OBJECTION HANDLER

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FRAMEWORK FOR OBJECTION HANDLING

Support	the HCP's concern
Obtain	the reason for the concern
Listen	to the reason in full
Validate	your understanding of the isssue
Explain	how you can SOLVE the concern

Doctor: Hi good morning/ evening there are some media reports today that use of GLP-1 RA has some safety concerns in people with type 2 diabetes.

Support, do not react to HCPs concern:

Dear doctor thank you so much for sharing your concerns with me.

Obtain the reason for concern:

Doctor may I request you to be please elaborate about the concerns you may have with the usage of GLP-1 RA in T2DM.

Doctor: Yes indeed, media report suggests that there may be increased risk of thyroid cancer with usage of GLP-1 RAs in people with type 2 diabetes.

Listen to the concern attentively:

Pay close attention to the HCP's tone of voice and body language to better understand them. Offer short comments such as "This is a serious concern" or "I understand your concern" to help the HCP feel comfortable sharing.

Validate your understanding of the issue:

I truly appreciate your concern, if I understand you right, you mean that there may be an increased risk of thyroid cancer with the use of GLP-1RAs in people with type 2 diabetes.

Explain with facts and empathy:

Allow me to present some facts and our responsibility toward the patient safety.

EVIDENCE as mentioned in subsequent pages.

For all safety concerns:

- Patient safety has top priority for Novo Nordisk, and we take all reports about adverse events from use of our medicines very seriously.
- GLP-1RAs have been used to treat type 2 diabetes for more than 15 years and for treatment of obesity for 8 years, including Novo Nordisk products based on semaglutide and liraglutide that have been on the market for more than 10 years.
- We have over 9.5 million total patient-years of experience on Semaglutide across RCTs and RWEs.
- Novo Nordisk remains confident in the benefit risk profile of the products and remains committed to ensuring patient safety

Summary : Summarize as mentioned in subsequent pages

Dear Sir/madam hope I could address your concerns please let me know if you need any further details on the same.

Thank you so much for your insightful discussion and understanding. I Look-forward for your kind support.

THYROID PROBLEM: MEDULLARY THYROID CANCER

- Across the safety trials of all GLP-1 RAs and the meta-analysis of existing studies has shown that there is no increased risk of thyroid cancers with GLP-1 RA usage[1,2,3&4]
- The risk of GLP-1 RAs and medullary thyroid cancer has been linked only in animal studies.
- The expression of GLP-1 receptors in human thyroid tissue is not as high as rodents hence the link for the risk of MTC in humans has not established yet[6]
- An Ongoing MTC Surveillance Registry has been developed to address any association between medullary thyroid carcinoma and GLP-1 RA usage. it is a joint sponsored cancer registry running since 2010 based on us cancer registry[7]

Evidence[1-14]

- The LEADER CVOT trial investigated the long-term effects of liraglutide on the thyroid and markers of thyroid function and showed no difference in calcitonin levels over time between liraglutide and placebo treated subjects and no cases of medullary thyroid carcinoma were seen with liraglutide (1 case in the placebo group).
- In a review of the SUSTAIN 1-7 trials including over 8000 patients across the spectrum of T2D, the low incidence of malignant neoplasms was similar between comparators and subcutaneous semaglutide.
- A similar review of the PIONEER 1-10 trials in over 9000 patients revealed that the number of malignant neoplasms reported were few with no clustering of events in any particular system organ or class.
- Recently Hu et al., performed a large-scale meta-analysis which included over 50,000 patients to evaluate the occurrence of thyroid disorders with GLP-1 RA treatment. In line with previous reporting, GLP-1 RA had no significant effects on the occurrence of thyroid cancer.

To summarise Dear sir/madam to date, the Novo Nordisk assessment of safety data collected from large clinical trial programs, post-marketing surveillance and other relevant sources of information have not shown a causal relationship between semaglutide (or liraglutide) and thyroid cancer.

