OBJECTION HANDLER

Welcome to Rybelsus® Objection Handler

This Objection Handler is designed to help you have useful conversations with HCPs and alleviate any key concerns that they might about using Rybelsus® in their patients.

Each objection is structured to ensure clarity and understanding of the HCP concerns, provision of substantiating evidence and data for Rybelsus®.

Navigating the Objection Handler

The objections are categorized into 8 sections

Section 1 : Dosing and Administration

Section 2 : Mechanism and Details

Section 3 : Efficacy

Section 4 : LOE

Section 5 : CV Safety

Section 6 : V/s SGLT-2 and DPP4i

Section 7 : Reactive

Section 8 : Safety and Side Effects

INDEX

INDEX

Section 1 :
Dosing and Administration

1. " I think the dosing with Rybelsus® is complicated."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	IF doctor's concern is dose escalation: "Let me walk you through our straightforward dosing schedule." "You'll start patients on 3 mg of Rybelsus® for 1 month, then increase to 7 mg. If you find more glycaemic control is needed after at least 1 month on 7 mg, you can increase the dose to 14 mg." "Doctor, would you agree dose escalation with Rybelsus® is straightforward?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. As for other GLP-1 RAs, gastrointenstinal adverse evenets can be minimized if the dose is escalated slowly.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at:

2. "The daily dosing conditions seem to be challenging/patients will not want to wait 30 minutes."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	"Doctor, based on your experience, I'm sure you have prescribed therapies with specific dosing conditions—how have you counseled your patients successfully on those treatments?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	"Our recommendation is for patients to take Rybelsus® with a sip of water (no more than 120 mL) when they wake up, and hold off on eating, drinking or taking any other oral medications for at least 30 minutes.[1] Patients can use this time to follow their normal routine and get ready for their day." "Doctor, I'm confident that your patients will be able to adapt to this type of dosing condition and potentially reap the benefits of Rybelsus®. Would you agree?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at:

3. "Why specifically upto 120 ml of water, does SNAC or oral semaglutide flush off with more water?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	"Doctor, based on your experience, I'm sure you have prescribed therapies with specific dosing conditions—how have you counseled your patients successfully on those treatments?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, exposure of semaglutide has been investigated with administration of oral semaglutide with water volumes of 50, 120 and 240 ml. With administration of oral semaglutide (10 mg, 300 mg SNAC), the semaglutide exposure (AUC and Cmax) was maximum when administration upto 120 ml of water. However, when administrating oral semaglutide with 240 ml of water, there was a decrease in exposure by approximately 70%.[2] The higher exposure with lower water volume was correlated with slower tablet erosion and slower gastric emptying. These data suggest, as recommended in the dosing conditions, that oral semaglutide should be administered with up to 120 ml of water.[1] Doctor, I'm confident that your patients will be able to adapt to this type of dosing condition and potentially reap the benefits of Rybelsus®. Would you agree?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

2. Baekdal et al. Poster 1179 P. ADA 77th Scientific Sessions. June 9 13, 2017.

4. "Can oral semaglutide tablet be taken afternoon or night in a day? If so, how many hours of fasting is required before dosing oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	"Doctor, based on your experience, I'm sure you have prescribed therapies with specific dosing conditions—how have you counseled your patients successfully on those treatments?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, it should be taken on empty stomach when you first wake up with a sip of water no more than 1/2 a glass (120 ml) . Wait atleast 30 minutes before eating, drinking or taking any other oral medication. It is recommended to work at best if you eat or drink after taking 30 minutes after taking it. [9] Six-hour fasting was applied in the oral semaglutide phase II study demonstrating clinical meaningful HbA1c reduction and weight loss. This was based on available clinical pharmacology data investigating optimal pre- and post-dose fasting times together with market research into patient acceptance of post-dose fasting time.[15] Doctor, I'm confident that your patients will be able to adapt to this type of dosing condition and potentially reap the benefits of Rybelsus®. Would you agree?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

9. Novo Nordisk Rybelsus® (semaglutide) Summary of Product Characteristics. December 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf.
15. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047.

5. "Considering the long half-life of oral semaglutide, once the steady state is reached, can we consider alternate day dosing?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, alternate day dosing of Oral Semaglutide will affect the plasma concentration and in effect its efficacy and thus is not advised. Oral Semaglutide structure has been strategically modified so that there is a fine balance to ultimately lead to an increase in the half life. Oral Semaglutide has a half-life of a 165 hours. This translates to approximately 7 days. Thus, to reach a steady state in the plasma, it takes around s4 weeks.[13] Once Oral Semaglutide has reached the steady state, a couple of missed doses do not affect the steady state and thus the efficacy of Oral Semaglutide. But it also must be borne in mind that regular missed doses will affect the plasma concentration of Oral Semaglutide and finally its efficacy. Doctor, Do you agree that dosing of Rybelsus® is straightforward? If **Yes**, Move to ask for commitment **OR** transition back to key selling messages based on call flow. If **NO**, Probe further to understand gap.

13. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular

6. "Patients sometimes drink 1-liter water after exercising early morning before taking oral semaglutide, it may affect absorption as you told, how to tackle this problem?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, dosing guidance must be a clearly instructed to the patients to obtain the maximum benefits of oral semaglutide. In the PIONEER programme patients are required to take oral semaglutide on an empty stomach at least 30 minutes prior to the first meal, drink or medication of the day. The dosing condition for oral semaglutide is similar to several widely used medicines.[15] Doctor, Do you agree that dosing of Rybelsus® is straightforward? If **Yes**, Move to ask for commitment **OR** transition back to key selling messages based on call flow. If **NO**, Probe further to understand gap.

15. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047.

