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RYBELSUS® DIGEST

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RYBELSUS®
semaglutide tablets

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semaglutide tablets

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Prescribing information comparison

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Oral semaglutide versus other anti-diabetic drugs

- GLP-1 RA in Heart Failure
- GLP-1 RA in Chronic kidney disease

Key messages

- The world's first and only oral GLP-1 RA
- Significantly better HbA_{1c} reduction and unsurpassed weight loss vs Januvia®, Jardiance®, and Victoza®
- Up to 7 out of 10 patients achieved an HbA_{1c} target below 7%
- 2.6% HbA_{1c} reduction for patients with baseline HbA_{1c} of 9%

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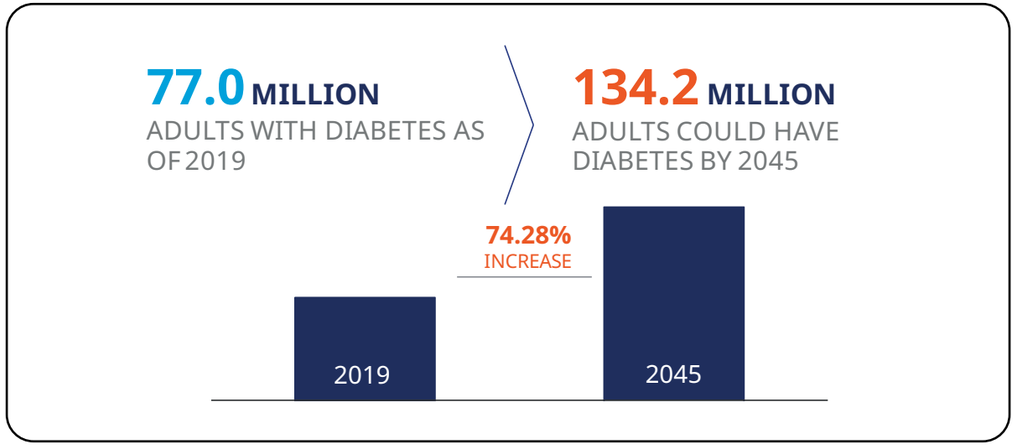
UNMET NEEDS IN DIABETES MANAGEMENT

This section highlights the burden of diabetes, associated comorbidities, and the key challenges for diabetes management

WHY IS DIABETES A GROWING CHALLENGE IN INDIA?

Burden of diabetes in India

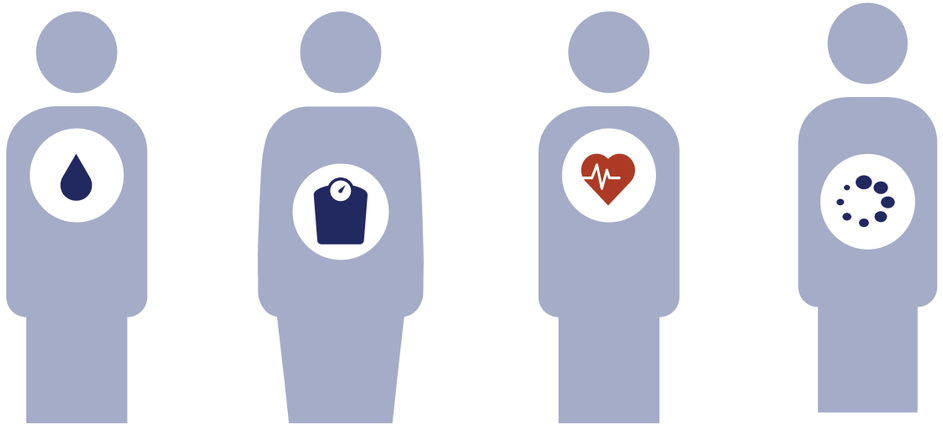
- India has the 2nd largest number (77 million) of adults with diabetes worldwide
- In 2019, India ranked 3rd in the number of people older than 65 years with diabetes (12.1 million)
- By 2045, it is expected that **India will rank 2nd** in the number of people older than 65 years with diabetes (27.5 million)
- **More than 10 lakh deaths** due to diabetes and diabetes-related complications are reported in India annually.



Source: IDF Diabetes Atlas 9th edition 2019. Available at: https://diabetesatlas.org/en/resources/. Accessed on 28/08/2021.

Unmet Needs

KEY CHALLENGES FOR DIABETES MANAGEMENT IN INDIA



Poor glycemic control

76.6% of adults with type 2 diabetes (T2DM) in India fail to achieve HbA_{1c}<7%[1]

Overweight obesity

~67% people with T2DM in India have obesity[1,2]

Cardiovascular disease

32% of the T2DM population also have cardiovascular disease[3]

Therapeutic inertia

Almost 50% of all people with diabetes have suboptimal adherence to treatment[4]

Burden of obesity in diabetes

- **Risk of developing T2DM is twice or more** among the overweight and obese as compared to non-overweight Indians[1]
- Relative risk for developing T2DM increases with increasing weight[2]
- People with T2DM and obesity have **an increased risk of mortality**[3]

Burden of cardiovascular disease in diabetes

- Cardiovascular disease (CVD) is the **major cause of disability and death** in patients with diabetes[4]
- People with diabetes are **2 to 3 times more likely to develop CVD** than those without diabetes[4]
- 85% of deaths from CVD are due to atherosclerotic CVD, including heart attack and stroke[5]

Unmet Needs

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Sources: 1. Borgharkar SS et al. BMJ Open Diab Res Care 2019;7:e000654. **2.** Rehman T et al.Indian J Community Med. 2020;45(3):315-319. **3.** Einarson et al. Cardiovasc Diabetol 2018 Jun 8;17(1):83. **4.** Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2017.

Sources: 1. Gupta S, Bansal S (2020) Does a rise in BMI cause an increased risk of diabetes?: Evidence from India. PLoS ONE 15(4): e0229716. **2.** Colditz et al. Ann Intern Med. 1995 Apr 1;122(7):481-6. **3.** Oldridge et al. J Clin Epidemiol 2001;54(9):928-34. **4.** Diabetes and cardiovascular disease. Available at: https://idf.org/our-activities/care-prevention cardiovascular-disease.html. Accessed on 28/08/2021. **5.** Cardiovascular diseases (CVDs). Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases (cvds). Accessed on 14/09/2021.

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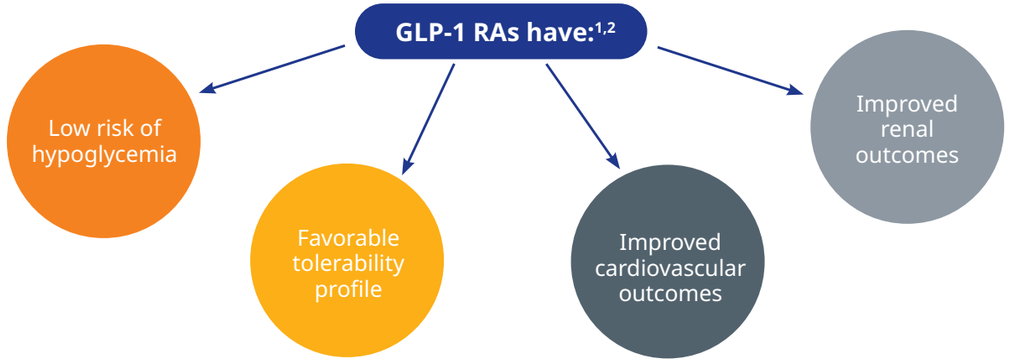
NEED FOR GLP-1 RAS

This section discusses the medical rationale for using GLP-1 RAs in diabetes management

WHAT IS THE MEDICAL RATIONALE FOR GLP-1 RAs IN DIABETES MANAGEMENT?

Glucagon-like peptide-1 receptor agonists

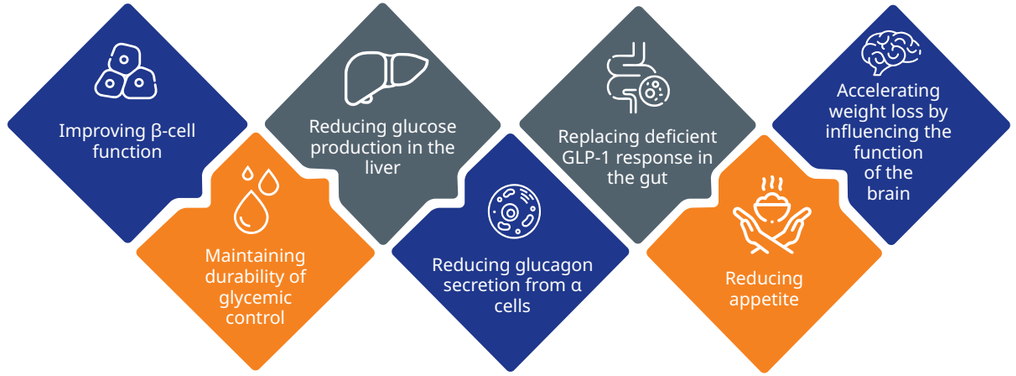
- Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of glucose-lowering drugs that act on the GLP-1 receptor on pancreatic beta cells



Sources: 1. Levin PA, Nguyen H, Wittbrodt ET, et al. Diabetes Metab Syndr Obes. 2017;10:123-139. **2.** Bucheit JD, Pamulapati LG, Carter N, et al. Diabetes Technol Ther. 2020;22(1):10-18.

Need for GLP-1 RAs

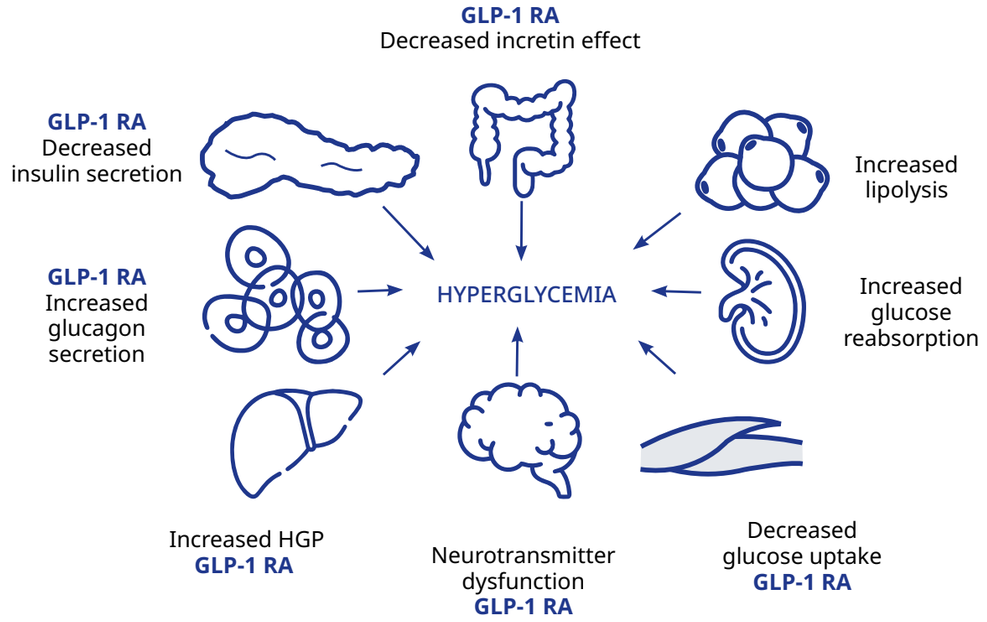
Effects of GLP-1 RAs on various tissues



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.

