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September 15, 2011

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
Department of Health and Human Services
WO51/Room 6133
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Woodcock:

In its letter approving Novo Nordisk's new drug application for liraglutide (rDNA origin) injection (Victoza), the Food and Drug Administration (FDA) required, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), that the sponsor conduct a phase 1 pharmacokinetic pediatric study and a randomized, controlled phase 3 pediatric study involving exposure of children with type 2 diabetes mellitus to liraglutide.[1] Given the risk of serious adverse side effects from liraglutide and the absence of any evidence that this drug offers to pediatric patients with type 2 diabetes mellitus benefits that cannot be achieved with other available, safer alternative treatments, Public Citizen believes that the required pediatric studies are unethical and fail to satisfy the requirements of the FDA regulations at 21 C.F.R. part 50, subpart D ("Additional Safeguards for Children in Clinical Investigations"). We therefore call on the FDA to:

(1) immediately place a clinical hold on any ongoing studies involving administration of liraglutide to children;
(2) cease to approve further clinical trials in the pediatric population;
(3) promptly investigate the adequacy of the institutional review board (IRB) review at all sites that participated in any such study; and
(4) promptly evaluate the agency's policies and procedures for determining whether pediatric studies required by the agency under PREA are ethical and conform to the requirements of the FDA regulations at 21 C.F.R. p art 50, subpart D.

Background on liraglutide

Liraglutide was approved by the FDA on January 25, 2010, for treatment of type 2 diabetes mellitus in adults who have failed to achieve glucose control after trying diet, exercise, and other drugs (i.e., this is a drug for second-line treatment). The phase 3 pivotal trials testing liraglutide in adults assessed efficacy by using a surrogate marker — change from baseline in hemoglobin A1c (HbA1c) at 26 and 52 weeks of treatment — rather than clinically significant outcome measures.

In contrast to the limited data on efficacy, preclinical and clinical studies of liraglutide identified several serious safety signals, including the risks of thyroid cancer, pancreatitis, severe hypoglycemia, and adverse immune reactions. Severe renal impairment has also been identified in postmarket reports as an adverse side effect associated with liraglutide use.[2]

Phase 1 pharmacokinetic pediatric study

The FDA required that Novo Nordisk first conduct a phase 1 pharmacokinetic pediatric study to determine doses for the subsequent phase 3 study that will be conducted under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years, 11 months. A search on the ClinicalTrials.gov website reveals that Novo Nordisk is conducting the following multicenter study, which we assume is the phase 1 pharmacokinetic study required by the FDA:[3]

> Title: Safety of Liraglutide in Pediatric Patients with Type 2 Diabetes (ClinicalTrials.gov identifier: NCT00943501)

Despite the title, this study is enrolling both children and adults. The inclusion criteria for this study for children are as follows:

- age eligibility for children: 10-17 years
- BMI greater than 85th percentile for age and gender in children
- type 2 diabetes mellitus
- currently being treated with diet and exercise or metformin alone
- HbA1c between 6.5 and 11.0%

Given the inclusion criteria, 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 superior to liraglutide, it is unclear how the FDA could have allowed, and any IRB could have approved, this study for involvement of children, considering the FDA regulations at 21 C.F.R. part 50, subpart D.

Since this study clearly involves much greater than minimal risk to the subjects, it does not satisfy the requirements for approval under the FDA regulations at 21 C.F.R. 50.51 (“Clinical investigations not involving greater than minimal risk”) or 21 C.F.R. 50.53 (“Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects’ disorder or condition”). Therefore, the study may be conducted only if it satisfies the requirements under the FDA regulations at 21 C.F.R. 50.52 (“Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects”) or 21 C.F.R. 50.54 (“Clinical investigations not otherwise

approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children").

With respect to the FDA regulations at 21 C.F.R. 50.52, an IRB may approve the study only if the IRB makes and documents all of the following required findings:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in 21 C.F.R. 50.55.