7. "If oral semaglutide half-life is 165 hours. why should you administer daily?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, even with the use of SNAC as an absorption enhancer, the absolute bioavailability of oral semaglutide is low (approximately ~1%). Consistent with the low bioavailability, the variability in exposure is relatively high. And therefore, due to the once-daily dosing frequency and the long half-life (t½ ~1 week), previous doses continue to contribute to the exposure at steady state. The dose-to-dose variability (within-subject variability) in exposure is therefore reduced after repeated doses compared to after a single dose.[25] Doctor, Do you agree that dosing of Rybelsus® is straightforward? If **Yes**, Move to ask for commitment **OR** transition back to key selling messages based on call flow.

25. Edward T. Hellriegel, T.D.B., Walter W. Hauck Interpatient variability in bioavailability is related to the extent of absorption: Implications for

8. " If the dose is missed what should be the guidance?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	I am happy to walk you through the recommended guidance so that your patients receive the full benefit of Rybelsus®.
TAKE ACTION	Doctor, If patient misses a dose of oral semaglutide, he/she should skip the missed dose and go back to regular schedule. This means that patient must continue taking the tab next day morning as per dosing condition.[1] Doctor, Do you agree that dosing of Rybelsus® is straightforward? If **Yes**, Move to ask for commitment **OR** transition back to key selling messages based on call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at:

9. "Are there any special populations which requires dose adjustment when treated with oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	I am happy to walk you through the recommended guidance so that your patients receive the full benefit of Rybelsus®.
TAKE ACTION	Doctor, no dosage adjustment is recommended irrespective of age, sex, race, ethnicity, upper GI Disease, renal and hepatic impairment. Based on a population pharmacokinetic analysis, age, sex, race, ethnicity, upper GI disease, renal and hepatic impairment do not have a clinically meaningful effect on the pharmacokinetics of semaglutide. The exposure of semaglutide decreases with an increase in body weight. However, oral semaglutide provides adequate systemic exposure over the body weight range of 40-188 kg evaluated in the clinical trials.[1,9] Doctor, Do you agree that dosing of Rybelsus® is straightforward? If **Yes**, Move to ask for commitment **OR** transition back to key selling messages based on call flow. If **NO**, Probe further to understand gap.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.
9. Novo Nordisk Rybelsus® (semaglutide) Summary of Product Characteristics. December 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf.

Section 2 :
Mechanism and Details

10. "I am curious to know the Mechanism of SNAC facilitating the quicker absorption of oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts.
ACKNOWLEDGE	I appreciate that you want to know about mechanism of action.
TAKE ACTION	Doctor, SNAC is an absorption enhancer with the ability to increase the absorption of semaglutide across the GI epithelium. SNAC interacts with the gastric cell membrane and secures transcellular absorption of semaglutide. In addition, SNAC also acts as a buffering agent and in this way promote a localized increase in pH in and around the tablet. This increase in pH to neutral will hinder the activity of pepsin, which is only active at low pH, and thus help to attenuate the extent to which semaglutide is degraded. The effects of SNAC are concentration-dependent, transient, and fully reversible in nature. The SNAC-induced increase in the absorption of semaglutide is strictly concentration- and time-dependent. Co-formulation of SNAC and semaglutide ensures their physical proximity at the mucosal surface, which is necessary to ensure sufficient absorption of semaglutide.[15] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

15. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047.

11. "What is the size of the oral semaglutide tablet?"

PAUSE	Take a brief moment to gather your thoughts.
ACKNOWLEDGE	I appreciate that you want to know about the details of the tablet.
TAKE ACTION	All the doses of oral semaglutide tablets are the same size, 13.5 x 7.5 mm. The tablets are white to light yellow, oval shaped and debossed with "3", "7" or "14" on one side and "novo" on the other side.[9] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

9. Novo Nordisk Rybelsus® (semaglutide) Summary of Product Characteristics. December 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf.

Section 3 : Efficacy

12. "Can we consider the efficacy of 7mg & 14mg of oral semaglutide to be equivalent to 0.5mg & 1mg of subcutaneous once weekly semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I appreciate you bringing that up."
TAKE ACTION	Doctor, no head to head studies exist with the approved doses of oral semaglutide vs once weekly s.c. semaglutide. Both oral and once weekly s.c. semaglutide have been extensively studied in the PIONEER and SUSTAIN, respectively. Average exposure for 1 mg once weekly s.c. semaglutide is slightly higher than 14 mg oral semaglutide. However, a network meta-analysis shows no statistical difference in efficacy between oral semaglutide 14 mg and once-weekly s.c. semaglutide 1 mg at week 26, although HbA_{1c} and body weight response is numerically greater with once-weekly s.c. semaglutide.[28] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

28. Overgaard R. et al. Abstract #777. PS 057. EASD 55th Annual Meeting. Sept 18, 2019.

13. "Do you have any long-term A1C-lowering data, beyond 26 weeks?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I'm glad to hear that you're considering RYBELSUS® as a long-term solution to improve glycemic control in your patients with type 2 diabetes.
CLARIFY	If I'm understanding correctly, you're curious if A1C reductions with Rybelsus® were sustained beyond the primary endpoints in clinical trials.
TAKE ACTION	As reflected in the Rybelsus® label, the primary endpoints of PIONEER 2, 3, and 4, some of our main efficacy studies, were mean A1C change from baseline to Week 26; these trials had durations of up to 52 or 78 weeks though. In all these studies at the end of the trial, we see a significant and sustained glycemic control with respect to sitagliptin, empagliflozin, and even Liraglutide with Rybelsus® 14mg. This 26-week primary endpoint data is compelling. Would you like me to go through these studies and results with you? Based on this, would you consider Rybelsus® for your patients with type 2 diabetes who are struggling to achieve glycaemic control on metformin or other OADs?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

Section 4 :
LOE

14. "What may be impact of oral semaglutide launch on liraglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I appreciate you bringing that up."
TAKE ACTION	Doctor, Novo Nordisk believes that GLP-1RA therapy is a good option for patients early and when intensification of treatment is needed. As leaders within the class, Novo Nordisk has developed injectable once-daily and once-weekly, as well as orally administered GLP-1RAs. Thus, Novo Nordisk is expanding treatment options and flexibility for patients and physicians and is hereby hoping that the addition of new products will expand the total GLP-1 market. Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