Need for GLP-1 RAs

Pancreas

- » Beta-cell function
- » Beta-cell death
- » Insulin production
- » Glucagon secretion

Liver

- » Glucose production
- » Insulin sensitivity
- » Conversion of carbohydrate to fat
- » Accumulation of lipids
- » Retention of lipids

Heart

- » CV risk
- » Fatty acid metabolism
- » Cardiac function
- » Systolic blood pressure
- » Inflammation
- » Plaque progression

Incretin

- » Replacement of deficient GLP-1 response

Brain

- » Body weight
- » Food intake
- » Satiety

GUIDELINE RECOMMENDATIONS FOR GLP-1 RAS

This section highlights recommendations from various international guidelines for the use of GLP-1 RAs in diabetes management

Sources: 1. Campbell JE, Drucker DJ. Cell Metab. 2013;17:819–37; **2.** Marso SP, et al. N Engl J Med. 2016;375:311–22; **3.** Ryan D, Acosta A. Obesity. 2015;23:1119–29; **4.** Hogan AE, et al. Diabetologia. 2014;57:781–4; **5.** Tong J, D'Alessio D. Diabetes. 2014;63:407–9; **6.** Armstrong MJ, et al. J Hepatol. 2016;64:399–408; **7.** Armstrong MJ, et al. Lancet. 2016;387:679–90.

ADA/EASD consensus statement (2019 Update)

- Considering the association between T2DM and cardiovascular and kidney disease, the ADA/EASD consensus statement provides separate recommendations for patients with established atherosclerotic cardiovascular disease or chronic kidney disease.

First-line therapy **Metformin + Comprehensive lifestyle (including weight management and physical activity)**	
⬇	
Patients with established ASCVD, HF or CKD	
Consider independently of baseline HbA_{1c} or individualized HbA_{1c} target	
⬇	⬇
ASCVD predominates	**HF or CKD predominates**
PREFERABLY	PREFERABLY
GLP-1RA with proven CVD benefit	SGLT2i with evidence of reducing HF and/or CKD progression in CVOT if eGFR adequate
OR	OR
SGLT2i with proven CVD benefit, if eGFR adequate	If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1RA with proven CVD benefit

T2DM, type 2 diabetes mellitus; ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide 1receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; eGFR, estimated glomerular filtration rate; CVOT, cardiovascular outcomes trials.

Sources: 1. Davies MJ et al. Diabetes Care 2018;41:2669–2701. **2.** Buse JB et al. Diabetes Care 2020;43:487–493

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases

- SGLT2is or GLP-1RAs are recommended in drug-naïve patients with ASCVD or high/very high CV risk as first-line therapy
- SGLT2is or GLP-1RAs are recommended in patients on metformin therapy with ASCVD or high/very high CV risk, irrespective of HbA_{1c}

Type 2 diabetes - Drug naïve patients				
ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)				
⬇	⬇			
SGLT2 inhibitor or GLP-1 RA Monotherapy	**Metformin Monotherapy**			
If HbA_{1c} above target	If HbA_{1c} above target			
Add Metformin	DPP-4i	GLP-1 RA	SGLT2i if eGFR adequate	TZD
If HbA_{1c} above target	**If HbA_{1c} above target**			
• Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit • DPP-4i if not on GLP-1 RA • Basal insulin • TZD (not in HF patients) • SU	SGLT2i or TZD	SGLT2i or TZD	GLP-1 RA or DPP-4i or TZD	SGLT2i or DPP-4i or GLP-1 RA

ESC, European Society of Cardiology; T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; GLP-1 RA, glucagon-like peptide 1receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; eGFR, estimated glomerular filtration rate; CVOT, cardiovascular outcomes trials; DPP4i, dipeptidyl peptidase-4; TZD, thiazolidinedione.

Source: Cosentino F et al. Eur Heart J 2020;41:255–323

Guidelines

- If the A1C target is not achieved after approximately 3 months, metformin can be combined with any one of the preferred six treatment options: sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 RA, or basal insulin
- For patients with established ASCVD or indicators of high ASCVD risk, heart failure, or CKD, an SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose lowering regimen independent of A1C, independent of metformin use, and in consideration of patient-specific factors
- The combination of basal insulin and GLP-1 RA has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens.

ADA, American Diabetes Association; T2DM, type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide 1receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; eGFR, estimated glomerular filtration rate; CVOT, cardiovascular outcomes trials; DPP4i, dipeptidyl peptidase-4; TZD, thiazolidinedione.

Source: American Diabetes Association. Standards of Medical Care in Diabetes. 2021. Diabetes Care 2021;44(Suppl. 1):S111–S124.

Next-gen Innovation

WHAT IS THE NEED FOR ORAL ADMINISTRATION OF GLP-1 RAs?

Although GLP-1 RAs are well-established with evidence

Proven clinical efficacy

- Effective in reducing HbA_{1c} levels
- Body weight reduction
- Low risk for hypoglycemia as monotherapy
- CV benefits

Prescribing GLP-1 RAs

- It is **simple to prescribe GLP-1 RA** even if visits in person are not possible
- GLP-1 RA **is not an insulin**
- Nausea is expected, but temporary

There are potential challenges with GLP-1 RAs treatment

Treatment initiation

Treatment adherence

Clinical inertia and **non-adherence** pose significant obstacles to reaching glycemic targets

CV, cardiovascular; GLP-1 RA, glucagon like peptide-1 receptor agonist.

Sources: 1. Marso SP et al. N Engl J Med. 2016;375:1834-1844. **2.** Gerstein HC et al. Lancet. 2019;394:121–130. **3.** https://www.medscape.org/viewarticle/829355_2. **4.** Meier JJ. Nat Rev Endocrinol. 2012;8(12):728-42. **5.** Pantalone KM et al. Diabetes Care. 2016;39:1527–1534. **6.** Carls G et al. Diabetes Ther. 2017;8:863–873.

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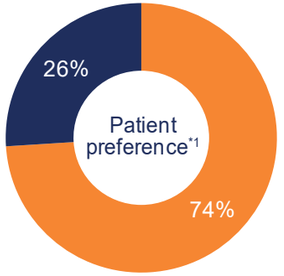
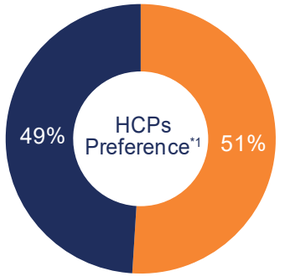
Patients with type 2 diabetes have a preference towards a daily oral rather than a weekly injection

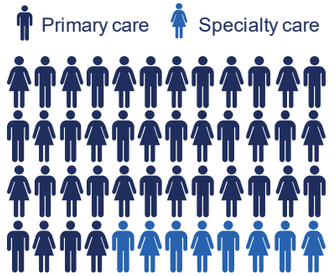


Patients with type 2 diabetes have a preference towards a daily oral rather than a weekly injection

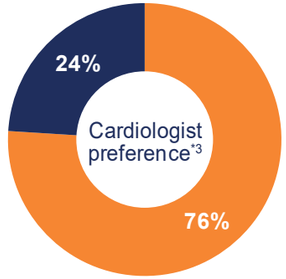


HCPs preference is equally split

Once daily | Once weekly



PCPs are responsible for ~80% of the initiations of oral glucose-lowering medications[2†] - this indicates a strong preference for oral medications in primary care



Cardiologists have a preference towards a daily oral rather than a weekly injection

HCP, healthcare professional; PCP, primary care physicians; *Profiles identical aside from route, frequency & dosing conditions. †Oral medications refer to DPP-4is and SGLT-2is.

Sources: 1. Novo Nordisk. Data on file (n=210 HCPs, n=302 T2D patients); **2.** Novo Nordisk. Data on file. **3.** Base: n=133 Cardiologists NN data on file.

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Next-gen Innovation

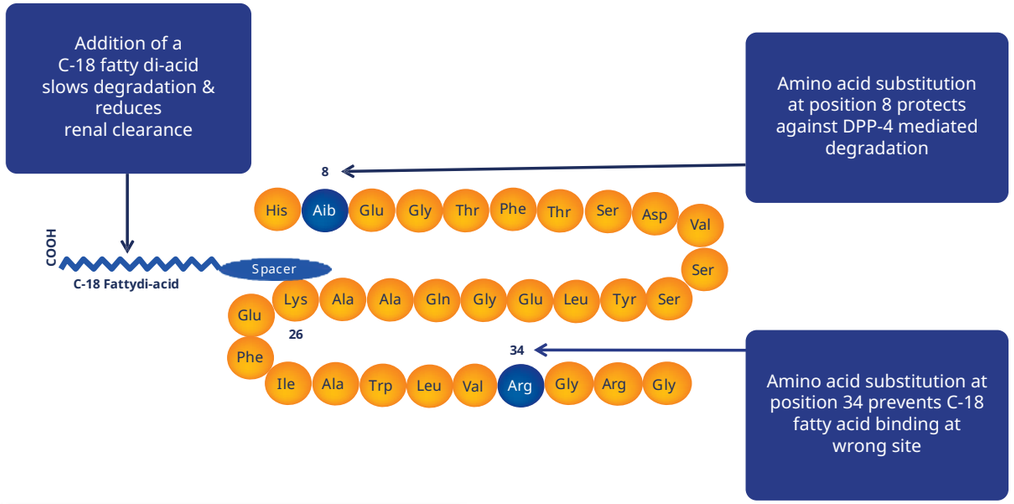
Next-gen Innovation

RYBELSUS® IS THE WORLD'S FIRST AND ONLY ORALLY ADMINISTERED SEMAGLUTIDE

- Semaglutide is a potent, long-acting GLP-1 analogue that has 94% structural homology to native GLP-1 and three key structural modifications:
  - » Amino acid substitution from alanine to alpha-aminoisobutyric acid at position 8 makes semaglutide less susceptible to enzymatic degradation by dipeptidyl peptidase-IV (DPP-IV
  - » Addition of an eighteen-length carbon chain and spacer to lysine at position 26 provides strong binding to albumin, thus reducing renal clearance and extending half-life of semaglutide
  - » Amino acid substitution at position 34 from lysine to arginine prevents C18 fatty acid binding at the wrong site and enhances the stability of semaglutide
- Together, these structural modifications extend the pharmacokinetics and provide a potent and long acting semaglutide.[1,2]

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.

