Closer Look

MEMORANDUM

FDA and EMA conclude their assessment on incretins and pancreatitis - February 27, 2014

Executive Highlights

- As published in NEJM, the FDA and EMA have concluded their review of relevant preclinical toxicology and diabetic animal model data, clinical trial data, long-term outcomes data, and observational trials related to incretins and pancreatitis.
- FDA and EMA agree that assertions of a casual connection between incretin therapies and pancreatitis are "inconsistent with the current data" and that the totality of the data "provides reassurance," although pancreatitis will continue to be investigated as a risk.

Today's issue of the New England Journal of Medicine (NEJM) features a medical perspectives piece detailing the FDA and EMA's parallel assessments of incretin-based drugs and pancreatic safety. The agencies reviewed data from toxicology studies, diabetic animal models, pre-marketing clinical development programs, cardiovascular outcomes trials, and observational studies (including the incendiary Butler et al. morphology study that sparked the re-emergence of this controversy last year [Diabetes 2013]*). The vast majority of the impressive volume of data analyzed (toxicology studies in ~18,000 healthy animals, database reviews of 41,000 patients in clinical safety databases, and the wealth of data from the SAVOR and EXAMINE CVOTs) demonstrates no clear correlation between incretin therapies and pancreatitis or pancreatic cancer. The article did note a few findings that merit further investigation. Studies in a high-fat-diet mouse model showed that exenatide led to minimal to moderate worsening of background phenomena such as inflammation and acinar-cell hyperplasia (the authors note that the model has not been conclusively identified as a model of drug-induced pancreatic events). In addition, and as is already well known, pre-marketing clinical trials found small imbalances in the incidence of pancreatitis, although the overall number of events was very small. Also, some clinical trials found slight increases in amylase or lipase in patients on an incretin therapy, although the mean levels were still within the normal range.*

On balance, the piece suggested that the virtual absence of evidence from preclinical models coupled with weak clinical ties signified that the present maelstrom in the media is unwarranted. At present, both agencies agree that assertions of a causal relationship between incretins and pancreatic adverse events are "inconsistent with the current data," and that "the totality of the data that have been reviewed provides reassurance." However, it also suggests that both agencies will continue to consider pancreatitis as "a risk associated with these drugs until more data are available," and that both agencies will continue to investigate the issue.

Overall, the FDA and EMA's conclusion reflects the current consensus on the issue in academic circles (that current data is insufficient to support a causal link between incretins and pancreatitis and that prescribers should not change prescribing practices). Other high-profile organizations such as the ADA and EASD have also stated that current data is insufficient to merit a change in prescribing behavior for incretin therapies. The CHMP also released a report its findings following a formal investigation of the issue last year. Regarding drug safety labeling, the NEJM article notes that the EMA plans to "harmonize" incretin drug labeling with regards to pancreatic safety - we presume this suggests a more consistent label section on pancreatic safety among the range of incretin therapies available in Europe.

We hope the controversy continues to subside as the medical community receives more data from long-term outcomes studies. For a timeline of the development of the incretin-pancreatitis controversy, read our Incretins and Pancreatitis Primer.

- **The February issue of the journal *Lancet* contained two articles on the incretin-pancreatitis issue:** A retrospective case-control study from a study group in Piedmont, Italy and a "Comment" piece from Dr. Michael Nauck and Dr. Juris Meier. See our coverage of these pieces in our February 27, 2014 Letter.

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