Section 5 :
CV Safety

15. " Due to the increased risk of developing CVD for people with type 2 diabetes, I prefer treatments with proven CV benefits like Jardiance®/another competitor."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I know there's a lot to consider when choosing a treatment for your patients with type 2 diabetes, and CVD is one of them."
CLARIFY	"Doctor, before I move on, can you please remind me what else you look for in a treatment for type 2 diabetes?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Rybelsus® is the first type 2 diabetes oral medication to launch and with CV safety based on a dedicated CV trial. PIONEER 6 was an event-driven CVOT with a 16-month median observation time, designed to rule out 80% CV risk compared to placebo. Rybelsus® demonstrated CV safety that established no increased risk of MACE, the composite endpoint consisting of CV death, nonfatal myocardial infarction, and nonfatal stroke. In patients with type 2 diabetes and at high risk for CV events (either with established cardiovascular disease/moderate renal impairment or with at least one risk factor), Rybelsus® demonstrated CV safety with no increased risk in time to first event of MACE compared to placebo ($p<0.001$ for non-inferiority). MACE is was the primary endpoint, a composite of time to first event of CV death, non-fatal myocardial infarction, or non-fatal stroke. We have also seen a very promising trend in CV death and all cause death reduction almost around 50% that is 1 in 2 patients. If the doctor would like more details of the Rybelsus® CV safety trial: "To further substantiate the evidence of CV risk reduction with Rybelsus®, we are currently conducting a large CVOT, SOUL, in people with type 2 diabetes." "As you know, good glucose control is a key contributor to lowering the risk for micro- and macrovascular complications."[4] "So let's look at glucose control for your patients who are not at HbA_{1C} target and would benefit from weight loss." **<Differentiate Rybelsus® from Jardiance®>** "Based on this, would you consider Rybelsus® for your patients with type 2 diabetes who are struggling to achieve glycaemic control on metformin or other OADs?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

CV=cardiovascular; CVD=cardiovascular disease; CVOT=cardiovascular outcomes trial; MACE=major adverse cardiovascular event; OADs=oral antidiabetic drugs.

3. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–851.

16. "Can we consider oral semaglutide to in CV risk reduction taking it as a GLP-1 class effect?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"It's a really interesting question."
CLARIFY	"Did you think that it would?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	"Rybelsus® is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus to improve glycaemic control as an adjunct to diet and exercise."[1] "Rybelsus®is world's first oral GLP-1 RA in a pill to launch with CV safety based on a dedicated CV trial. PIONEER 6 was an event-driven, pre-approval CVOT with 16 months follow-up time, powered to rule out excess CV risk of 80%."[3] "As you can see, Rybelsus® had 21% non-significant fewer MACEs vs placebo both in addition to standard of care. This helped establish no increased risk of MACE."[3] "To further substantiate the evidence of CV risk reduction with Rybelsus®, we are currently conducting a large CVOT, SOUL, in people with type 2 diabetes." If further information is requested: "Both the PIONEER 6 and SUSTAIN 6 trials were designed as noninferiority, pre-approval trials to exclude an unacceptable increase in CV risk compared with placebo."[3,5] "While SUSTAIN 6 was both event- and time-driven, PIONEER 6 was solely event-driven and did not include a minimum trial duration. Due to this, PIONEER 6 accrued substantially fewer MACE (137) and had a shorter treatment duration (median observation time 16 months) than SUSTAIN 6 (254 events and median observation time 2.1 years). The results from PIONEER 6 are consistent with the results from SUSTAIN 6, but statistical significance could not be achieved. However, the effect appeared to be consistent across the subcutaneous and oral formulations of semaglutide despite different routes of administration." In a pooled analysis of SUSTAIN 6 and PIONEER 6 (i.e. for mulecule semaglutide irrespective of route of adminitration) it has shown 24% significant MACE reduction.[3,5] "Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. **3.** Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–851. **5.** Marso S, Bain S, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844.

Section 6 :
V/s SGLT-2 and DPP4i

17. " I'd rather use an SGLT2i than Rybelsus

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you sharing that with me."
CLARIFY	"What leads you to that decision?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, in head to head 52 weeks trial of Rybelsus® vs Jardiance® , at week 52, Rybelsus® reduced HbA1c by 1.3% vs 0.8% with Jardiance® a significant 63% greater reduction."[1] "Overall, 70.3% of patients achieved an HbA1c target below 7% with Rybelsus® vs 40.7% of patients with Jardiance®."[1] "Additionally, there are fewer restrictions on Rybelsus® than SGLT2is.[1,6,7] Rybelsus® can be used in a broad range of patients. No dose adjustment is needed in patients with mild, moderate or severe renal impairment or hepatic impairment, nor in patients over age 65."[1] "Knowing this, would you now use Rybelsus® for your patients with type 2 diabetes who you would have previously prescribed an SGLT2i and for patients uncontrolled on metformin?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

SGLT2i=sodium-glucose cotransporter-2 inhibitor.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.
6. Jardiance® [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; October 2020.

18. "It's easier for me to add an SGLT2i to a patient on a DPP4i than initiate Rybelsus®"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I can understand your desire to keep things easy."
CLARIFY	"Can you please share why you think it would be easier to do that?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	"Doctor, you may consider the option to simply switch a patient on a DPP4i to Rybelsus® instead of adding on an SGLT2i. Let me show you why." "In this 78-week trial (as per trial product estimand), Rybelsus® 14 mg reduced HbA1c by 1.1% vs 0.4% with Januvia®, a significant 57% greater reduction than Januvia®, and showed a 3.5 kg weight loss for Rybelsus® vs 1.1 kg with Januvia®."[1] "Also, Rybelsus® can be used in a broad range of patients with no dose adjustments required. This includes patients with mild, moderate or severe renal impairment, patients with hepatic impairment or elderly patients.[1] Possible restrictions will have to be kept in mind before initiating an SGLT2i."[6,7] "Based on these results, would you consider using Rybelsus® for your patients with type 2 diabetes who are not achieving glycaemic control with a DPP4i?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

DPP4i=dipeptidyl peptidase-4 inhibitor.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.
6. Jardiance® [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; October 2020.
7. Invokana® [summary of product characteristics]. Cambridge, United Kingdom: Napp Pharmaceuticals Ltd; August 2020.