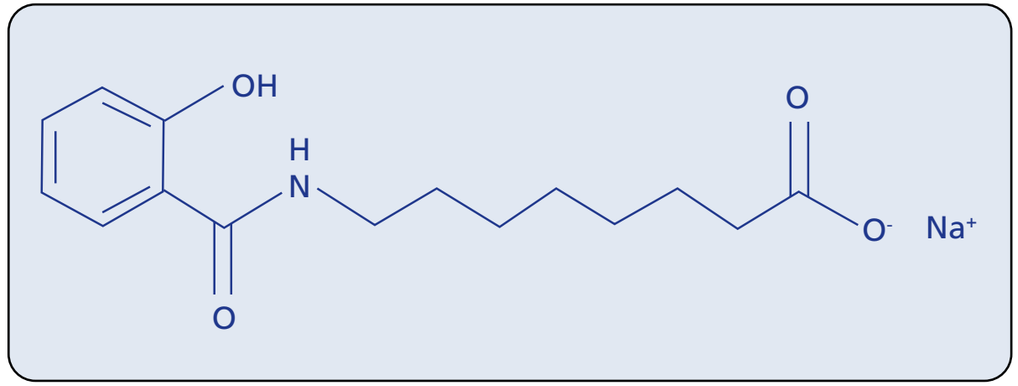
Semaglutide



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

Next-gen Innovation

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.



- 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.

PRODUCT KNOWLEDGE

This section highlights the various pharmacotherapeutic aspects of Rybelsus®, its pleiotropic benefits, and an overview of the PIONEER clinical trials

Product knowledge

RYBELSUS®: A GAME CHANGER, A LIFE CHANGER

Indications

- Rybelsus® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Dosage and Administration

- Orally administered semaglutide should be taken on an empty stomach, at least 30 minutes before the first meal, drink, or other oral medications of the day
- It should be swallowed whole with up to half a glass of water (approximately up to 120 mL) only
- Do not split, crush or chew the tablet.
- Waiting less than 30 minutes, or taking with food, drink (other than plain water) or other oral medications may decrease the absorption of semaglutide
- Orally administered semaglutide should be started with 3 mg once daily for 30 days. After 30 days on the 3 mg dose, the dose should be increased to 7 mg once daily
- If additional glycemic control is needed after at least 30 days on the 7 mg dose, dose may be increased to 14 mg once daily

Dosage Forms and Strengths

- 3 mg, 7 mg, and 14 mg oral tablet formulations

Contraindications

- History of serious hypersensitivity reaction to semaglutide or any of the excipients in the formulation.
- Personal or family history of certain types of thyroid cancer, such as medullary thyroid carcinoma, or in patients with multiple endocrine neoplasia syndrome type 2

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Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021. **2.** Semaglutide - Drug Summary. Available at: https://www.pdr.net/drug-summary/Rybelsus-semaglutide-24383. Accessed on 28/08/2021.

Warnings and Precautions

- **Pancreatitis:** There have been reports of pancreatitis with semaglutide therapy during clinical trials. Semaglutide should be discontinued promptly if pancreatitis is suspected and it should not be restarted if pancreatitis is confirmed
- **Diabetic Retinopathy Complications:** Has been reported in a cardiovascular outcomes trial with semaglutide injection. Patients with a history of diabetic retinopathy should be monitored for visual changes
- **Hypoglycemia:** Risk of hypoglycemia is increased with the concomitant use of semaglutide with an insulin secretagogue or insulin. Reducing dose of insulin secretagogue or insulin may be necessary
- **Acute Kidney Injury:** Renal function should be monitored in patients with renal impairment reporting severe adverse gastrointestinal reactions

Adverse Reactions

- The most common adverse reactions are: Nausea, abdominal pain, diarrhea, vomiting, and constipation.

Drug interactions

- **Insulin secretagogue or insulin:** When initiating orally administered semaglutide, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- **Oral medications:** Orally administered semaglutide delays gastric emptying of other oral medications administered concomitantly. Medications that have a narrow therapeutic index or that require clinical monitoring should be considered for increased clinical or laboratory monitoring.

Product knowledge

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021. **2.** Semaglutide - Drug Summary. Available at: https://www.pdr.net/drug-summary/Rybelsus-semaglutide-24383. Accessed on 28/08/2021.

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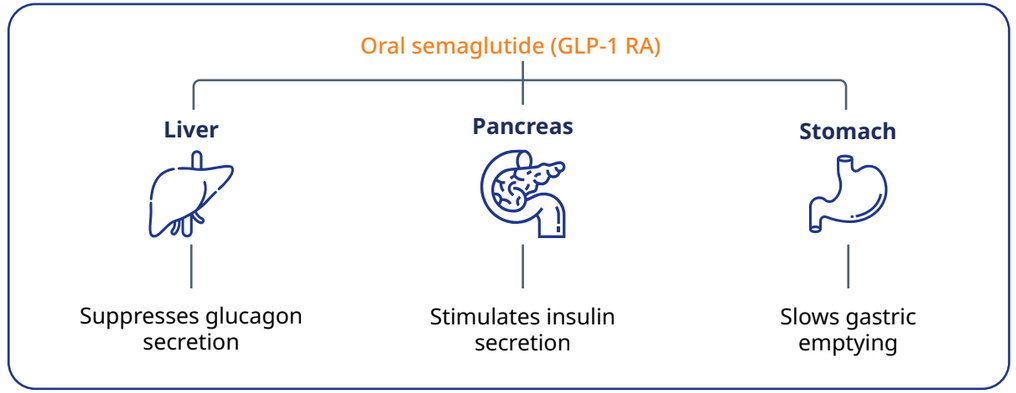
Clinical pharmacology

Mechanism of action

- Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1.
- GLP-1 is an important physiological hormone that acts as glucose homeostasis regulator and is mediated by the GLP-1 receptors.
- GLP-1 enhances insulin secretion, suppresses glucagon secretion, slows gastric emptying, and promotes beta-cell proliferation.
- Semaglutide, being a GLP-1RA, reduces high blood glucose level by stimulating insulin secretion and suppressing glucagon secretion, both in a glucose-dependent manner.
- Semaglutide also causes a delay of early postprandial gastric emptying, thus reducing the rate at which glucose appears in the circulation following a meal.

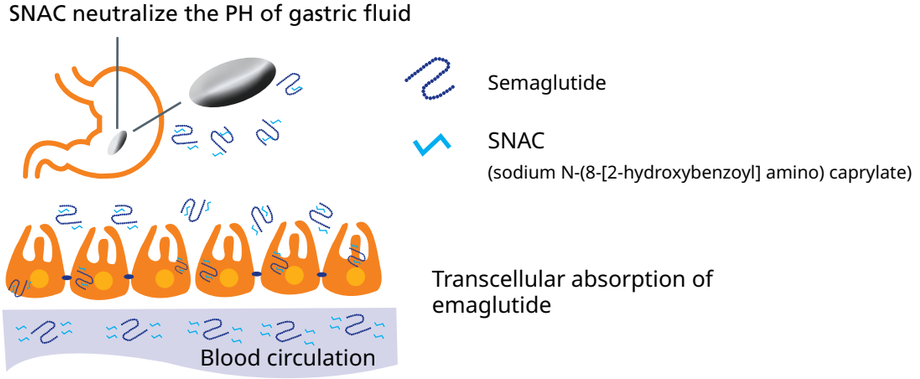


Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Semaglutide - Drug Summary. Available at: https://www.pdr.net/drug-summary/Rybelsus-semaglutide-24383. Accessed on 28/08/2021.

Pharmacokinetics

Absorption

- Oral semaglutide is co-formulated with SNAC, which facilitates the absorption of semaglutide following oral administration[1]
- 300 mg of SNAC provides the most optimum absorption of the oral semaglutide formulation[2]
- Absorption of semaglutide predominantly occurs in the stomach, which is unique to this medication as most oral medications are absorbed in the intestines[1,2]
- Following oral administration, maximum concentration of semaglutide is reached 1 hour post-dose[1,3]
- Steady-state exposure is achieved following 4-5 weeks administration.[1,3]



Absorption of semaglutide and SNAC co-formulation tablet[4]

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Niman S, Hardy J, Goldfaden RF, et al. Drugs in R&D. 2021; 21:133–148. **3.** Semaglutide - Drug Summary. Available at: https://www.pdr.net/drug-summary/Rybelsus-semaglutide-24383. Accessed on 28/08/2021. **4.** Kalra S, Sahay R. Diabetes Ther. 2020;11(9):1965-1982.

Product knowledge

Distribution

- The estimated volume of distribution of semaglutide following oral administration in healthy subjects is approximately 8 L[1]
- Semaglutide is extensively bound to plasma protein (>99%), particularly albumin[1]
- Since there is a substantial excess of albumin binding sites for oral semaglutide at clinically relevant doses; it is expected that effects of oral semaglutide will not be significantly altered by usual changes in plasma albumin levels.[2]

Metabolism

- Semaglutide is metabolized in plasma through proteolytic cleavage of the peptide backbone and beta-oxidation of the fatty acid side chain.[1,3]
- It is slowly and extensively metabolized, with about 83% of the administered dose measured in the plasma as unchanged drug.[3]

Excretion

- No single organ acts as the major route of elimination for semaglutide; however, degradation products of semaglutide are primarily excreted through urine and feces, implying at least partial involvement of the liver in the elimination of semaglutide.[1,4,5]
- Approximately 3% of the dose is excreted in the urine as intact semaglutide.[1,4]
- With an elimination half-life of approximately 1 week, semaglutide is present in the circulation for about 5 weeks after the last dose.[1,4]

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021. **2.** Data on File. **3.** Semaglutide. Available at: https://go.drugbank.com/drugs/DB13928. Accessed on 28/08/2021. **4.** Semaglutide - Drug Summary. Available at: https://www.pdr.net/drug-summary/Rybelsus-semaglutide-24383. Accessed on 28/08/2021. **5.** Baekdal TA, Thomsen M, Kupčová V, et al. J Clin Pharmacol. 2018;58(10):1314-1323.