Given 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, there is no reasonable basis on which to affirm the first two required findings cited above. For children with HbA1c levels at 6.5-6.9%, diet and exercise would likely be sufficient treatment and certainly would have a more favorable benefit-to-risk profile than liraglutide. Furthermore, for most children with an HbA1c greater than or equal to 7.0% despite an appropriate diet and exercise regimen, other medications, such as metformin, sulfonylureas, and insulin, would likely be sufficient treatment and certainly would have a more favorable benefit-to-risk profile than liraglutide.

With respect to the FDA regulations at 21C.F.R. 50.54, the research may be conducted only if the FDA commissioner, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, and law) and following an opportunity for public review and comment, determines either of the following:

- That the clinical investigation in fact satisfies the conditions of 21 C.F.R. 50.51, 50.52, or 50.53, as applicable; or
- That the following conditions are met:
    - The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
    - The clinical investigation will be conducted in accordance with sound ethical principles; and
    - Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 C.F.R. 50.55.

To our knowledge, this study was not approved in accordance with the requirements of 21 C.F.R. 50.54. Moreover, we believe that conducting such a trial is not consistent with sound ethical principles.

We therefore call upon the FDA to immediately place a clinical hold on this study, to promptly investigate the adequacy of the IRB review for all sites participating in this study, and to provide a timely response to the following questions:

- Under what category of research stipulated by 21 C.F.R. part 50, subpart D did the IRBs approve the study?

- Did each IRB make the required determinations under subpart D and provide a reasonable justification for its determinations?

- Were the IRBs made aware of the FDA's safety review of liraglutide and the FDA pharmacology and medical officer reviewers' recommendation that this drug not be approved for adults with type 2 diabetes mellitus?

Phase 3 pediatric study

The FDA also required that Novo Nordisk, after completion of the above-referenced phase 1 study, conduct a randomized, controlled phase 3 pediatric study under PREA to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in subjects ages 10 to 16 years 11 months.

It is our understanding that this study is not expected to start until the above-referenced phase 1 study is completed. Based on the same reasoning described for the phase 1 study, the phase 3 study, if it used inclusion criteria similar to those of the phase 1 study referenced above, would not be ethical and would not satisfy the requirements of the FDA regulations at 21 C.F.R. part 50, subpart D.

On the other hand, a pediatric phase 3 study that enrolled only pediatric subjects with type 2 diabetes mellitus who either (a) had inadequate glucose control despite an appropriate regimen of diet, exercise, and appropriately dosed first-line drug therapy (including metformin and insulin) or (b) had inadequate glucose control that could not be controlled with an appropriate regimen of diet and exercise and could not tolerate first-line drug therapy might be ethical and able to satisfy the requirement of the FDA regulations at 21 C.F.R. 50.52. However, given the wide variety of available treatments for type 2 diabetes mellitus, it is inconceivable that there are not safer alternatives for pediatric patients that have more favorable benefit-to-risk profiles than liraglutide.

In closing, we also call upon the FDA to promptly evaluate the its own policies and procedures for determining whether pediatric studies required by the agency under PREA are ethical and conform to the requirements of the FDA regulations at 21 C.F.R. part 50, subpart D.

Thank you for your attention to this important matter.

Sincerely,

Elizabeth Barbehenn, Ph.D.
Research Associate
Public Citizen's Health Research Group

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

cc: Dr. Margaret A. Hamburg, Commissioner, FDA

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[1] Rosebraugh CJ. Food and Drug Administration approval letter for New Drug Application 022341. January 25, 2010. Available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/022341s000ltr.pdf. Accessed September 14, 2011.

[2] Novo Nordisk Inc. Drug label for Victoza (liraglutide [rDNA origin] injection), revised May 2011. Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf. Accessed September 14, 2011.

[3] ClinicalTrials.gov. Safety of Liraglutide in pediatric patients with type 2 diabetes. Last updated August 26, 2011. Available at http://clinicaltrials.gov/ct2/show/NCT00943501. Accessed September 14, 2011.