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EYE PROBLEM RETINOPATHY

- Among safety trials conducted for the different GLP-1RAs, the results are inconsistent as one shows increased risk others show either protective effect or no difference to placebo[8]
- This increased risk noticed is also referred as early worsening of diabetic retinopathy which is due to intensive glycemic control and seen in various anti-diabetic therapies, bariatric surgery and pregnancy[9,10]
- This early worsening is not agent-specific[10]
- A cohort study by Zheng et al also established the protective effect of early GLP-1RA usage on diabetic retinopathy[8]
- A meta-analysis of data from all cardiovascular outcome studies showed no association between GLP-1 RA treatment and retinopathy per se[11].
- In general, retinopathy status should be assessed before intensifying any glucose lowering therapy[11]

To summarise Dear sir/madam to date, the Novo Nordisk assessment of safety data collected from large clinical trial programs, post-marketing surveillance and other relevant sources of information have not shown a causal relationship between semaglutide (or liraglutide) increased risk of retinopathy.

MENTAL HEALTH SUICIDAL AND SELF-HARM THOUGHTS

- The safety data collected from large clinical trial programs and post marketing surveillance have not demonstrated a causal association between semaglutide or liraglutide and suicidal and self-harming thoughts

- GLP-1RAs are being studied as a potential therapy for mental health disorders like Depression[12] and Alzheimer's Disease*

- GLP-1RAs are known to show pro-cognitive and neuroprotective properties, and exert modulatory effects on immune, endocrine, and metabolic processes in the central nervous system[12]

- Potential antidepressant effects of GLP-1RAs, especially in the context of their action on the processes related to neuroprotection, inflammation, stress response, energy metabolism, gut-brain crosstalk and the stability of the gut microbiota was discussed in a review article by Dekta j et al[12]

- GLP-1 R Agonists Improves Depression Scores in Diabetes and Obesity - a poster presented in the at OBESITY WEEK[13]

- In addition, Schizophrenia and other psychiatric disorders which are commonly presented with suicidal ideations have also been treated with semaglutide for treating Anti-psychotic induced weight gain and there is also an ongoing clinical trial on the same[14]

To summarise Dear sir/madam to date, the Novo Nordisk assessment of safety data collected from large clinical trial programs, post-marketing surveillance and other relevant sources of information have not shown a causal relationship between semaglutide (or liraglutide) increased risk mental health.

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EARLY DROP-OUT DUE TO ADVERSE GI EFFECT

Incident of early drop-out:
16% early drop-out (<3 months)
due to adverse GI effect

Reasons cited by PwD

- Adverse GI effects with Rybelsus®
- Slow results

Key Questions to Probe HCPs for Early Drop-Out

PS

Dear Doctor thank for an insightful discussion today about your experience with Rybelsus®, as you mentioned that there are early drop-out in patients receiving Rybelsus®.

May I understand what are the key reasons cited by the patient for an early discontinuation?

HCP

Patients are mentioning that they are experiencing GI adverse effects with Rybelsus® hence do not wish to continue the treatment.

PS

Nausea, Vomiting, Constipation, Headache etc.

HCP

Doctor thank you so much for highlighting the same, I am sure you must be considering following before initiating Rybelsus® in your patient uncontrolled for T2DM and excess weight.

As you rightly mentioned few patients may experience GI adverse effect with Rybelsus® which is reported adverse event in clinical trials and also indicative of the drug works on slow gastric emptying however these side effects are transient in nature and can be further mitigated/ minimized by coaching patients on following.

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Onboarding PwD with Rybelsus®

Market Research conducted by IQVIA in India suggested that 10% patients advised to take medication outside recommended schedule i.e. afternoon post meal, after/ before dinner in some cases BID.

PS

Doctor requesting you to please strictly advice your patients to take Rybelsus® 1st thing in the morning and have 30 minutes gap before taking tea/coffee or breakfast.

Suggested Time for Taking Medication

- ✓ **Morning Before Breakfast (Yes)**
- ✗ **Afternoon before lunch (No)**
- ✗ **Night before dinner (No)**
- ✗ **Night after dinner (No)**
- ✗ **Use BID (No)**

Note: (Due to unavailability of 14 mg, HCP suggested BD dose- 7 mg in the morning and afternoon before meals) = No

Rapid Escalation of dose

IQVIA market research indicates that there is rapid escalation of dosage like 10 days with 3mg then 7mg and 14mg, rapid escalation of dosing may also lead to increased incidents of adverse GI events and may lead to early drop -out.