PLEIOTROPIC BENEFITS OF ORAL SEMAGLUTIDE

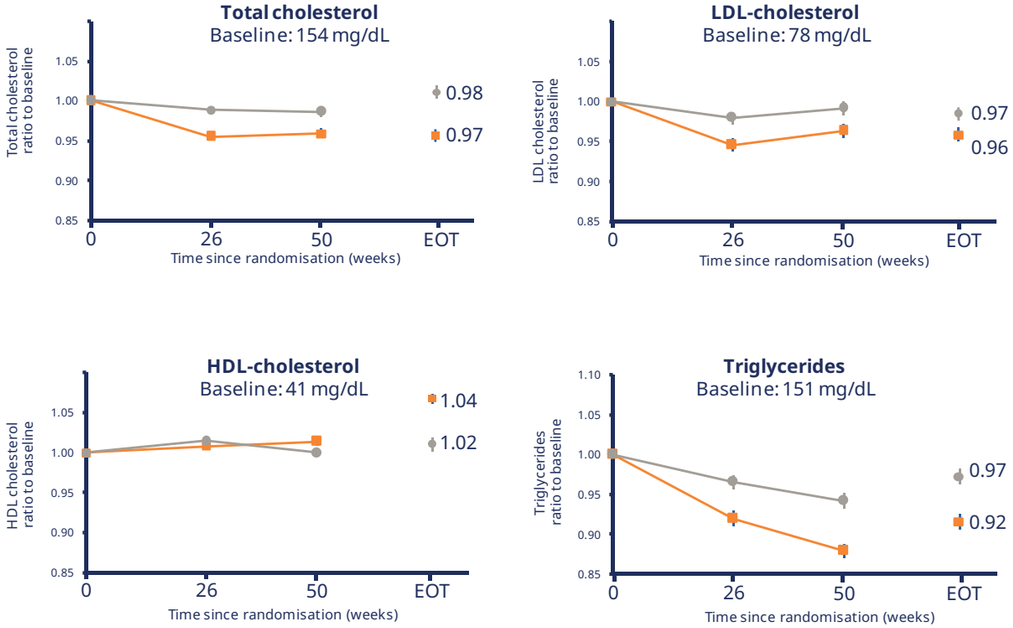
Effect on body weight

BMR, Basal metabolic rate

Source: Blundell et al. Diabetes Obes Metab. 2017;19:1242–51.

Product knowledge

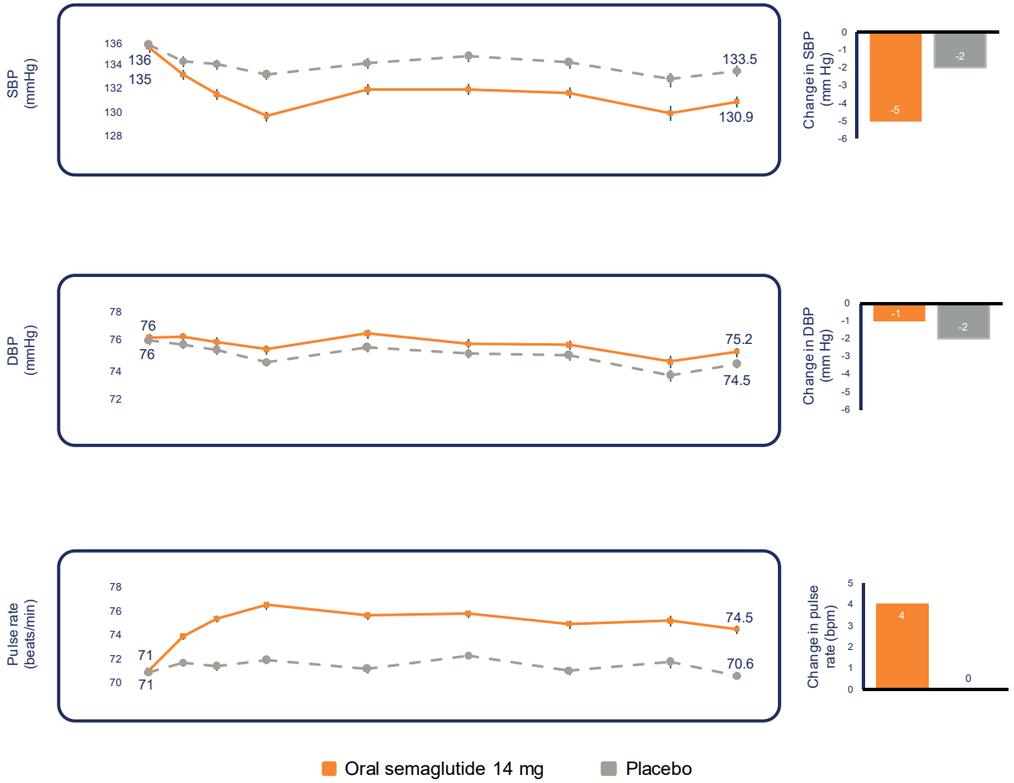
Effect on lipid parameters



EOT, end of treatment; HDL, high density lipoprotein; LDL, low density lipoprotein

Source: Husain M et al. N Engl J Med. 2019;381:841–51.

Effect on lipid parameters

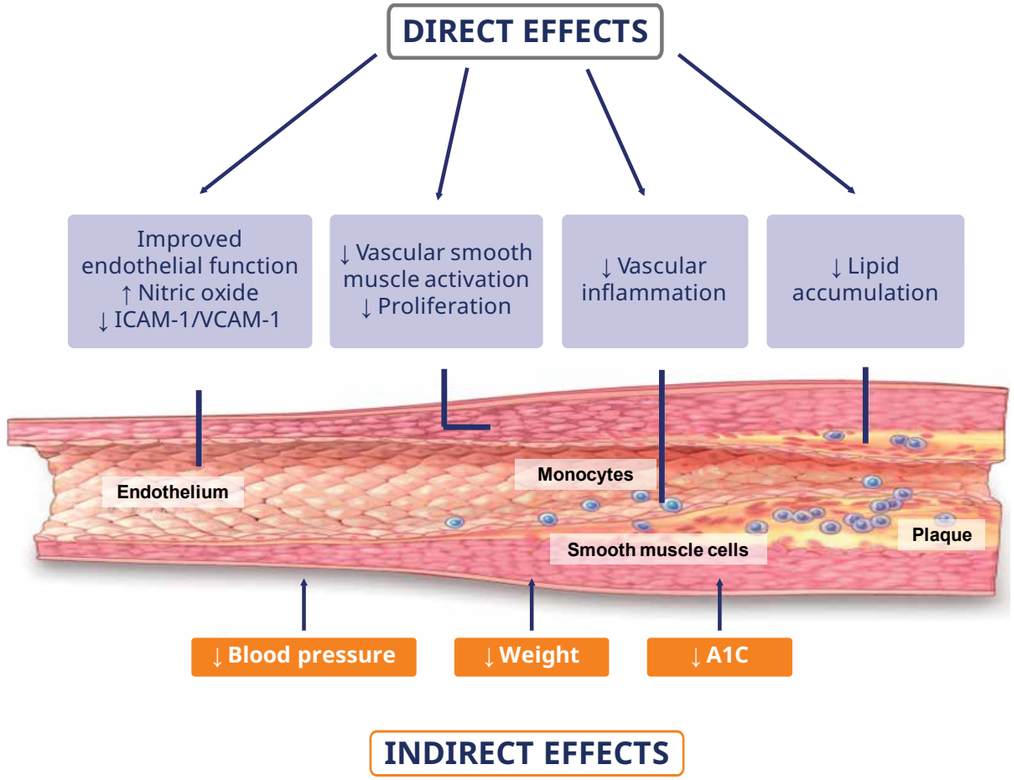


Numbers shown in the lower panel represent the number of patients contributing to the means for SBP.
DBP, diastolic blood pressure; EOT, end of treatment; SBP, systolic blood pressure.

Source: Husain M et al. N Engl J Med. 2019;381:841–51.

Product knowledge

Anti-atherosclerotic benefits



GLP-1RA, glucagon-like peptide-1 receptor agonist; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion protein 1.

Source: Sharma A, Verma S. Can J Diabetes. 2020;44:93–102.

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THE PIONEER CLINICAL TRIALS

PIONEER (Peptide Innovation for Early Diabetes Treatment) Trials

- A global clinical development program that evaluated the efficacy and safety of semaglutide in several patient populations and versus several other classes of therapies

Diet and exercise	OAD	Insulin users	Japan
PIONEER 1 vs placebo (Diet and exercise)	**PIONEER 2** vs SGLT2i (Met) **PIONEER 3** vs DPP-4i (1-2 OADs: Met ± SU) **PIONEER 4** vs GLP-1RA/placebo (1–2 OADs: Met ± SGLT2i) **PIONEER 7** Flexible dose adjustment vs DPP-4i with extension (1–2 OADs: Met, SU, TZD, SGLT2i)	**PIONEER 8** Add-on to insulin (Insulin ± Met) **Special Populations** **PIONEER 5** Renal impairment (± Met, ± SU, or ± insulin) **PIONEER 6** CV safety (Standard of care)	**PIONEER 9** vs GLP-1RA/placebo (Diet and exercise) **PIONEER 10** vs GLP-1RA (1 OAD: SU/TZD/α-GI/SGLT2i)

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.

Sources: **1.** Aroda VR et al. Diabetes Care 2019;42:1724–32; **2.** Rodbard HW et al. Diabetes Care. 2019;42(12):2272–2281; **3.** Rosenstock J et al. JAMA 2019;321:1466–80; **4.** Pratley R et al. Lancet 2019;394:39–50; **5.** Mosenzon O et al. Lancet Diabetes Endocrinol 2019;7:515–27; **6.** Husain M et al. N Engl J Med 2019. 381:841–51; **7.** Pieber TR et al. Lancet Diabetes Endocrinol 2019;7:528–39; **8.** Zinman B et al. Diabetes Care. 2019;42(12):2262–2271; **9.** Yamada et al. Lancet Diabetes Endocrinol 2020;8:377–91; **10.** Yabe et al. Lancet Diabetes Endocrinol 2020;8:392–6.

