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GLP-1s Show No Causal Link To Suicidal Thoughts, Actions In Preliminary FDA Review; Sentinel Scan Is Next

by Sue Sutter

US FDA will share final conclusions about safety of the class, which carries indications for type 2 diabetes and weight management, after conducting a meta-analysis of clinical studies across all GLP-1 receptor agonist products and a postmarketing data analysis in the Sentinel system.

The US Food and Drug Administration's preliminary review has found no causal link between use of glucagon-like peptide-1 receptor agonists for diabetes or weight management and suicidal thoughts or actions, but the agency's investigation will continue with a meta-analysis of clinical trial data and a Sentinel system postmarketing data analysis.

In an 11 January drug safety communication, the agency said it has conducted detailed reviews of cases in the FDA's Adverse Event Reporting System and examined clinical trial data but found no evidence that the GLP-1s cause suicidal thoughts or actions.

The agency nevertheless noted the limitations of the analyses it has performed to date.

> *"Because of the small number of suicidal thoughts or actions observed in both people using GLP-1 RAs and in the comparative control groups, we cannot definitively rule out that a small risk may exist; therefore, FDA is continuing to look into this issue." – FDA*

With regard to FAERS reports, "because the information provided was often limited and because these events can be influenced by other potential factors, we determined that the information in these reports did not demonstrate a clear relationship with the use of GLP-1 RAs."

"Similarly, our reviews of the clinical trials, including large outcome studies and observational studies, did not find an association between use of GLP-1 RAs and the occurrence of suicidal thoughts or actions," the agency said. "However, because of the small number of suicidal thoughts or actions observed in both people using GLP-1 RAs and in the comparative control groups, we cannot definitively rule out that a small risk may exist; therefore, FDA is continuing to look into this issue."

Additional evaluations of a potential link between GLP-1s and suicidal thoughts or ideation will include a meta-analysis across all products in the class, and an analysis of data in the FDA's Sentinel system, which uses health claims and electronic medical records.

The FDA told the *Pink Sheet* it is leading both the meta-analysis and Sentinel studies. "The planning phase is ongoing for both studies, so FDA does not have additional details to provide currently. We anticipate this work will take several months."

"We will communicate our final conclusions and recommendations after we complete our review and have more information to share," the agency said.

FAERS Reports

The FDA said the safety signal was raised on 11 July when the European Medicines Agency issued a statement that it was reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1s. The EMA review was triggered by the Icelandic Medicines Agency following spontaneous reports of suicidal thoughts and self-injury in people using GLP-1s containing liraglutide or semaglutide as the active ingredient. (Also see "*EMA Probe Into Suicide Risk With Liraglutide & Semaglutide Extended To Other GLP-1 Receptor Agonists*" - Pink Sheet, 11 Jul, 2023.)

The US regulator also opened an investigation into reports of alopecia and aspiration with drugs in the class.

The first GLP-1, *AstraZeneca PLC*'s Byetta (exenatide), was approved in the US for type 2 diabetes 19 years ago. However, use of the class has grown exponentially in recent years with the introduction of new compounds and the expansion of indications to include weight management in people who are overweight or obese.

Two GLP-1 receptor agonists, and one dual gastric inhibitory polypeptide receptor and GLP-1, are now approved for weight management indications.

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Since the FDA's evaluation of the safety issue is ongoing, the agency said it was unable to provide exact counts of adjudicated cases (i.e., cases assessed by the agency to meet specific case definition and causality assessment criteria) at this time.

The agency also cited limitations with FAERS data that are accessible through the public dashboard. "For example, the FDA does not require that a causal relationship between a product and event be proven for an adverse event to be reported to FAERS, and reports do not always contain enough detail to properly evaluate an event. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Duplicate reports and stimulated reporting may inflate the reported occurrence of an adverse event."

Current Class Warning On Weight Management Drugs

None of the labels for the GLP-1 type 2 diabetes treatments mentions information about suicidality or suicidal thoughts.

However, the labels for the weight management products – *Novo Nordisk A/S*'s Saxenda (liraglutide) and Wegovy (semaglutide) and *Eli Lilly and Company*'s Zepbound (tirzepatide) – carry a warning and precaution about suicidal behavior and ideation reported in clinical trials with older chronic weight management products.

This class warning language advises health care providers to monitor patients for the emergence of worsening depression, suicidal thoughts or behaviors, or any unusual changes in mood or behavior. Labeling also advises to discontinue treatment in patients who experience suicidal thought or behaviors, and to avoid use in those with a history of suicidal attempts or active suicidal ideation.

The Saxenda label notes that in adult clinal trials, nine (0.3%) of 3,384 Saxenda-treated patients and two (0.1%) of 1,941 placebo-treated patients reported suicidal ideation; one of these Saxenda-treated patients attempted suicide. In a pediatric study, one (0.8%) of the 125 Saxenda-treated patients died by suicide. "There was insufficient information to establish a causal relationship to Saxenda," labeling states.

Sponsor Reaction

Novo Nordisk is the sponsor of six approved GLP-1s: the diabetes treatments Victoza (liraglutide), Xultophy (liraglutide/insulin degludec), Ozempic (semaglutide injectable) and

Rybelsus (semaglutide oral); and two weight management products, Saxenda and Wegovy.

The company said its own review of clinical trials, including large outcomes studies and observational studies, did not find an association between use of GLP-1s and the occurrence of suicidal thoughts or actions. "We look forward to working with FDA as they complete their review. The known risks associated with use of those medicines are reflected in their current FDA-approved product labeling."

Sanofi has two GLP-1 products approved for type 2 diabetes: Adlyxin (lixisenatide) and Soliqua (lixisenatide/insulin glargine).

The company said it received notice from the FDA on a potential connection between GLP-1s and alopecia, aspiration or suicidal ideation. "Our continuous patient safety and pharmacovigilance monitoring system and a dedicated safety evaluation have not identified any causal association to any such safety concerns" regarding Adlyxin or Soliqua, Sanofi said.

"Sanofi has provided this assessment to the FDA and will continue to work with relevant health authorities moving forward."

Lilly has three approved products – the diabetes drugs Trulicity (dulaglutide) and Mounjaro (tirzepatide), and the weight management drug Zepbound. AstraZeneca markets the exenatide-containing products Byetta and Bydureon BCise, both of which are indicated for type 2 diabetes.

"Following rigorous study for many years in clinical trials and a robust approval process, medicines continue to be monitored by the FDA and manufacturers for safety," Lilly said. "We will continue to collaborate with the FDA as the agency completes its evaluation."