Hence doctor, may I request you to please consider systematic escalation of Rybelsus® dosing, like starting with 3mg for 1 month and follow it up with 7Mg. escalate to 14mg only if additional glycemic and weight benefits are warranted.

Doctor we can further minimize the side effects by considering and informing patients about following.

1 Eating habits

- Eat slowly
- Only if really hungry
- Smaller portions
- No lying down after meal
- Stop when satiated
- Increase meal frequency
- X No straw
- X No distractions, enjoy savouring
- X Not to active after meal
- X No meals near bedtime

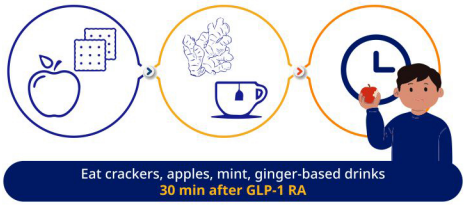
2 Food composition

- Low-fat diet
- Boiling, oven, griddle
- Clear drinks (small slips, not too much)
- Water-rich foods
- Avoid sweets dressings spicy or canned foods

3 Lifestyle

- Fresh air, light exercise
- Food diary to identify what works better

Nausea



Eat crackers, apples, mint, ginger-based drinks
30 min after GLP-1 RA

Avoid strong smells

Vomiting

- Generous hydration
- More frequent meals, in smaller amounts

Diarrhoea

- Generous hydration (water, lemon, bicarbonate)
- No sport drinks
- No high fibre content foods (gradually restore them upon improvement)"
- Yes: chicken broth, rice, carrots, ripe peeled fruit, baked fruit
- No: dairy producta laxatives, coffee, alcohol, soft drinke, very cold/hat foods, products with "ol-ending sweeteners X

Diarrhoea

- Enough fiber in diet
- Increase physical activity
- Healthy, balanced diet
- Generous hydration (water, sugar - free liquids)

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Starting Patients on GLP-1: Consider slow escalation in dosing for better tolerability and outcomes.

1 Before

Save time to speak with the patient

- Transmit realistic expectations regarding treatment results
- Inform about GI AEs, pointing out that they will soon pass
- Highlight the importance of following the available guidelines

2 Dose-escalation

If GI AEs occur **Slow down** the planned dose increments to reach success

For this purpose, choose one/several among these

- Extend current phase for 2-4 more weeks before moving forward to next dose
- Suspend treatment temporarily
- If GI AEs appear just after escalation, go back to prior for a few days, then increase dose gradually
- If problem persists, consider setting up as maintenance therapy a dose lower than the maximum one

2 Dose-escalation or maintaenance phase

If GI AEs occur **Slow down** the planned dose increments to reach success

Consider one/several of these

- Start a differential diagnosis procedure to rule out underlying conditions that may be responsible
- Check patient understands/ compiles with diet/lifestyle guidelines
- Start measures specifically focused on the troublesome symptoms
  - Additional patient guidelines (see Figure 2)
  - Pharmacological support (at short term)

Nausea	Vomiting	Diarrhoea	Constipation
- Anti emetics **- Prokinetics** (domperidone)	**- Anti emetics** **- Prokinetics** (domperidone) **- Standard procedures for severe causes** (do not rule out i.v. rehydration)	**- Probiotics** **- Antidiarrhoeals** (liperamide) **- Consider metformin dose reduction when needed**	**- Stool softeners** **- Consider reducing GLP-1 RA dose**

- Switch to another GLP-1 RA (start at lowest escalation dose)

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Note: If sever GI adverse events persists, consult your doctor

In case of severe/persistent nausea/vomiting, no drinks during meals, rather 30-60 minutes before and/or after

Should any GI AE be severe/persistent in spite of following all guidelines, contact HCP as soon as possible