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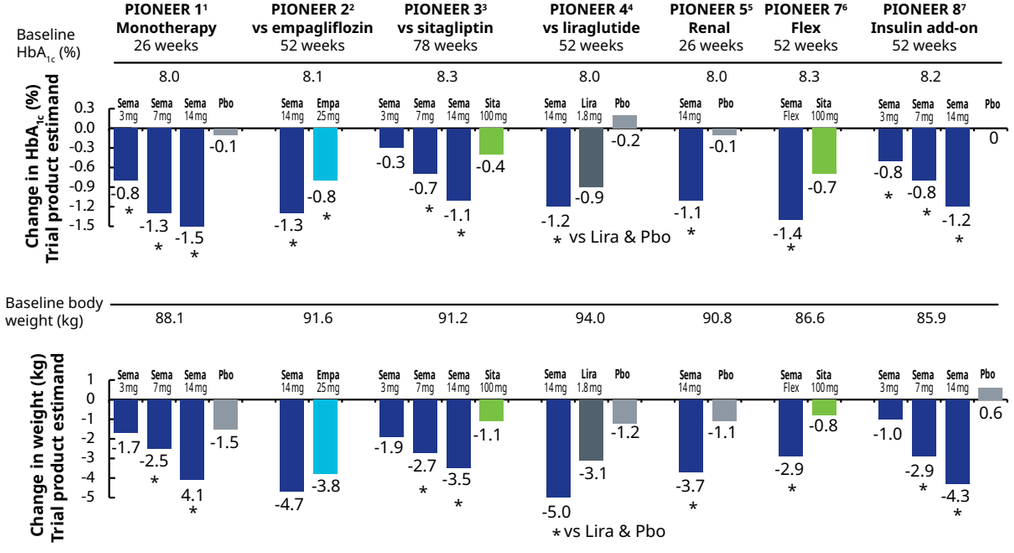
Product knowledge

PIONEER 1-5, 7, 8

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

Oral semaglutide reduced HbA_{1c} in a clinically relevant and dose-dependent manner; the reductions were up to 1.5% and sustained weight loss of up to 5 kg



*Statistically significantly greater vs placebo or active comparator. Lira, liraglutide; Pbo, placebo; Sema, semaglutide; Sita, sitagliptin

Sources: **1.** Aroda VR et al. Diabetes Care. 2019;42(9):1724-1732. **2.** Rodbard HW et al. Diabetes Care. 2019;42(12):2272-2281 **3.** Rosenstock et al. JAMA 2019;321:1466-80. **4.** Pratley et al. Lancet 2019;394:39-50. **5.** Mosenzon et al. Lancet Diabetes Endocrinol 2019;7:515-27. **6.** Pieber et al. Lancet Diabetes Endocrinol 2019;7:528-39. **7.** Zinman B et al. Diabetes Care. 2019;42(12):2262-2271.

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

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

Sources: 1. Aroda VR et al. Diabetes Care. 2019;42(9):1724-1732. **2.** Rodbard HW et al. Diabetes Care. 2019;42(12):2272-2281 **3.** Rosenstock et al. JAMA 2019;321:1466-80. **4.** Pratley et al. Lancet 2019;394:39-50. **5.** Mosenzon et al. Lancet Diabetes Endocrinol 2019;7:515-27. **6.** Pieber et al. Lancet Diabetes Endocrinol 2019;7:528-39. **7.** Zinman B et al. Diabetes Care. 2019;42(12):2262-2271. **8.** https://www.easd.org/virtualmeeting/home.html#!resources/4ea9eeb7-096f-4c7c-9fd7-59c19faa083b

Product knowledge

PIONEER 1 (ORAL SEMAGLUTIDE VS. PLACEBO)

PIONEER 1 Trial compared the efficacy and safety of oral semaglutide as monotherapy with placebo in patients with T2DM managed by diet and exercise only.

STUDY DESIGN

Comparator: **Placebo**

Population: **Drug-naïve adults with T2DM**

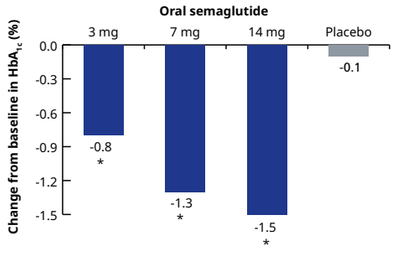
Participants: **703**

Duration: **26 weeks**

KEY RESULTS

Change in HbA_{1c}

- Oral semaglutide provided a superior reduction in HbA_{1c} compared with placebo



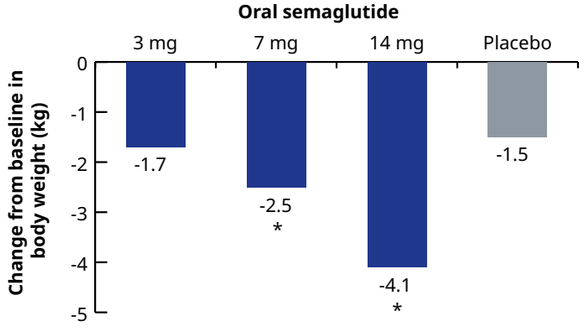
*p<0.05 in favour of oral semaglutide.

Source: Aroda VR, Rosenstock J, Terauchi Y, et al; PIONEER 1 Investigators. Diabetes Care. 2019;42(9):1724-1732

KEY RESULTS

Change in body weight

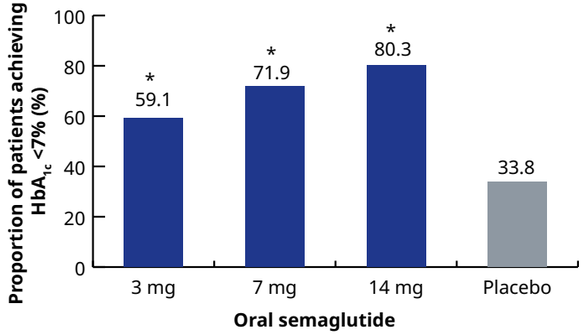
- Oral semaglutide provided superior reductions in body weight compared with placebo



*p<0.05 in favour of oral semaglutide.

Patients achieving HbA_{1c} <7.0%

- The proportion of patients achieving the HbA_{1C} target of <7% was greater with oral semaglutide vs placebo



*p<0.05 for odds of achieving HbA_{1c} <7.0% with oral semaglutide vs placebo.

Source: Aroda VR, Rosenstock J, Terauchi Y, et al; PIONEER 1 Investigators. Diabetes Care. 2019;42(9):1724-1732

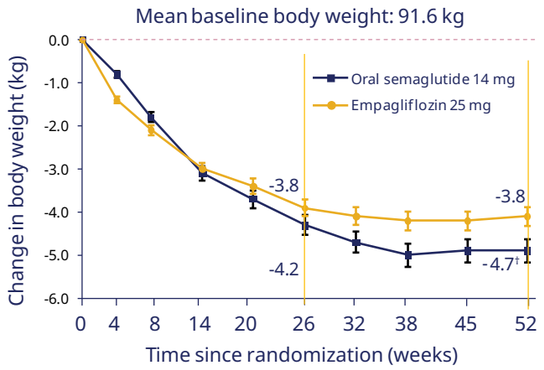
Product knowledge

Product knowledge

KEY RESULTS

Change in body weight

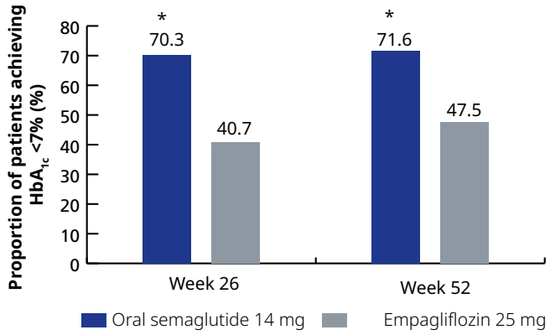
- Oral semaglutide 14 mg provided significantly greater reduction in body weight versus empagliflozin at week 52



† Statistically significant ETD versus empagliflozin in favor of oral semaglutide. *p<0.0001

Patients achieving HbA_{1c} <7.0%

- Significantly more patients achieved HbA_{1c} target <7% with oral semaglutide compared to empagliflozin



*p<0.05 for odds of achieving HbA_{1c} <7.0% with oral semaglutide vs empagliflozin.

Sources: Rodbard HW, Rosenstock J, Canani LH, et al; PIONEER 2 Investigators. Diabetes Care. 2019;42(12):2272-2281.

PIONEER 2 (ORAL SEMAGLUTIDE VS. EMPAGLIFLOZIN)

PIONEER 2 was an open label trial which was the first to directly compare oral semaglutide with an SGLT-2 inhibitor, empagliflozin, in patients with type 2 diabetes who were uncontrolled on metformin.

STUDY DESIGN

Comparator: **Empagliflozin 25 mg**

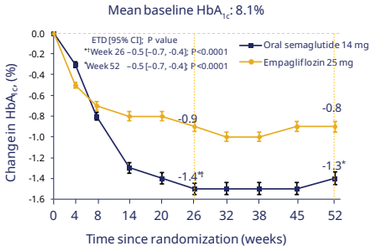
Population: **T2DM patients on metformin only**

Participants: **822**

Duration: **52 weeks**

KEY RESULTS

Oral semaglutide 14 mg provided a superior reduction in HbA_{1c} compared with empagliflozin 25 mg at week 26 and 52



*Statistically significant ETD versus empagliflozin in favor of oral semaglutide. †Superiority confirmed for oral semaglutide versus empagliflozin. ETD, estimated treatment difference.

Source: Rodbard HW, Rosenstock J, Canani LH, et al; PIONEER 2 Investigators. Diabetes Care. 2019;42(12):2272-2281.

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Product knowledge

PIONEER 3 (ORAL SEMAGLUTIDE VS. SITAGLIPTIN)

PIONEER 3 compared the efficacy and assessed the long-term safety of oral semaglutide vs DPP4 inhibitor, sitagliptin, as add-on therapy to metformin with or without sulfonylurea in patients with type 2 diabetes.