19. " The weight loss for Jardiance® is comparable to Rybelsus®."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I know weight loss is important for many of your patients."
CLARIFY	"What were your expectations?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	"Rybelsus® was superior in terms of HbA_{1c} reduction at both 26 and 52 weeks. Rybelsus® was significantly better at weight reduction at the end of the trial with 4.7kg weight reduction from baseline."[1] "More importantly, I want to point out that no matter the comparator in the PIONEER trials, Rybelsus® 14 mg showed consistent weight loss ranging from 3.5 kg, all the way up to 5 kg."[1] "Rybelsus® reduced HbA1c by 1.4% vs 0.9% with Jardiance®,and 70% of patients achieved an HbA_{1c} target below 7% with Rybelsus® vs 41% of patients with Jardiance® at week 26."[1] "Finally, Rybelsus® can be used in a broad range of patients with no dose adjustments required. This includes patients with mild, moderate or severe renal impairment, hepatic impairment or in elderly patients."[1] "Would HbA_{1c} reduction and control plus consistent weight reductions be important to your patients?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.

20. "What may be the reason behind the superior weight reduction seen with oral semaglutide, and is this reduction sustainable?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I know weight loss is important for many of your patients."
CLARIFY	"What were your expectations?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, across the PIONEER trials, the average baseline weight was around 88 – 94 kgs. As is well known, GLP1-RA acts in the Nucleus Tractus Solitarius and leads to an increase in satiety and decrease in appetite. Also, it decreases gastric motility. These mechanisms together bring about a reduction in the body weight of a patient.[16] In many of the PIONEER trials, there were background OADs and also insulin. Majority of anti-diabetic medications are known to increase the body weight of a patient. In such scenarios, addition of a GLP1-RA lead to a decrease in body weight not seen with other medications. In one of the longest trials PIONEER-3 we saw a consistent weight reduction (Rybelsus® 14 mg) from baseline of 3.3 kg at week 26 and sustained upto week 78 of 3.5kg. Also in PIONEEER 2 vs Empagliflozin 25 mg, there was a stagnation of weight reduction with SGTL2i at week 32. Whereas with Rybelsus® 14mg, we saw a consistent, sustained weight reduction which led to a significant 24% greater weight loss compared to Empagliflozin 25mg at the end of trial.[17-23] Would HbA1c reduction and control plus consistent weight reductions be important to your patients?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

16. Blundell J. et al. Abstract #753. PS 055. EASD 55th Annual Meeting. Sept 17, 2019. **17.** Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9): 1724-1732. **23.** Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. Diabetes Care. 2019;42(12):2262-2271 .

21. "Can Rybelsus® be used in patients with heart failure, like an SGLT2i?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"Novo Nordisk is encouraged by the increasing recognition of the cardioprotective effects of glucose-lowering medicines."
CLARIFY	"Is the risk of heart failure a major concern for many of yours patients with type 2 diabetes?" Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	"Rybelsus® has not been studied specifically in patients with heart failure; however, heart failure resulting in hospitalisation was included as a secondary outcome in PIONEER 6, the Rybelsus® CVOT. In the trial, fewer patients on Rybelsus® experienced this outcome compared with those on placebo."[3] "Looking at the larger CV picture, according to a 2018 review, heart failure affects approximately 15% of people with type 2 diabetes, compared to over 60% being affected by ASCVD.[8] Atherosclerosis is also the predominant cause of CVD and death in people with type 2 diabetes.[9] "It is hypothesised that the CV benefits seen with some GLP-1 RAs are most likely derived through their reduction of atherosclerosis-related events, whereas SGLT2is are thought to predominantly derive their CV benefits through heart failure-related endpoints."[10–14] "If you would like further information, I can have a medical summary sent to you that outlines the atherosclerotic data with GLP-1 RAs." "Have I answered your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

ASCVD=atherosclerotic cardiovascular disease.

3. Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–851. **9.** Novo Nordisk Rybelsus® (semaglutide) Summary of Product Characteristics. December 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf **10.** Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre- diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J.2020;41(2):255–323. **14.** Sinha B, Ghosal S. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduce hospitalization for heart failure only and have no effect on atherosclerotic cardiovascular events: a meta-analysis. Diabetes Ther. 2019;10:891–899

22. "SGLT2is provide renal protection, does Rybelsus® do the same?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I Know renal disease is a serious condition, and it's important to choose the right medication."
TAKE ACTION	"Rybelsus® does not currently have data in renal protection; however, the effect of once-weekly semaglutide (injectable) on renal outcomes is currently being investigated by Novo Nordisk in the FLOW trial. The FLOW trial is the first dedicated renal outcomes trial for a GLP-1 RA in people with type 2 diabetes and chronic kidney disease."[15] "As per Indian label is that Rybelsus® does not require dosage adjustment for mild, moderate or severe renal impairment.[1] eGFR is a measurement of kidney function,[16] and renal impairment does not impact the pharmacokinetics of Rybelsus® in a clinically relevant manner."[1] "On the other hand, the glucose-lowering efficacy of SGLT2is is dependent on renal function, thus initiation of Jardiance® is not recommended in patients with an eGFR of <60 mL/min/1.73 m2.6 SGLT2is are less effective as the eGFR decreases."[6,7] "If you are interested, I can have more information sent to you about GLP1-RAs and use in patients with kidney disease." "Have I answered your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

eGFR=estimated glomerular filtration rate.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. **6.** Jardiance® [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; October 2020. **7.** Invokana® [summary of product characteristics]. Cambridge, United Kingdom: Napp Pharmaceuticals Ltd; August 2020. **15.** Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047 **16.** Blundell J. et al. Abstract #753. PS 055. EASD 55th Annual Meeting. Sept 17, 2019.

