Separating Fact from Fiction: Potential Use of Post-Authorization Safety Studies to Assess Safety of GLP-1s in Obesity Treatment

EPH256

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Background

- Glucagon-like peptide-1 receptor agonists (GLP-1) are a class of medications primarily used to manage Type 2 diabetes and most recently obesity
- These medications mimic the action of the naturally occurring GLP-1 hormone, which helps regulate blood sugar levels by:
  - Stimulating insulin release from the pancreas
  - Inhibiting glucagon secretion, which prevents the liver from producing too much glucose
  - Slowing gastric emptying, which helps control blood sugar spikes after meals
  - Increasing feelings of fullness, which can aid in weight loss
- As a result, GLP-1 agonists can lead to weight loss which has resulted in these medications gaining traction in the treatment of obesity
- Common GLP-1 medications include Dulaglutide, Exenatide, Semaglutide, Liraglutide and Lixisenatide

- However, only Semaglutide, Liraglutide and Tirzepatide are approved for obesity treatment, while other GLP-1 agonists are widely used off label
- Despite the proven efficacy of these medication for weight management, patients may experience a broad range of side effects
- With the increasing attention due to effectiveness in weight loss and the anecdotal safety concerns, this research sought the following:
  - To review current state of post authorisation safety studies (PASS) performed
  - To explore the requirements for a PASS to be required for GLP-1s used for obesity treatment and weigh loss

Methods

- Desktop research and targeted literature review were employed for this study
- We focused on GLP-1 use in obesity, GLP-1 PASS, and reviewed regulatory requirements for PASS for key agencies such as EMA & FDA

Results

- We identified two PASS studies for GLP-1 agonist used in treating obesity.
  - The first studies focused on investigating the potential non-authorized use of two different formulations of liraglutide (Saxenda and Victoza) utilising secondary data at 41 sites in Italy and Germany [1] and CPRD data in the UK [2]. The data captured in the studies did not give rise to safety concerns and provided reassurance that both liraglutide formulations are primarily used in accordance with the approved European label [1, 2].
  - The second study was conducted by the European Medicine Agency (EMA) and focused on the association between GLP-1 receptor agonists and the risk of suicide-related and self-harm-related events among 6027 patients prescribed GLP-1 compared to 20,855 patients prescribed SGLT-1 inhibitors . The study focused on patients with type 2 diabetes mellitus (T2DM) and obesity. The key findings indicated no significant increase in the risk of suicidal ideation or self-harm among patients using GLP-1 receptor agonists compared to those using other treatments [3].
  - The EMA concluded however that further research will be needed to replicate and confirm findings and strengthen evidence supporting the use of GLP-1 receptor agonists [3].

- Based on our review certain criteria indicate the likelihood of a therapy being required to undertake PASS: these include adverse events that are [4,5];
  - previously unknown,
  - affect a particular group of patients or
  - are associated with specific patient characteristic such age or weight or underlying conditions
  - during pre-approval were most likely be mandated or required or given a post marketing requirement
- Although many GLP-1s are being used for the treatment of obesity, only semaglutide, liraglutide and tirzepatide are approved for this purpose. This could means that GLP-1s without approval are being used without proper assessment of safety information which would normally be made available to regulatory bodies during pre-approval.
- Without marketing authorization, regulatory agencies such as the EMA and FDA are unable to require manufacturers to conduct both imposed and voluntary PASS to monitor the long-term safety of medications [4, 5].

Conclusions

- GLP-1s have potential to disrupt obesity treatment but potential side effects are yet to be fully understood.
- PASS may provide a systematic module to evaluate potential adverse events associated with the use of GLP-1s in obesity treatment over time.
- While these treatments reflect a paradigm shift there is an urgent evidentiary need to attain a consensus on the long-term safety of GLP-1s in obesity treatment.

REFERENCES

[1] Sbraccia, Paolo, et al. "Investigating the potential non-authorized use of two different formulations of liraglutide in Europe: A real-world drug utilization study." Diabetes, Obesity and Metabolism 25.4 (2023): 985-991.

[2] NN8022-4246 In market utilisation of liraglutide used for weight management in the UK: a study in the CPRD primary care database | HMA-EMA Catalogues of real-world data sources and studies https://catalogues.ema.europa.eu/node/3549/methodological-aspects. Accessed: 2024-11-04

[3] Barbulescu, Andrei, María Clara Restrepo-Méndez, and Robert Flynn Daniel Leaver Morales. Final study report: Suicidal ideation and GLP-1 receptor agonists. European Medicines Agency, 2024, https://catalogues.ema.europa.eu/system/files/2024-04/Final%20study%20report_Suicidal%20ideation%20and%20GLP1.pdf.

[4] Pharmacovigilance: post-authorisation | European Medicines Agency (EMA)

https://www.ema.europa.eu/en/human-regulatory-overview/post authorisation/pharmacovigilance-post-authorization. Accessed: 2024-11-04

[5] Post-Approval Studies (PAS) Database https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm. Accessed: 2024-11-04]