STUDY DESIGN

Comparator:
Sitagliptin 100 mg

Population:
T2DM patients on metformin, with or without a sulfonylurea

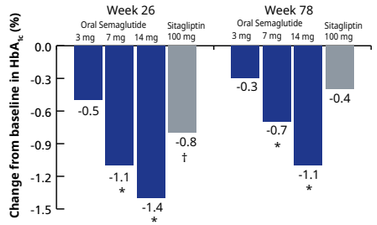
Participants:
1,864

Duration:
78 weeks

KEY RESULTS

Change in HbA_{1c}

- Oral semaglutide resulted in statistically significantly greater reduction in HbA_{1c} compared to sitagliptin at 26 weeks



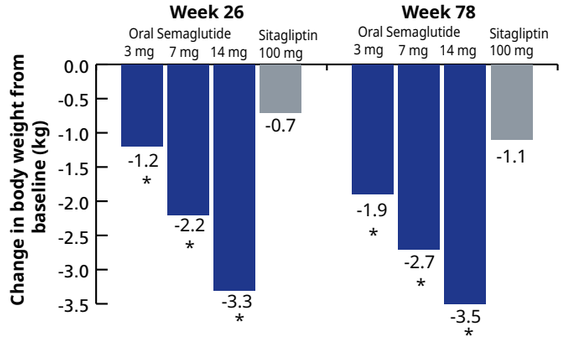
Trial product estimand. *p<0.05 in favour of oral semaglutide. †p<0.05 in favour of sitagliptin vs oral semaglutide 3 mg

Source: Rosenstock J, Allison D, Birkenfeld AL, et al; PIONEER 3 Investigators. JAMA. 2019;321(15):1466-1480.

KEY RESULTS

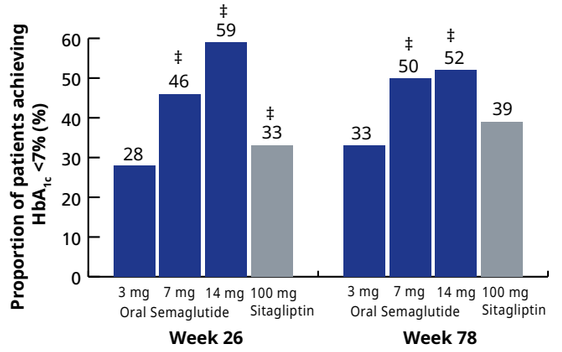
Change in body weight

- Oral semaglutide (7 and 14 mg dose) was superior to sitagliptin in reducing bodyweight from baseline at weeks 26 and 78



Patients achieving HbA_{1c} <7.0%

- Significantly greater proportions of patients achieved HbA_{1c} levels lower than 7% with oral semaglutide vs. sitagliptin



Trial product estimand. *p<0.05 in favour of oral semaglutide. ‡p<0.05 for odds of achieving HbA_{1c} <7.0% with oral semaglutide vs sitagliptin

Source: Rosenstock J, Allison D, Birkenfeld AL, et al; PIONEER 3 Investigators. JAMA. 2019;321(15):1466-1480.

Product knowledge

PIONEER 4 (ORAL SEMAGLUTIDE VS. LIRAGLUTIDE)

PIONEER 4 was the first trial to compare the efficacy and safety of oral semaglutide with a subcutaneously injected GLP-1 RA, liraglutide, and placebo in patients with type 2 diabetes inadequately controlled on metformin with or without SGLT2 inhibitor

STUDY DESIGN

Comparator:
Liraglutide 1.8 mg (daily subcutaneous) or placebo

Population:
T2DM patients on metformin, with or without an SGLT2i

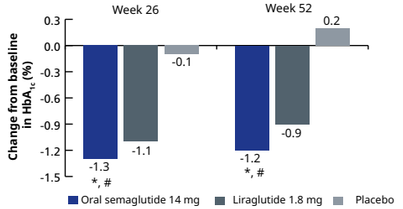
Participants:
711

Duration:
52 weeks

KEY RESULTS

Change in HbA_{1c}

- Oral semaglutide resulted in significantly greater reduction in HbA_{1c} than both subcutaneous liraglutide and placebo at weeks 26 and 52



Trial product estimand. *p<0.05 for odds of achieving HbA_{1c} <7.0% with oral semaglutide vs placebo. *p<0.05 in favour of oral semaglutide vs placebo. #p<0.05 in favour of oral semaglutide vs liraglutide 1.8 mg.

Source: Pratley R, Amod A, Hoff ST, et al; PIONEER 4 investigators. Lancet. 2019;394(10192):39-50.

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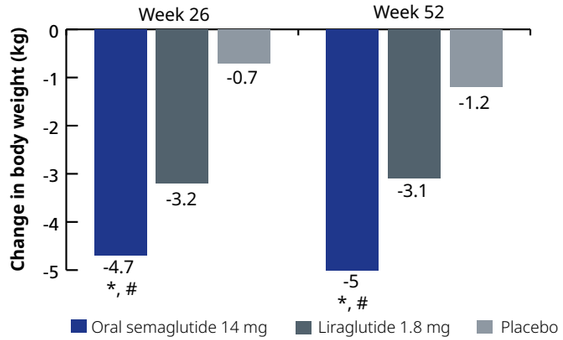
KEY RESULTS

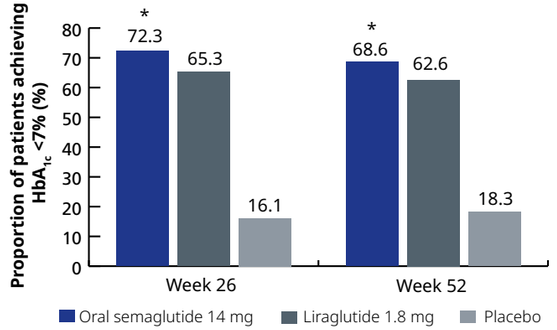
Change in body weight

- Oral semaglutide resulted in superior weight loss compared with subcutaneous liraglutide and placebo at weeks 26 and 52



Patients achieving HbA_{1c} <7.0%

- A greater proportion of patients achieved HbA_{1c} levels <7% with oral semaglutide compared with subcutaneous liraglutide and placebo.



Trial product estimand. *p<0.05 for odds of achieving HbA_{1c} <7.0% with oral semaglutide vs placebo. *p<0.05 in favour of oral semaglutide vs placebo

Source: Pratley R, Amod A, Hoff ST, et al; PIONEER 4 investigators. Lancet. 2019;394(10192):39-50.

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Product knowledge

PIONEER 6 (ORAL SEMAGLUTIDE VS. PLACEBO) (CARDIOVASCULAR OUTCOMES)

PIONEER 6 assessed the CV outcomes of oral semaglutide in patients with type 2 diabetes with established CVD or at high CV risk.

STUDY DESIGN

Comparator:
Placebo

Population:
T2DM patients with established CVD or at high CV risk

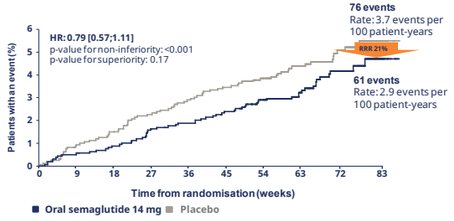
Participants:
3,183

Duration:
Event-driven

KEY RESULTS

First 3-point MACE

- Primary outcome of first occurrence of 3-point MACE occurred in 3.8% of patients in the semaglutide group and 4.8% in the placebo group (HR, 0.79).



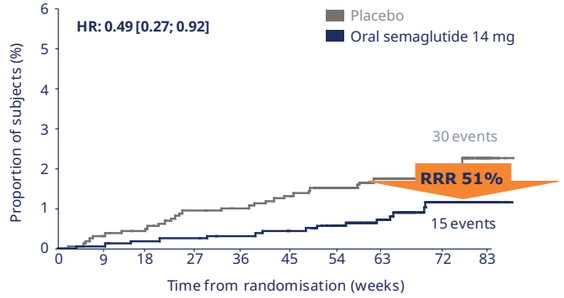
MACE, major adverse cardiovascular event; HR, hazard ratio. 3-point MACE = composite of CV death, nonfatal myocardial infarction or nonfatal stroke.

Source: Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. N Engl J Med. 2019;381(9):841-51.

KEY RESULTS

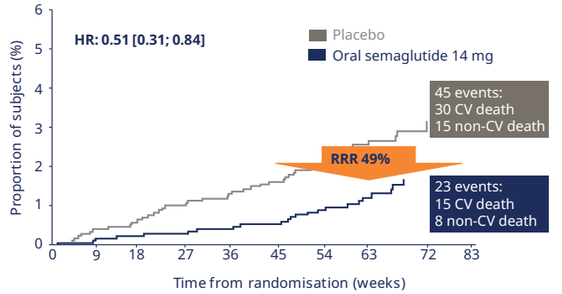
Cardiovascular death

- Among the individual components of the primary outcome, death from cardiovascular causes occurred in 15 patients (0.9%) in the oral semaglutide group versus 30 patients (1.9%) in the placebo group (hazard ratio 0.49).



All-cause death

- Death from any cause occurred in 23 patients (1.4%) in the oral semaglutide group versus 45 patients (2.8%) in the placebo group (hazard ratio 0.51)



In PIONEER 6, non-inferiority was established for oral semaglutide vs placebo and CV safety for oral semaglutide was confirmed.

Source: Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. N Engl J Med. 2019;381(9):841-51.

Product knowledge

RYBELSUS®: PIONEER SUMMARY

PIONEER 1, 2, 3, 4, 5, 6, 7 & 8

HbA_{1c}

Oral semaglutide superior vs:

- Empagliflozin
- Sitagliptin
- Liraglutide

Weight

Oral semaglutide superior vs:

- Sitagliptin
- Liraglutide
- Empagliflozin (EoT)

End of trial

Oral semaglutide demonstrated significant greater HbA_{1c} and weight reductions vs sitagliptin, empagliflozin and liraglutide.

Cardiovascular safety

Confirmed for oral semaglutide in PIONEER 6, showing a 21% non-significant reduction in MACE in favor of oral semaglutide compared with placebo

Overall safety

Oral semaglutide was well-tolerated with a safety profile consistent with the GLP-1 RA class. The most common adverse event was mild to moderate nausea.

Efficacy was established when given early in therapy, late in therapy and regardless of renal or hepatic impairment.

Sources: 1. Aroda VR. 2019; **2.** Rodbard H. 2019; **3.** Rosenstock J. 2019; **4.** Pratley R. 2019; **5.** Mosenzon O. 2019; **6.** Husain M. 2019; **7.** Pieber TR. 2019; **8.** Zinman B. 2019; **9.** Yamada Y. 2019; **10.** Yabe D. 2019.