Section 7 : Reactive

23. "Many of my patients are on Thyroxine, which they take in the morning. The dosing regimen of Rybelsus® wouldn't work for them."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I'm glad to hear that you're considering Rybelsus® your patients with type 2 diabetes.
CLARIFY	"For such patients you are thinking of, how would you initiate treatment with and Rybelsus®?"
TAKE ACTION	"Doctor, the good news is that Rybelsus® is not contraindicated."[1] "For your patients who are on, and for whom you're considering Rybelsus®, instruct them to follow Rybelsus® administration instructions (take Rybelsus® upon waking with a sip of water and wait at least 30 minutes before eating, drinking or taking any other oral medication), along with monitoring of thyroid parameters[1] and treating hypothyroidism according to local guidelines." "By doing this, you can help develop a dosing schedule for Rybelsus® that works for your patients so they are able to receive the benefits of both therapies." If the HCP wants information about dosing at an alternate time, please refer to your Medical Information department or medical science liaison. "Do you have any questions on this approach?" If **YES**: Probe further to understand gap; address as appropriate. If **NO**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at:

24. "What is the retinopathy data on Oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
TAKE ACTION	Doctor, Diabetic retinopathy is included as a caution in the SmPC for oral semaglutide, in alignment with the OW s/c semaglutide SmPC. This is based on the data from SUSTAIN 6, however, the risk of diabetic retinopathy complications cannot be excluded for oral semaglutide.[15] Similar proportions of diabetic retinopathy related events were reported in the pooled data from the PIONEER trials, 4.2% vs 3.8% of the patients treated with oral semaglutide and comparator, respectively. "A similar incidence of " in PIONEER 6 , 7.1% and 6.3% on oral semaglutide and placebo, respectively, reported diabetic retinopathy related adverse events.[4] When looking at the individual PIONEER trials, there were no consistent pattern of proportions of adverse events of diabetic retinopathy and related complications reported with oral semaglutide and comparators or placebo. Also, there was no difference between oral semaglutide and comparators or placebo with respect to the nature of the reported events, and no indication of an increase in severity with oral semaglutide. Most events were non-proliferative diabetic retinopathy, asymptomatic and captured at routine eye examinations; and did not require treatment, only observation. [17-23] Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied but is currently being investigated in the FOCUS trial. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy. Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

15. Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047 **17.** Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-1732 **18.**Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019;42(12):2272-2281 **19.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-1480 **20.** Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial [published correction appears in Lancet. 2019 Jul 6;394(10192):e1]. Lancet. 2019;394(10192):39-50 **21.** Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):515-527 **22.** Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):528-539 **23.** Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2

Section 8 :
Safety and Side Effects

25. "Does renal impairment affect the pharmacokinetics or tolerability of oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	It is really an interesting question.
CLARIFY	Did you think it would?
TAKE ACTION	Doctor, subjects with varying degree of renal impairment (normal, mild, moderate, severe, end stage renal disease) were investigated on pharmacokinetics and safety with oral semaglutide (10 mg, 300 mg SNAC). There was no consistent pattern of an increase or decrease in semaglutide exposure (AUC, Cmax, Tmax) by renal function group. In addition, hemodialysis did not affect the exposure. Oral semaglutide was well tolerated in the investigated subjects.[26] In PIONEER 5, patients with T2D and moderate renal impairment were investigated for efficacy and safety, showing consistent results with patients with normal renal function.[21] Based on these results, renal impairment should not affect dose recommendations for oral semaglutide. As per the approved label, no dose adjustment is required for any degree of renal impairment while prescribing Rybelsus®. Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

21. Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):515-527 **26.** Granhall C, Søndergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, Safety and Tolerability of Oral Semaglutide in Subjects with Renal Impairment. Clin Pharmacokinet. 2018;57(12):1571-1580

26. "Does hepatic impairment affect the pharmacokinetics or safety of oral semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	It is really an interesting question.
CLARIFY	Did you think it would?
TAKE ACTION	Doctor, Subjects with varying degree of hepatic impairment (mild, moderate, severe) were investigated on pharmacokinetics and safety with oral semaglutide (10 mg, 300 mg SNAC). Semaglutide exposure (AUC and Cmax, Tmax) appeared similar across the hepatic function groups with no apparent effect of hepatic impairment. The safety profile of oral semaglutide was as expected for the GLP-1RA drug class independent of the degree of hepatic impairment. Based on these results, dose adjustment of oral semaglutide is not necessary in subjects with hepatic impairment.[27] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

27. Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, Safety, and Tolerability of Oral

27. Being an oral therapy, should we expect higher GI effects with this molecule as compared to injectable therapies?

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	" I appreciate you bringing that up."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, overall, in all the global PIONEER trials (1-8), oral semaglutide was well tolerated with a safety profile consistent with any other injectable GLP-1RA, and we did not see an increased incidence of GI effects in comparison with any other GLP-1RA. The most common adverse event for oral semaglutide was mild-to-moderate nausea (experienced by 15–23% of patients on 14 mg), which diminished over time. Around 80-85% of patients didn't experience any nausea with Rybelsus® 14 mg. Treatment discontinuation rates were also low due to adverse effects and 85-98%continued on treatment across PIONEER trials (1-5 and 7-8). Discontinuation rate (other)comparators and placebo) was 3–5% with sitagliptin (100 mg), 4% with empagliflozin (25 mg), 9% with liraglutide (1.8 mg) and 2–6% on placebo.[17-23] Doctor, we suggest you always mention the potential of GI-related side effects to patients, and let them know the majority of reports of nausea, vomiting and/or diarrhoea occurred during dose escalation."[1] "Knowing the benefits of Rybelsus®, would you agree your patients might be willing to tolerate nausea if it were to occur during the dose escalation?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate. Consider asking: "Do you have any other questions about side effects with Rybelsus®

17. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-1732 **18.** Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019;42(12):2272-2281 **19.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-1480 **20.** Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial [published correction appears in Lancet. 2019 Jul 6;394(10192):e1]. Lancet. 2019;394(10192):39-50 **21.** Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):515-527 **22.** Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):528-539 **23.** Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. Diabetes Care. 2019;42(12):2262-2271

28. "We see an increased incidence of diarrhea as a part of GI effect with oral semaglutide as compared to other injectable GLP-1RAs, what could be the reason?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	"What concerns you most about the dosing of Rybelsus®? Listen carefully and utilise their response to help formulate your answer.
TAKE ACTION	Doctor, Diarrhea is also part of the GI side effects spectrum associated with the GLP-1 class therapy. In PIONEER 6 trial the percentage of patients who discontinued therapy due to diarrhea was 1.4% in Oral Semaglutide arm vs. 0.4% in the placebo arm.[4] Overall, in all the global PIONEER trials, oral semaglutide was well tolerated with a safety profile consistent with other GLP-1RAs. The most common adverse event for oral semaglutide was mild-to-moderate nausea(experienced by 15–23% of patients on 14 mg), which diminished over time. Around 80-85% of patients didn't experience any nausea with Rybelsus® 14 mg. Treatment discontinuation rates were also low due to adverse effects and 85-98%continued on treatment across PIONEER trials (1-5 and 7-8). Discontinuation rate (other)comparators and placebo) was 3–5% with sitagliptin (100 mg), 4% with empagliflozin (25 mg), 9% with liraglutide (1.8 mg) and 2–6% on placebo. .[17-23] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

17. Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-1732 **18.** Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019;42(12):2272-2281 **19.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-1480 **20.** Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial [published correction appears in Lancet. 2019 Jul 6;394(10192):e1]. Lancet. 2019;394(10192):39-50 **21.** Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):515-527 **22.** Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):528-539 **23.** Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to

29. "Above the age of 50 or 55 years, number of patients with Chronic atrophic gastritis with diabetes, what is the potential impact of oral semaglutide in such patients? Are the drug effects enhanced or depressed?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	I appreciate you bringing that up and will reiterate the specifics.
TAKE ACTION	Doctor, Oral semaglutide was well tolerated in subjects with gastrointestinal disease, and no dose adjustment is expected in this population. The effect on absorption were investigated in a phase 1 study, including 55 subjects with T2D +/- upper gastrointestinal disease (gastroesophageal reflux disease and/or chronic gastritis). The primary objective was to investigate if upper gastrointestinal disease influenced the pharmacokinetic properties of oral semaglutide in subjects with T2D. There was no statistically significant difference in AUC0-24h, sema, Day 10 between the patients with and without gastrointestinal disease.[29] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

29. Meier J et al. 1013 P. ADA 79th Scientific Sessions. June 09, 2019.

30. "How to de-escalate the dose of oral semaglutide to manage nausea, what anti-emetics are suggested?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	I appreciate you bringing that up and will reiterate the specifics.
TAKE ACTION	Doctor,The gastrointestinal adverse events can be minimized if the dose is escalated slowly. Hence, patients on oral semaglutide should start on the 3 mg dose and escalate to the 7 mg dose after 4 weeks of treatment. If additional glycemic control is needed, the dose can be increased to 14 mg after additional 4 weeks.[1] The de-escalation of dose in clinical practice is as per clinical judgement of treating clinician and no guidance on this exists as of now. There were no protocol restrictions for use of antiemetics in the PIONEER phase 3 trials. There are studies showing that a prophylactic use of centrally acting anti-emetic medications reduces nausea and vomiting associated with GLP-1 RAs.[30] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

1. Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.
30. Ellero C, Han J, Bhavsar S, et al. Prophylactic use of anti-emetic medications reduced nausea and vomiting associated with exenatide treatment: a retrospective analysis of an open-label, parallel-group, single-dose study in healthy subjects. Diabet Med. 2010;27(10):1168-1173

31. "Frequent use of Proton pump inhibitor in Indian patients, does oral semaglutide have any interaction with PPIs?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	"I understand your concern. I want to make certain that all of your patients achieve the benefits that come with taking Rybelsus® as intended."
CLARIFY	I appreciate you bringing that up and will reiterate the specifics.
TAKE ACTION	Doctor, Oral semaglutide was well tolerated when administered in combination with omeprazole. The pharmacokinetics of oral semaglutide was investigated in a drug-drug interactions study with omeprazole. Omeprazole (40 mg) was administered 2 hours before oral semaglutide to ensure maximum effect on pH. There was a slight non-statistically significant increase in semaglutide exposure when oral semaglutide was administered with omeprazole, and this was not considered clinically relevant. However the dosing conditions of Rybelsus® should be followed for optimum effect i.e take the tab with a sip of water (upto 120ml or half a glass) on waking up and observe 30 minutes of fasting before taking any oral medication , drinks or food.[31] Does this answer your question?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow.

31. Baekdal TA, Breitschaft A, Navarria A, Hansen CW. A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide. Expert Opin Drug Metab Toxicol. 2018;14(8):869-877. doi:10.1080/17425255.2018.1488965

32. "I am curious to know Albumin Interactions with Rybelsus® (oral semaglutide)"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
CLARIFY	What concerns do you have with interactions of Rybelsus®?
TAKE ACTION	Semaglutide, is extensively bound to plasma protein (>99%), particularly to albumin.[1] Changes in plasma protein binding rarely affect the clinical exposure to a drug, because there is typically a vast excess of plasma albumin binding sites (approximately 400,000-fold) available to each drug molecule.[2,3] In vitro Study demonstrated that therapeutic doses of oral semaglutide will have a negligible impact upon the binding capacity of the serum albumin pool, even in conditions that are typically associated with decreased concentrations of albumin.[4] Pharmacokinetics of semaglutide in patients with varying degrees of hepatic impairment: median fraction of unbound semaglutide was <1% across all groups, corresponding to a plasma protein binding of >99% in all patients across the hepatic function groups. In vivo Pharmacokinetics and tolerability of oral semaglutide in subjects with renal impairment[5] : The study found no clinically relevant differences in semaglutide exposure across renal function groups There is a substantial excess of albumin binding sites for Rybelsus® at clinically relevant doses; therefore, it is not anticipated that Rybelsus® effects will be materially altered by any changes in plasma albumin levels that are likely to occur in clinical practice.

