likely that such efficacy will be shown until the vaccines are licensed and postmarketing surveillance commences.

Recent evidence suggests that EV71 vaccines do not provide cross-protection against all circulating genetic lineages of EV71 or against coxsackievirus A16.[5] Thus, the Chinese C4A-based vaccines may not generate protective immunity against EV71 in regions where other extant or newly emerged lineages circulate. Consequently, it may be necessary to develop multivalent vaccines to ensure that protection is provided against all EV71 strains.

Nevertheless, this is an exciting development in the global response to the emergence of EV71 as a cause of severe neurologic disease. It is also worth noting that in the past 17 years, EV71 research and vaccine development have been primarily centered in Asia — a fact that not only reflects the predominance of EV71 epidemics in this region but also underscores the increasing importance of Asia as a center of medical research. Finally, if these vaccines prove to be effective in preventing EV71-associated neurologic disease, an important tool for controlling, or even eradicating, EV71 infection in regions where it is endemic may have been developed. If its promise is realized, a priceless gift will have been given to the children of the Asia–Pacific region and to the rest of the world.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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# Pancreatic Safety of Incretin-Based Drugs — FDA and EMA Assessment

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With approximately 25.8 million diabetic patients in the United States and 33 million in the European Union alone, the growing prevalence of diabetes worldwide poses a major public health challenge. Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are committed to ensuring the safety of drug products marketed for the treatment of diabetes, and postmarketing reports of pancreatitis and pancreatic cancer in patients taking certain antidiabetic medications have been of concern to both agencies. Working in parallel, the agencies have reviewed nonclinical toxicology studies, clinical trial data, and epidemiologic data pertaining to blood glucose–lowering drug products (e.g., exenatide and sitagliptin) that stimulate postprandial insulin release by potentiating the incretin hormone pathways.

In keeping with the pathophysiological complexity of diabetes, several classes of blood glucose–lowering drugs, encompassing diverse mechanisms of action, have been developed to treat the disease. The incretins (i.e., glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide) are intestinal hormones that stimulate the postprandial production of insulin and glucagon by the pancreas. In the past decade, drugs that act as incretin receptor agonists (e.g., exenatide) or that inhibit the proteolytic degradation of incretins (e.g., sitagliptin) have been approved by both the FDA and the EMA (see table), in part on the basis of clinical data establishing

**Incretin-Based Drugs Approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).***

| Drug | Incretin-Based Mechanism | Approval Date | |
|---|---|---|---|
| | | FDA | EMA |
| Exenatide | GLP1 agonist | April 28, 2005 | November 20, 2006 |
| Sitagliptin | DPP4 inhibitor | October 16, 2006 | March 21, 2007 |
| Vildagliptin | DPP4 inhibitor | (Not approved by the FDA) | September 26, 2007 |
| Saxagliptin | DPP4 inhibitor | July 31, 2009 | October 1, 2009 |
| Liraglutide | GLP1 agonist | January 25, 2010 | June 30, 2009 |
| Linagliptin | DPP4 inhibitor | May 2, 2011 | August 24, 2011 |
| Exenatide extended-release | GLP1 agonist | January 27, 2012 | June 17, 2011 |
| Alogliptin | DPP4 inhibitor | January 25, 2013 | September 19, 2013 |
| Lixisenatide | GLP1 agonist | (Not approved by the FDA) | February 1, 2013 |

* GLP1 denotes glucagon-like peptide 1, an incretin; DPP4 denotes dipeptidyl peptidase 4, an exopeptidase that inactivates the incretins.

efficacy in improving glycemic control. The benefit–risk assessment also considered clinical advantages such as reduced risk for drug-related hypoglycemia and possible improvement in bodyweight maintenance.

Within the past year, the FDA and the EMA independently undertook comprehensive evaluations of a safety signal arising from postmarketing reports of pancreatitis and pancreatic cancer in patients using incretin-based drugs. These investigations, now complete, included examination of data from a 2013 research report revealing a possible pancreatic safety signal.[1,2] Both agencies committed themselves to assessing the evidence pertinent to reported adverse events, as well as any factors that might confound safety analysis in the context of antidiabetic drugs. Although the disproportionate spontaneous reporting of adverse events is commonly interpreted as a safety signal, there are inherent limitations to the ability to establish causal relationships, including the evaluation of events with high background rates, long latency periods, or a possible contribution by the disease itself.