COMPETITOR KNOWLEDGE

This section presents a comprehensive overview of the primary competitors of Rybelsus®

COMPREHENSIVE COMPETITOR COMPARISON TABLE

Active drug	Indication	Contraindication	Formulation	Presentation	Dosing	Mechanism of action	Positioning and key messages
Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors							
Dapagliflozin	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	History of a serious hypersensitivity reaction to the product **Severe renal impairment, end-stage renal disease (ESRD), or patients on dialysis**	Film-coated tablets	5 mg and 10 mg	Once-daily oral dosing	Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose (RTG), and thereby increases urinary glucose excretion	• First diabetes drug approved (US) to **reduce the risk of hospitalization for heart failure** in broad type-2-diabetes population with or without established CVD, based on the DECLARE trial • The first diabetes drug approved for treatment of patients with heart failure with reduced ejection fraction, with or without type 2 diabetes, based on DAPA-HF data. • Reduce HbA_{1c}, with additional weight and SBP benefits
Empagliflozin	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM & **to reduce the risk of CV death in adults with T2DM and established CVD**	History of serious hypersensitivity reaction to the product **Severe renal impairment, ESRD, or dialysis**	Film-coated tablet	10 mg and 25 mg	Once-daily dosing	Empagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, empagliflozin reduces renal reabsorption of filtered glucose and lowers the RTG, and thereby increases urinary glucose excretion.	• Only diabetes drug **approved for risk reduction of CV death** • Offers convenient once-daily oral dosing w/wo food • Proven to significantly reduce HbA_{1c} and in addition significantly reduced weight as: » » Monotherapy » » Add-on therapy including with insulin » » Similar HbA_{1c} reduction as sulfonylurea, but with weight benefit
Canagliflozin	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	History of serious hypersensitivity reaction to the product **Severe renal impairment, ESRD, or on dialysis**	Film-coated tablets	100 mg (starting dose and dosing in CKD with eGFR <60) and 300 mg (for additional glycaemic control in patients with eGFR >60)	Once-daily dosing	Canagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose and lowers the RTG, and thereby increases urinary glucose excretion	• Only SGLT2i **proven to slow the progression of DKD** • MACE risk reduction in type 2 diabetes with established CVD • A convenient, once-daily oral tablet • For early use in type 2 diabetes treatment cascade, as alternative to Januvia or SU
Dipeptidyl peptidase-4 inhibitor (DPP-4i)							
Sitagliptin	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema	Film-coated tablet	100 mg (recommended dose), 50 mg (moderate renal impairment), 25 mg (severe renal impairment/ end stage renal disease)	Once-daily oral dosing	Inhibition of DPP-4 by sitagliptin slows DPP-4 mediated inactivation of incretins like GLP-1 and GIP. Incretins are released throughout the day and upregulated in response to meals as part of glucose homeostasis. Reduced inhibition of incretins increases insulin synthesis and decreases glucagon release in a manner dependent on glucose concentrations. It leads to an overall increase in blood glucose control which is demonstrated by reduced HbA_{1c}.	• Provides strong HbA_{1c} reduction • Broad use as **initial or add-on therapy including with insulin** • Similar efficacy vs sulfonylureas, but **no weight gain and low risk of hypoglycaemia** • Appropriate to **use in elderly and renal impairment** • Well-established safety profile • TECOS is the longest CVOT of a DPP4i, demonstrating no increased CV risk and no increase in hospitalization for heart failure • Available as fixed-dose combination with SGLT2i ertugliflozin

Competitor Knowledge

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RYBELSUS® semaglutide tablets

Competitor Knowledge

Active drug	Indication	Contraindication	Formulation	Presentation	Dosing	Mechanism of action	Positioning and key messages
Linagliptin	As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	History of hypersensitivity reaction to linagliptin, such as urticaria, angioedema, or bronchial hyperreactivity	Film-coated tablet	5 mg (recommended dose), no dose adjustment in patients with renal impairment	Once-daily oral dosing	Linagliptin is a competitive, reversible DPP-4 inhibitor. Inhibition of DPP-4 slows the breakdown of GLP-1 and GIP. GLP-1 and GIP stimulate the release of insulin from beta cells in the pancreas while inhibiting release of glucagon from pancreatic beta cells. These effects together reduce the breakdown of glycogen in the liver and increase insulin release in response to glucose.	• Provides strong HbA_{1c} reduction as monotherapy or add-on to metformin • Single-strength DPP4i with robust CV outcomes program to confirm safety across broad range of type 2 diabetes patients • CVOT (CARMELINA) trial demonstrated **CV and renal safety similar to placebo** • CVOT CAROLINA (head to head vs SU) confirmed CV safety vs glimepiride • Only DPP4i with **no dose adjustment or restriction of use in renal impairment**

Sources: 1. Dapagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf. Accessed on 15/09/2021. 2. Empagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf. Accessed on 15/09/2021. 3. Canagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf. Accessed on 15/09/2021. 4. Sitagliptin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s019lbl.pdf. Accessed on 15/09/2021. 5. Sitagliptin. Available at: https://go.drugbank.com/drugs/DB01261. Accessed on 15/09/2021. 6. Linagliptin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201280lbl.pdf. Accessed on 15/09/2021. 7. Linagliptin. Available at: https://go.drugbank.com/drugs/DB08882. Accessed on 15/09/2021. 8. Data on file.

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PRESCRIBING INFORMATION: RYBELSUS®

For the use only of registered medical practitioner or a hospital or a laboratory
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: 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.

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 contains10 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-transporter2 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.

RYBELSUS® semaglutide tablets

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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. Patients treated with Rybelsus® 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 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.

Impact on semaglutide on the exposure of co-administered oral medicinal products:

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.

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 version dated 18 Aug 2021. 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 Pvt Ltd, Plot no 32, 47-50, EPIP area, Whitefield, Bangalore -560066

Note: For detailed information on this product, please refer to full package insert*.

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PRESCRIBING INFORMATION COMPARISON

Competitor Knowledge

Rybelsus®

Use in special populations[1]

Elderly: No dose adjustment is required based on age

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment

Contraindications[1]

Hypersensitivity to the active substance or to any of the excipients

Dapagliflozin

Use in special populations[2]

Elderly: Higher incidence of adverse reactions related to reduced intravascular volume

Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function

Contraindications[2]

History of serious hypersensitivity reaction to dapagliflozin

Severe renal impairment, end-stage renal disease, or dialysis

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Dapagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s003lbl.pdf. Accessed on 15/09/2021.

RYBELSUS® semaglutide tablets

PRESCRIBING INFORMATION COMPARISON

Competitor Knowledge

Rybelsus®

Use in special populations[1]

Elderly: No dose adjustment is required based on age

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment

Contraindications[1]

Hypersensitivity to the active substance or to any of the excipients

Empagliflozin

Use in special populations[2]

Elderly: Higher incidence of adverse reactions related to volume depletion and reduced renal function

Renal Impairment: Higher incidence of adverse reactions related to reduced renal function

Contraindications[2]

History of serious hypersensitivity reaction to empagliflozin

Severe renal impairment, end-stage renal disease, or dialysis

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021. **2.** Empagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204629s008lbl.pdf. Accessed on 15/09/2021.

Rybelsus®

Use in special populations[1]

Elderly: No dose adjustment is required based on age

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment

Contraindications[1]

Hypersensitivity to the active substance or to any of the excipients

Canagliflozin

Use in special populations[2]

Elderly: Higher incidence of adverse reactions related to reduced intravascular volume

Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function

Contraindications[2]

History of serious hypersensitivity reaction to canagliflozin

Severe renal impairment, ESRD, or on dialysis

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Canagliflozin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204042s011lbl.pdf. Accessed on 15/09/2021.

Competitor Knowledge

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RYBELSUS® semaglutide tablets

Competitor Knowledge

PRESCRIBING INFORMATION COMPARISON

Rybelsus®

Use in special populations[1]

Elderly: No dose adjustment is required based on age

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment

Contraindications[1]

Hypersensitivity to the active substance or to any of the excipients

Sitagliptin

Use in special populations[2]

Elderly: Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter

Contraindications[2]

History of a serious hypersensitivity reaction to sitagliptin

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Sitagliptin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s019lbl.pdf. Accessed on 15/09/2021.

Rybelsus®

Use in special populations[1]

Elderly: No dose adjustment is required based on age

Renal impairment: No dose adjustment is required for patients with mild, moderate or severe renal impairment

Contraindications[1]

Hypersensitivity to the active substance or to any of the excipients

Linagliptin

Use in special populations[2]

Elderly: Higher incidence of adverse reactions related to reduced intravascular volume

Renal Impairment: Higher incidence of adverse reactions related to reduced intravascular volume and renal function

Contraindications[2]

History of serious hypersensitivity reaction to canagliflozin

Severe renal impairment, ESRD, or on dialysis

Sources: 1. Rybelsus Prescribing information. Available at: https://www.novo-pi.com/rybelsus.pdf. Accessed on 28/08/2021.
2. Linagliptin. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201280lbl.pdf. Accessed on 15/09/2021.

Competitor Knowledge

Competitor Knowledge

SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS

Empagliflozin

Indication[1]

- For the treatment of type 2 diabetes mellitus in combination with diet and exercise.
- For the reduction of cardiovascular mortality due to MACE and the reduction of heart failure hospitalizations in T2DM patients with established cardiovascular disease

The EMPEROR-Reduced Trial[2]

- Objective: To evaluate the efficacy and safety of empagliflozin in a patients with chronic heart failure and a reduced ejection fraction (with or without diabetes)

- Primary composite outcome: Death from cardiovascular causes or hospitalization for heart failure
  - » 361 patients (19.4%) in the empagliflozin group
  - » 462 patients (24.7%) in the placebo group

- Secondary outcome: Total number of hospitalizations for heart failure
  - » 388 events in the empagliflozin group
  - » 533 events in the placebo group

Sources: 1. Empagliflozin - Drug Summary. Available at: https://pdr.net/drug-summary/Jardiance-empagliflozin-3597. Accessed on 02/09/2021. **2.** Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. N Engl J Med. 2020;383(15):1413-1424.

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Dapagliflozin

Indication[1]

- For the treatment of type 2 diabetes mellitus in combination with diet and exercise.
- For the reduction of heart failure hospitalizations in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple CV risk factors.
- For the treatment of heart failure with reduced ejection fraction (NYHA class II to IV) to reduce the risk of cardiovascular death and hospitalization for heart failure
- For the treatment of chronic kidney disease to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in those at risk of disease progression.

