DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
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JAN 22 2013

Elizabeth Barbehenn, Ph.D., Research Associate
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Public Citizen Health Research Group
1600 20th Street, NW
Washington, D.C. 20009

Dear Drs. Barbehenn and Carome,

Thank you for your letter dated September 15, 2011, in which you raised questions about clinical studies of Victoza (liraglutide).

We note your comments regarding clinical trials that involved administration of liraglutide to children. In particular, you refer to a phase 1 pharmacokinetic pediatric study and request that FDA immediately place a clinical hold on the study based on ethical concerns. This phase 1 study has now concluded. You also refer to a phase 3 pediatric study to evaluate the safety and efficacy of liraglutide and request that the Food and Drug Administration (FDA or Agency) also place a clinical hold on the study based on ethical concerns. As a general matter, FDA is unable to specifically discuss, per applicable regulations and statutes, clinical studies being performed or planned by a sponsor. However, with this caveat in mind, we would like to offer several comments.

In your letter, you write that "[G]iven the known serious risks of liraglutide and the availability of many other treatments for type 2 diabetes mellitus in children, treatments that have well-established safety profiles that are better than liraglutide … such as metformin, sulfonylureas, and insulin, would likely be sufficient treatment and certainly would have a more favorable benefit-to-risk profile." Please note that only metformin and insulins have FDA-approved indications for use in children with type 2 diabetes; sulfonylureas are not indicated for use in children.

Further, some of the safety concerns expressed in your letter as being specific to liraglutide are also associated with metformin, sulfonylureas and insulin. Both sulfonylureas (not indicated for use in children) and insulins have a risk of hypoglycemia. In July 2009, several published observational studies raised the possibility of cancer risk associated with insulin use (see http://www.fda.gov/Drugs/DrugSafety/ucm239376.htm). Although these studies did not provide conclusive evidence of such a risk, they do undermine a conclusion that all other available therapies offer a more advantageous safety profile than liraglutide. Both insulins and sulfonylureas cause weight gain, a contributor to childhood and adult diabetes. Liraglutide does not cause weight gain. While metformin is recognized as a very safe and effective therapy for type 2 diabetes in adults and children, some patients may have contraindications to their use (e.g., renal

disease) requiring treatment with another drug product. Diabetes is a chronic and progressive condition that often requires combination drug treatment. Data on safety and effectiveness of available therapies are best obtained from clinical investigations with appropriate protocols to ensure the safety of study participants.

You also asked us to "promptly investigate the adequacy of the IRB review for all sites participating in this study" and to provide a response to several questions related to IRB study approvals and informed consent. Pediatric post-marketing requirements established under the Pediatric Research Equity Act of 2007 (PREA) [21 U.S.C. 355(B)] are reviewed by the internal Pediatric Review Committee which has among its required members a pediatric ethicist. The compliance of a proposed pediatric post-marketing requirement with the requirements of 21 CFR 50 subpart D (Additional Safeguards for Children in Clinical Investigations) is part of the internal committee review. Please be assured that the Agency takes very seriously issues involving the ethics of clinical trials, and has carefully reviewed the concerns that you raised to determine if any action would be appropriate. While we note your request, we are unable, per regulation, to comment on your questions that relate to IRB involvement in these clinical studies.

We appreciate your observations and will include them in future considerations involving liraglutide that come before the Agency.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research