Using the extensive nonclinical assessments completed as part of all marketing applications for incretin-based drugs, the FDA reevaluated more than 250 toxicology studies conducted in nearly 18,000 healthy animals (15,480 rodents and 2475 nonrodents). Microscopic examinations from these toxicology studies yielded no findings of overt pancreatic toxic effects or pancreatitis. The EMA conducted a similar review of the studies for the incretin-based drugs currently authorized for use in the European Union (see table). In addition, drug-induced pancreatic tumors were absent in rats and mice that had been treated for up to 2 years (their life span) with incretin-based drugs, even at doses that greatly exceed the level of human clinical exposure.

A potential limitation of these toxicology data lies in the use of only healthy animals. To address this concern, the FDA required sponsors of marketed incretin-based drugs to conduct 3-month pancreatic toxicity studies in a rodent model of diabetes. These studies included extensive histopathological evaluation of the endocrine and exocrine pancreas, including analysis of ductal morphology and histochemical staining capable of disclosing pathological proliferation and apoptosis. Three of these studies have been completed and submitted for review by the FDA, and no treatment-related adverse effects on the pancreas were reported. In addition, approximately 120 pancreatic histopathology slides from one of the three sponsor-conducted studies were subjected to independent and blinded examination by three FDA pathologists. The FDA experts' conclusions regarding these slides were generally concordant with the sponsor's report.

As part of its evaluation of the postmarketing reports of pancreatic adverse events, the FDA also performed its own pancreatic

toxicology studies with exenatide. Rodent models of disease, each accompanied by a nondiseased control, included a mouse model with chemically induced pancreatitis, the Zucker diabetic fatty rat, and C57BL/6 mice fed a high-fat diet. Data from the studies of the pancreatitis mouse and diabetic rat models did not identify exenatide-related pancreatic injury. In the high-fat-diet mouse model, minimal-to-moderate exacerbation of background findings (e.g., acinar-cell hyperplasia, atrophy, and periductal inflammation or fibrosis) were detected after 12 weeks of treatment with exenatide; that mouse model has not been definitively qualified as a model of drug-induced pancreatic responses, but it merits further investigation.

Clinical safety databases reviewed by the FDA included data from more than 200 trials, involving approximately 41,000 participants, more than 28,000 of whom were exposed to an incretin-based drug; 15,000 were exposed to drug for 24 weeks or more, and 8500 were exposed for 52 weeks or more. A similar review was conducted by the EMA, including all studies performed with the incretin-based drugs authorized in the European Union. Small imbalances in the incidence of pancreatitis were reported in premarketing trials, although the overall number of events was small. A pooled analysis of data from 14,611 patients with type 2 diabetes from 25 clinical trials in the sitagliptin database provided no compelling evidence of an increased risk of pancreatitis or pancreatic cancer.[3] Clinical trials in which amylase and lipase levels had been monitored in a systematic manner showed that incretin-based drugs may increase enzyme levels, but the mean levels were in the normal range. Furthermore, changes in enzyme levels were not associated with gastrointestinal adverse events (i.e., abdominal pain, nausea, and vomiting).

Two cardiovascular outcome trials in patients with type 2 diabetes who were treated with incretin-based drugs have been completed: the Saxagliptin Assessment of Vascular Outcomes Recorded (SAVOR) trial and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial. The SAVOR trial was a randomized, double-blind, placebo-controlled trial involving 16,492 patients. The EXAMINE trial was a randomized, double-blind, placebo-controlled trial involving 5380 patients. Reported rates of acute pancreatitis in the SAVOR and EXAMINE trials were low, with similar rates of events in the drug and placebo groups (22 and 16, respectively, in SAVOR; 12 and 8, respectively, in EXAMINE).[4,5] The reported incidence of pancreatic cancer was 5 and 12 cases, respectively, in the drug and placebo groups in the SAVOR trial, with no incidence of pancreatic cancer in either group in the EXAMINE trial.

The FDA and the EMA have also independently reviewed a number of observational studies to explore a possible association between incretin-based drugs and acute pancreatitis. Cohort and nested case–control studies, using a variety of large administrative claims databases, have yielded inconsistent results. These studies suffered, to different degrees, from methodologic shortcomings, including limited power, inadequate outcome validation, incomplete covariate ascertainment, and inadequate confounding control.

Thus, the FDA and the EMA have explored multiple streams of data pertaining to a pancreatic safety signal associated with incretin-based drugs. Both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. The FDA and the EMA believe that the current knowledge is adequately reflected in the product information or labeling, and further harmonization among products is planned in Europe. Ongoing strategies include systematic capture of data on pancreatitis and pancreatic cancer from cardiovascular outcome trials and ongoing clinical trials, which should facilitate meta-analyses, and accumulation of further knowledge regarding these signals in the future.

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