1. Rybelsus® Prescribing Information. Plainsboro, NJ: Novo Nordisk Inc.
2. Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clinical Pharmacology & Therapeutics. 2002;71(3):115-121. Link to Access the Full Text
3. Kurtzhals P, Havelund S, Jonassen I, et al. Effect of fatty acids and selected drugs on the albumin binding of a long-acting, acylated insulin analogue. J Pharm Sci. 1997;86(12):1365-8. Link to Access the Full Text
4. Baekdal TA, Thomsen M, Kupcova V, et al. Pharmacokinetics, Safety, and Tolerability of Oral Semaglutide in Subjects With Hepatic Impairment. J Clin Pharmacol. 2018;58(10):1314-1323. Link to Access the Full Text
5. Granhall C, Sondergaard FL, Thomsen M, et al. Pharmacokinetics, Safety and Tolerability of Oral Semaglutide in Subjects with Renal Impairment. Clin Pharmacokinet. 2018;57(12):1571-1580. Link to Access the Full Text

33. "Can a individual take 7 tablets in a single go and what are the drug to drug interactions that have been studied?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
CLARIFY	What concerns do you have with interactions of Rybelsus®?
TAKE ACTION	Doctor, absorption kinetics might differ, having maximum t-max with in initial 2 hours which would lead to very severe GI side effects. With a bioavailablity of 1% and in patient variablity in bio availability , it could also be challenging to achieve a stable state. Once daily dosing helps in achieving a stable state ,even with 1% bio-availability and in patient variability. Also, in studies oral semaglutide co administered with 5 placebos had reduced absorption, hence it is not advisable to take more than one tablet at once. Despite these recommendations we have studies with more than 10 different drugs when co-administered with oral semaglutide for drug-drug interactions, however we have not found any clinically significant interactions. Based on this, would you consider Rybelsus® for your patients with type 2 diabetes who are struggling to achieve glycaemic control on metformin or other OADs?" If **YES:** Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

34. "Why have you chosen odd dosing of 3,7 and 14 mg rather than 2.5 ,5 and 10 mg?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
CLARIFY	What concerns do you have with interactions of Rybelsus®?
TAKE ACTION	We have tried with many different doses in dose finding studies, but the decision was made based on cost, safety and efficacy benefits. Various doses of Oral Semaglutide were explored in dose finding studies (2.5mg, 5mg, 10mg, 20mg, 40mg and with 300 mg of SNAC) based on cost, safetyand better understanding of dosing conditions to have clinically meaningful concentrations. 3, 7,14mg of Rybelsus® were identified. 3mg dose helps the patient to get aquainted to the drug and develop tolerance to GLP-1 class effects of GI AEs which are transient , mild or moderate. After 4 weeks of dose escalation to 7mg of therapeutic dose of Rybelsus®, incremental benefits with acceptable safety and efficacy were observed. Further dose escalation to 14mg offers same base of further glycemic control requirement as per healthy physician decision. Our recommendation is for patients to take Rybelsus® with a sip of water upto 120 ml when they wake up, and hold off on eating, drinking or taking any other oral medications for at least 30 minutes.1 Patients can use this time to follow their normal routine and get ready for their day." "Doctor, I'm confident that your patients will be able to adapt to this type of dosing condition and potentially reap the benefits of Rybelsus®. Would you agree?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate

35. "I wanted to know about the incidence of pancreatitis and cholecystitis with oral semaglutide."

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
CLARIFY	What concerns do you have with interactions of Rybelsus®?
TAKE ACTION	Doctor, the frequency of pancreatitis was low (MedDRA search)and there was no difference between Rybelsus® and the comparator nor the placebo. In PIONEER-6, there were 4 confirmed events of acute pancreatitis , 1 in Rybelsus® and 3 in placebo. Rybelsus® was not associated with increased risk of pancreatitis vs comparators. Frequency of cholecyctitis was 0.6% with Rybelsus(R) and 0.1 of the subjects in placebo pool. Patients should be informed of cholecyctitis and acute pancreatitis. If suspected , Rybelsus® should be discontinued. PI caution should be exercises in patients with pancreatitis. "Knowing the benefits of Rybelsus®, would you agree Rybelsus® is a right choice for your patients?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate

36. "Will Oral Semaglutide replace injectable Semaglutide?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
TAKE ACTION	At present injectable semaglutide is not available in India. Considering that both are available, it will be a choice for the physicians and patient preference on which to be used in which cases. Novo Nordisk believes that GLP-1RA therapy is a good option for patients early and when intensification of treatment is needed. As leaders within the class, Novo Nordisk has developed injectable once-daily and once-weekly, as well as orally administered GLP-1RAs . Thus, Novo Nordisk is expanding treatment options and flexibility for patients and physicians and is hereby hoping that the addition of new products will expand the totalGLP-1 market. Oral semaglutide has the potential to allow initiation of oral GLP-1RA-based therapy early in the treatment cascade and should be considered as the oral GLP-1RA therapy of choice both as add-on to metformin or in combination with other OADs. We do not believe in restricting either the physician or the patient due to unavailability of a certain molecule.

37. "Is there any need not to lie down after taking the tablet like we see with alendronate?"

