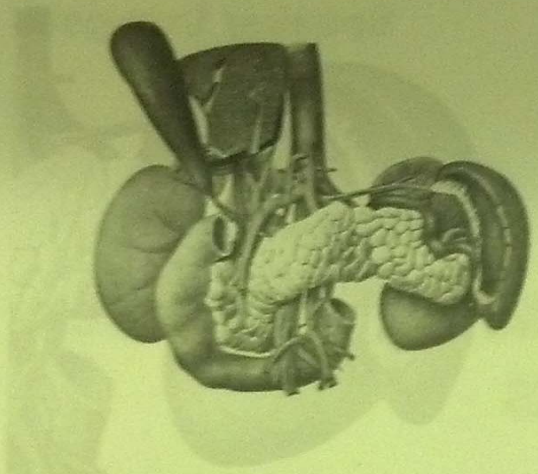

FDA's Approach to Addressing a Pancreatic Safety Signal With Incretin Mimetics: Pharmacovigilance and Pharmacoepidemiology

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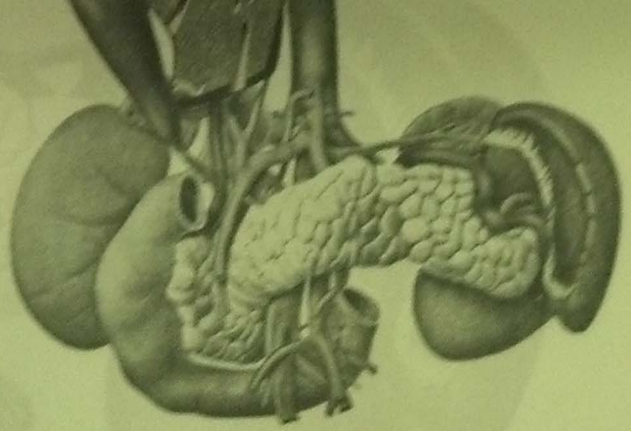
Cases of acute pancreatitis (AP), including necrotizing and hemorrhagic types in association with GLP-1 incretin mimetic drug treatment of patients with Type 2 diabetes, have been reported to FDA's Adverse Event Reporting System (AERS) in the postmarketing setting. The safety of GLP-1-based therapies, including potential pancreatic toxicity related to AP, have been continuously monitored soon after approval of exenatide, the first drug approved in the class. These concerns have been the subject of multiple FDA reviews, labeling changes, and FDA communications. Additionally, external researchers published data mining analyses of the publicly available AERS data (Elashoff, *Gastroenterology* 2011;141:150. Quarterwatch 2013) and have raised concerns regarding the risk of AP and pancreatic and thyroid cancer in association with GLP-1-based drug therapies. The limitations of AERS data (under-reporting of events due to the voluntary nature of reports, lack of an accurate population denominator, and inadequate documentation of the clinical details, including the presence of comorbidities, concomitant medications, and important risk factors) do not allow one to calculate incidence rates, establish a causal association between the drug and the adverse event, or to estimate the magnitude of the association or determine any differences in risk for pancreatic toxicity among GLP-1 agents. Interpretation of AERS data is limited by the lack of an adequate control data and evidence that suggests a possible increased background risk in the indicated patient population. AERS data mining signals, such as for pancreatitis and pancreatic and thyroid cancers reported in the literature and FDA's own reviews utilizing similar methods for GLP-agents and other drug therapies, are considered to be hypothesis generating and cannot be used to establish or refute a drug effect.

FDA has issued safety communications and added labeling to the Warnings and Precautions section of all GLP-1 based drugs warning prescribers and patients about post-marketing reports of fatal and non-fatal cases of AP. Information also has been added in the Important Limitations of Use subsection of the Indications and Usage Section, the Adverse Reactions, Postmarketing subsection, and the Patient Counseling Information Section of the labeling in addition to requiring patient labeling (a Medication Guide) to warn patients of the risk of acute pancreatitis. FDA has required the manufacturers to conduct epidemiological studies of pancreatic toxicity safety signals in order to confirm and quantify the potential association with GLP-1 therapies in Type 2 diabetics.

FDA has required that cases of pancreatitis and pancreatic cancer be reported as adverse events of special interest in large cardiovascular outcome trials that are required for the GLP-1 based therapies. The signal for medullary thyroid cancer, a rare form of thyroid cancer that has been observed in animal studies with long-acting GLP-1 agonists, is labeled in a Boxed Warning in all approved long-acting GLP-1 agonists (Victoza and Bydureon), and FDA has required that all manufacturers of approved GLP-1 agonists participate in a Medullary Thyroid Cancer Registry as a postmarketing requirement. The clinical relevance of this animal finding remains unknown.

Review of the FDA-required epidemiological studies submitted to the Agency and the published epidemiological literature have provided conflicting results and do not provide reliable evidence to refute or support a causal link between GLP-1-based therapies and the risk of AP. Six observational studies investigated the risk of acute pancreatitis associated with GLP-1-based therapies (exenatide or sitagliptin). Among them, one study detected an increased risk with recent or past, but not current, use (Dore, *Diabetes Obes Metab* 2011;13:559), and one study



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d an increased risk for acute pancreatitis with current recent use (Singh, *JAMA Intern Med* 2013;173:534). ncrease in risk was found in the remaining four ies (Dore, *Curr Med Res Opin* 2009;25:1019. Garg, *etes Care* 2010;33:2349. Romley, *Diabetes Technol* 2012;14:904. Wenten, *Diabet Med* 2012;29:1412). us methodological shortcomings shared by the studncluding lack of outcome validation and incomplete riate adjustment, preclude conclusive results.

s AERS data are useful in identifying potential related serious safety signals, particularly events that have a low background rate in the population but are less suitable for detecting relatively more common events and events with long latency periods, such as pancreatitis, pancreatic cancer, and thyroid cancer. Additional data mining analysis of AERS is unlikely to shed more light on these safety signals. Evaluation of the potential association between GLP-1-based therapies and pancreatitis and pancreatic and thyroid cancers will require adequately powered, long-term epidemiological studies.