The DAPA-HF Trial[2]

- **Objective:** To evaluate the efficacy and safety of dapagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

- **Primary composite outcome:** Worsening heart failure or death from cardiovascular causes
  - » 386 patients (16.3%) in the dapagliflozin group
  - » 502 patients (21.2%) in the placebo group

The DAPA-CKD Trial[3]

- **Objective:** To evaluate the long-term efficacy and safety of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes.
- **Primary composite outcome:** Sustained decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal or CV causes
  - » 197 patients (9.2%) in the dapagliflozin group
  - » 312 participants (14.5%) in the placebo group.

Sources: 1. Dapagliflozin - Drug Summary. Available at: https://pdr.net/drug-summary/Farxiga-dapagliflozin-3427. Accessed on 02/09/2021. **2.** McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. N Engl J Med. 2019;381(21):1995-2008. **3.** Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al; DAPA-CKD Trial Committees and Investigators. N Engl J Med. 2020;383(15):1436-1446.

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Competitor Knowledge

Competitor Knowledge

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS

Sitagliptin/Linagliptin/Vildagliptin

Indication[1]

- As an adjunct to diet and exercise to improve glycemic control in adults with T2DM

TECOS Study[2]

- **Objective:** To assess the long-term CV safety of adding sitagliptin to usual care, as compared with usual care alone, in patients with T2DM and established CVD.
- **Primary composite cardiovascular outcome:** First confirmed event of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina
  - » 839 patients (11.4%) in the sitagliptin group
  - » 851 patients (11.6%) in the placebo group

The CARMELINA Trial[3]

- **Objective:** To evaluate the effect of linagliptin on CV outcomes and kidney outcomes in patients with T2DM at high risk of CV and kidney events.
- **Primary outcome:** Time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke
  - » 434 patients (12.4%) in the linagliptin group
  - » 420 patients (12.1%) in placebo group

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Sources: 1. Liu D, Jin B, Chen W, et al. BMC Pharmacol Toxicol. 2019;20:15. **2.** Green JB, Bethel MA, Armstrong PW, et al; TECOS Study Group. N Engl J Med. 2015;373(3):232-42. **3.** Rosenstock J, Perkovic V, Johansen OE, et al; CARMELINA Investigators. JAMA. 2019;321(1):69-79.

ORAL SEMAGLUTIDE VERSUS OTHER ANTI-DIABETIC DRUGS[1,2]

Trials/Molecules		Reduction in HbA_{1c}		Patients achieving HbA_{1c} <7.0%		Reduction in body weight	
		26 weeks	52 weeks	26 weeks	52 weeks	26 weeks	52 weeks
PIONEER 2	Oral semaglutide, 14 mg	1.4%	1.3%	70.3%	71.6%	4.2 kg	4.7 kg
	Empagliflozin, 25 mg	0.9%	0.8%	40.7%	47.5%	3.8 kg	3.8 kg
PIONEER 3	Oral semaglutide, 14 mg	1.3%	-	59	-	3.1 kg	-
	Sitagliptin, 100 mg	0.8%	-	32	-	0.6 kg	-

- In high-risk individuals with established type 2 diabetes, the decision to treat with a GLP-1 RA or SGLT2i to reduce major adverse cardiovascular events (MACE), hospitalization for heart failure (hHF), CV death, or CKD progression should be considered independently of baseline HbA_{1c} or individualized HbA_{1c} target.[3]

Sources: 1. Rodbard HW, Rosenstock J, Canani LH, et al; PIONEER 2 Investigators. Diabetes Care. 2019;42(12):2272-2281. **2.** Rosenstock J, Allison D, Birkenfeld AL, et al; PIONEER 3 Investigators. JAMA. 2019;321(15):1466-1480. **3.** Buse JB, Wexler DJ, Tsapas A, et al. Diabetes Care. 2020;43(2):487-493.

RYBELSUS® semaglutide tablets

Competitor Knowledge

GLP-1 RA in Heart Failure

- A recent meta-analysis of seven large cardiovascular outcomes trials suggests that GLP-1 RA considerably reduces the risk of HHF (by 9%) among adults with type 2 diabetes[1]
- A number of international guidelines have recommended use of GLP-1 RAs for the reduction of HHF, if SGLT2i is contraindicated[2]

GLP-1 RA in Chronic kidney disease

- GLP-1 RAs have been shown to have favorable kidney benefits with substantial reduction in albuminuria and likely preservation of eGFR[3]
- Long-acting GLP1-RA is recommended in patients with type 2 diabetes and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i, or who are unable to use those medications[3]
- A GLP-1 RA shown to reduce CKD progression should be considered in patients with type 2 diabetes and CKD, with or without CVD, if SGLT2i is contraindicated or not preferred[4]
- The cardioprotective effects of GLP-1 RAs, in addition to reductions in the risk of heart failure and worsening kidney function, represent an important treatment opportunity to reduce morbidity and mortality in patients with type 2 diabetes.[1]

Sources: 1. Kristensen SL, Rørth R, Jhund PS, et al. Lancet Diabetes Endocrinol. 2019;7(10):776-785. **2.** Cosentino F, Grant PJ, Aboyans V, et al; ESC Scientific Document Group. Eur Heart J. 2020;41(2):255-323. **3.** Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int. 2020 Oct;98(4S):S1-S115. **4.** Davies MJ, D'Alessio DA, Fradkin J, et al. Diabetes Care. 2018;41(12):2669-2701.

The world's first and only oral GLP-1 RA

- **Being an oral GLP-1 RA allows for an immediate connection to the known benefits of the GLP-1 RA class: HbA_{1c} control, weight loss, and CV safety**
- **Being an oral formulation of a GLP-1 RA speaks to the unique innovation of the product, and the potential to reach many more patients**

Significantly better HbA_{1c} reduction and unsurpassed weight loss vs Januvia®, Jardiance®, and Victoza®

- **The comparison vs Victoza® is critical to set the scene and establish a greater efficacy profile vs a daily injectable GLP-1 RA**
- **The comparisons vs other OADs demonstrate better efficacy and thus pave the way for Rybelsus® into the space of our core business: the OAD market**

Up to 7 out of 10 patients achieved an HbA_{1c} target below 7%
2.6% HbA_{1c} reduction for patients with baseline HbA_{1c} of 9%

- **The overall objective of an antidiabetics agent is to lower HbA_{1c} and get patients to target. Therefore, getting up to 7 out of 10 patients to target is a strong message for HCPs and will allow us to build an emotional connection between Rybelsus®, HCPs, and patients.**

Sources: 1. Data on file. **2.** RYBELSUS [summary of product characteristics]. Bagsvard, Denmark: Novo Nordisk A/S; April 2020. **3.** Pratley R, Amod A, Hoff ST, et al. Lancet. 2019;394(10192):39-50. **4.** Rosenstock J, Allison D, Birkenfeld AL, et al. JAMA. 2019;321(15):1466-1480. **5.** Rodbard HW, Rosenstock J, Canani LH, et al. Diabetes Care. 2019;42(12):2272-2281.

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FREQUENTLY ASKED QUESTIONS

This section provides some of the queries that HCPs may have about Rybelsus® along with appropriate responses to address these queries.

RYBELSUS® semaglutide tablets

FAQs

DOSING AND ADMINISTRATION

Query: How many hours of fasting are required to have an empty stomach?

Answer: In the clinical trial program for Rybelsus®, investigators did not specify a given number of hours that a patient needed to fast. Instead, patients should follow instructions mentioned in the PI.

Query: How strict must the patients be about taking with upto 120 mL of water?

Answer: Patients should take it with no more than 120 mL of plain water. Anything more than that could impact the amount of Rybelsus® that is absorbed. Taking Rybelsus® with less than 120 mL of plain water is perfectly fine.

Query: Can patients take Rybelsus® with just a sip of tea/coffee??

Answer: No. Patients should take Rybelsus® with plain water only, to ensure proper absorption in order to achieve intended efficacy.

Query: Does Rybelsus® have to be taken in the morning, or at the same time every day?

Answer: Taking Rybelsus® is dependent on having an empty stomach, which in most cases is when a patient first wakes up.

Query: What if a patient misses a dose of Rybelsus®?

Answer: If a dose is missed, the missed dose should be skipped and the next dose should be taken the following day.

Query: Can more than one Rybelsus® pill be taken at the same time?

Answer: No, just take 1 pill of the prescribed dose of Rybelsus®. Patients should not take two 7 mg pills to achieve a 14 mg dose.

Query: Can patients take other pills with Rybelsus®?

Answer: Because of the way Rybelsus® is absorbed, the pill is intended to sit in the stomach by itself. Taking multiple pills at the same time as Rybelsus® is not recommended. Patients should be instructed to wait at least 30 minutes before the first other oral medications of the day.

Query: Can Rybelsus® pills be cut?

Answer: Rybelsus® should be swallowed whole. Semaglutide, the active ingredient in Rybelsus®, is co-formulated with an absorption enhancer. Therefore, to ensure efficacy, patients are instructed to avoid cutting, splitting, crushing, or chewing pills.

Query: How will a patient tell the difference between dosage strengths?

Answer: Both the outer packaging and blister card of each dose are color-coded: the packaging is green for the 3 mg dose; red for the 7 mg dose; and blue for the 14 mg dose. Furthermore, the milligram amount is indicated with debossed numbers on each pill.

Query: If I have a patient who's on Thyroxine, how should I dose Rybelsus®?

Answer: In order for Rybelsus® to be absorbed appropriately, it must be taken as instructed. Patients need to take Rybelsus® on an empty stomach when they first wake up, take with no more than 120 mL of plain water, and at least 30 minutes before the first food, beverage, or other oral medications of the day. Rybelsus® causes a delay of gastric emptying, potentially impacting the absorption of other oral medications. Levothyroxine exposure was increased 33% when administered with Rybelsus® in a drug-interaction study. When coadministering oral medications, instruct patients to closely follow Rybelsus® administration instructions.

Use with other medications

Query: Can Rybelsus® be used with an SGLT-2i?

Answer: Yes, they can be used together. Rybelsus® has been studied in combination with SGLT-2is in PIONEER 4 and 7.

Query: Can patients take this with an injectable GLP-1 RA?

Answer: It is not recommended to take Rybelsus® with another GLP-1 RA.

Additional questions

Query: Why do I need Rybelsus®? I already have a GLP-1 RA in pill form.

Answer: Rybelsus® is actually the first and only GLP-1 RA in pill form. You may be referring to the DPP-4i class of drugs, which works differently from GLP-1 RAs. While both drug classes work by increasing levels of the GLP-1 hormone, DPP-4is do so by preventing its breakdown, whereas GLP-1 RAs like Rybelsus® activate the GLP-1 receptor itself.

FAQs

NOTES

Notes

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semaglutide tablets