotherapy or in combination with 1-2 glucose-lowering agents resulted in statistically significant reduction in body weight compared with placebo, sitagliptin, liraglutide and empagliflozin(EoT).[13]
- Up to 49% and 18% of patients achieved a weight loss of ≥5% and ≥10%, respectively. The odds of achieving a weight loss of ≥5% and ≥10% were statistically significantly greater with oral semaglutide14 mg than with placebo, sitagliptin and liraglutide.[14]



Efficacy of oral semaglutide according to baseline HbA_{1c}

Oral Semaglutide provides unsurpassed HbA_{1c} reduction in T2D patients with baseline HbA_{1c} >9%

Up to

-2.6%

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.

Fasting plasma glucose

- Treatment with oral semaglutide reduced FPG by up to 45 mg/dL (2.5 mmol/L) across the phase 3a trials. The reductions were sustained through week 78.

Beta-cell function and insulin resistance

- Beta-cell function measured by homeostasis model assessment for beta-cell function (HOMA-B) and insulin resistance measured by homeostasis model assessment for insulin resistance (HOMA-IR) overall improved with oral semaglutide 7 mg and 14 mg.

Cardiovascular risk reduction

- Consistent cardiovascular risk reduction was shown in SUSTAIN 6 and PIONEER 6, supported by an analysis including data from both trials. In this analysis, patients treated with semaglutide had a statistically significant lower risk of the first occurrence of MACE compared to placebo. The estimated HR was 0.76 [0.62; 0.92]95% CI.

Cardiovascular risk factors

- Treatment with oral semaglutide reduced systolic blood pressure by up to 7 mmHg and C-reactive protein concentrations by up to 35% and improved the fasting lipid profile (e.g. triglycerides reduction of up to around 13%).

Pharmacokinetics

- The absorption of semaglutide predominantly occurs in the stomach. The estimated absolute bioavailability of semaglutide is approximately 1% following oral administration. The primary excretion routes of semaglutide-related material are via the urine and faeces. Approximately 3% of the absorbed dose is excreted as intact semaglutide via the urine, with an elimination half-life of approximately 1 week.

Biotransformation/Metabolism

- Semaglutide is metabolised through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid sidechain. The enzyme neutral endopeptidase (NEP) is expected to be involved in the metabolism of semaglutide.
- SNAC metabolism: As with other fatty acid derivatives, SNAC is metabolized via β-oxidation and glucuronidation and eliminated mainly via urine.

Summary of safety profile

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 reactions in clinical trials were gastrointestinal disorders, including nausea (Up to 80% did not experience nausea), diarrhoea and vomiting. In general, these reactions were mild or moderate in severity and of short duration.

Posology and method of administration[20]

Posology

- 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. 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.

Therapeutic indication

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

When oral semaglutide 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 oral semaglutide 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.

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.

Children and adolescents

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

Pregnancy and Breastfeeding

- There are limited data from the use of semaglutide in pregnant women. Therefore, Oral semaglutide should not be used during pregnancy. Oral semaglutide should not be used during breast-feeding.

Renal and hepatic impairment

- Renal and hepatic impairment did not impact the pharmacokinetics of semaglutide in a clinically relevant manner. No dose adjustment is require for patients with renal impairment. Experience with the use of semaglutide in patients with severe renal imparment

Method of administration[24]

- Oral semaglutide is a tablet for once-daily oral use.
- Oral semaglutide should be taken on an empty stomach. Oral semaglutide 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.

Take on an empty stomach upon waking › Swallow tablet whole with a sip of water (up to 120 mL) › Wait at least 30 minutes before eating, drinking, or taking any other oral medication

Contraindications[24]

Hypersensitivity to the active substance or to any of the excipients listed in section 8.0 Pharmaceutical Particulars

Special warnings and precautions for use[24]

Oral semaglutide 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, Oral semaglutide should be discontinued; if confirmed, Oral semaglutide 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. Patients treated with Oral semaglutide in combination with a sulfonylurea or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia can be lowered by reducing the dose of sulfonylurea or insulin when initiating treatment with Oral semaglutide.

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. Other undesirable effects being delayed gastric emptying dysgeusia and dizziness.

Drugs interactions

- 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.

Effects of oral semaglutide 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 (C_{max}) 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 C_{max} 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.

Special warnings and precautions for use

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

Interaction with food

- Concomitant intake of food reduces the exposure of semaglutide (see section 4.2 Posology and method of administration).
- 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 Oral semaglutide.

Advantages of Oral semaglutide[12-23]

Oral semaglutide reduces HbA_{1c} in a clinically relevant and dose-dependent manner

The risk of hypoglycaemia is low with oral semaglutidewhen used as monotherapy

Clinical inertia and non-adherence seen with injectables pose significant obstacles in reaching glycaemic targets in T2DM, this is overcome with oral semaglutide due to patient convenience and ease of administration

No dose adjustment recommended regardless of renal or hepatic impairment

No dose adjustment recommended in elderly patients

Additional pleiotropic benefits of oral semaglutideis very much needed in multidimensional diseases like type 2 diabetes mellitus

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