PAUSE	Take a brief moment to gather your thoughts and formulate a response.
ACKNOWLEDGE	I appreciate you bringing that up. It is in the best interest of patients receiving full benefits of Rybelsus®
TAKE ACTION	Doctor, there is no such postural requirement with oral semaglutide intake. Our recommendation is for patients to take Rybelsus® with a sip of water upto 120 ml when they wake up, and hold off on eating, drinking or taking any other oral medications for at least 30 minutes.1 Patients can use this time to follow their normal routine and get ready for their day." "Doctor, I'm confident that your patients will be able to adapt to this type of dosing condition and potentially reap the benefits of Rybelsus®. Would you agree?" If **YES**: Move to "ask for commitment" **OR** transition back to Rybelsus® key selling messages based on your call goal/call flow. If **NO**: Probe further to understand gap; address as appropriate.

References : **1.** Novo Nordisk Rybelsus® (semaglutide) Prescribing Information. September 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf **2.** Baekdal et al. Poster 1179 P. ADA 77th Scientific Sessions. June 9 13, 2017. **3.** Husain M, Birkenfeld AL, Donsmark M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381:841–851. **4.** Unachukwu C, Ofori S. Diabetes mellitus and cardiovascular risk. The Internet Journal of Endocrinology. 2012;7(1):1–10. **5.** Marso S, Bain S, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844. **6.** Jardiance® [summary of product characteristics]. Ingelheim am Rhein, Germany: Boehringer Ingelheim International GmbH; October 2020. **7.** Invokana® [summary of product characteristics]. Cambridge, United Kingdom: Napp Pharmaceuticals Ltd; August 2020. **8.** Einarson TR, Acs A, Ludwig C, et al. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17:83. **9.** Novo Nordisk Rybelsus® (semaglutide) Summary of Product Characteristics. December 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/rybelsus-epar-product-information_en.pdf **10.** Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre- diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J.2020;41(2):255–323. **11.** Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020;63:221–228. **12.** American Diabetes Association. Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44:S1–S232. **13.** Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. Circulation. 2019:CIR0000000000000678. **14.** Sinha B, Ghosal S. Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) reduce hospitalization for heart failure only and have no effect on atherosclerotic cardiovascular events: a meta-analysis. Diabetes Ther. 2019;10:891–899 **15.** Buckley ST, Bækdal TA, Vegge A, et al. Transcellular stomach absorption of a derivatized glucagon-like peptide-1 receptor agonist. Sci Transl Med. 2018;10(467):eaar7047. doi:10.1126/scitranslmed.aar7047 **16.** Blundell J. et al. Abstract #753. PS 055. EASD 55th Annual Meeting. Sept 17, 2019. **17.** Aroda VR, Rosenstock J, Terauchi Y, et al. PIONEER 1: Randomized Clinical Trial of the Efficacy and Safety of Oral Semaglutide Monotherapy in Comparison With Placebo in Patients With Type 2 Diabetes. Diabetes Care. 2019;42(9):1724-1732 **18.** Rodbard HW, Rosenstock J, Canani LH, et al. Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care. 2019;42(12):2272-2281 **19.** Rosenstock J, Allison D, Birkenfeld AL, et al. Effect of Additional Oral Semaglutide vs Sitagliptin on Glycated Hemoglobin in Adults With Type 2 Diabetes Uncontrolled With Metformin Alone or With Sulfonylurea: The PIONEER 3 Randomized Clinical Trial. JAMA. 2019;321(15):1466-1480 **20.** Pratley R, Amod A, Hoff ST, et al. Oral semaglutide versus subcutaneous liraglutide and placebo in type 2 diabetes (PIONEER 4): a randomised, double-blind, phase 3a trial [published correction appears in Lancet. 2019 Jul 6;394(10192):e1]. Lancet. 2019;394(10192):39-50 **21.** Mosenzon O, Blicher TM, Rosenlund S, et al. Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5): a placebo-controlled, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):515-527 **22.** Pieber TR, Bode B, Mertens A, et al. Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7): a multicentre, open-label, randomised, phase 3a trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Sep;7(9):e21]. Lancet Diabetes Endocrinol. 2019;7(7):528-539 **23.** Zinman B, Aroda VR, Buse JB, et al. Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial. Diabetes Care. 2019;42(12):2262-2271 **24.** Drucker DJ. Advances in oral peptide therapeutics. Nat Rev Drug Discov. 2020;19(4):277-289 **25.** Edward T. Hellriegel, T.D.B., Walter W. Hauck Interpatient variability in bioavailability is related to the extent of absorption: Implications for bioavailability and bioequivalence studies. Clinical Pharmacology & Therapeutics, 1996. 60: p. 601-607 **26.** Granhall C, Søndergaard FL, Thomsen M, Anderson TW. Pharmacokinetics, Safety and Tolerability of Oral Semaglutide in Subjects with Renal Impairment. Clin Pharmacokinet. 2018;57(12):1571-1580 **27.** Baekdal TA, Thomsen M, Kupčová V, Hansen CW, Anderson TW. Pharmacokinetics, Safety, and Tolerability of Oral Semaglutide in Subjects With Hepatic Impairment. J Clin Pharmacol. 2018;58(10):1314-1323 **28.** Overgaard R. et al. Abstract #777. PS 057. EASD 55th Annual Meeting. Sept 18, 2019. **29.** Meier J et al. 1013 P. ADA 79th Scientific Sessions. June 09, 2019. **30.** Ellero C, Han J, Bhavsar S, et al. Prophylactic use of anti-emetic medications reduced nausea and vomiting associated with exenatide treatment: a retrospective analysis of an open-label, parallel-group, single-dose study in healthy subjects. Diabet Med. 2010;27(10):1168-1173 **31.** Baekdal TA, Breitschaft A, Navarria A, Hansen CW. A randomized study investigating the effect of omeprazole on the pharmacokinetics of oral semaglutide. Expert Opin Drug Metab Toxicol. 2018;14(8):869-877. doi:10.1080/17425255.2018.1488965

Rebel Academy

Novo Nordisk India Private Limited
Plot No. 32, 47-50, EPIP Area, Whitefield, Bangalore- 566 066. India.
visit us at: www.novonordisk.co.in

novo nordisk®