



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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MAR 25 2014

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1600 20th Street, N.W.
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Re: Docket No. FDA-2012-P-0404

Dear Drs. Barbehenn and Wolfe:

This letter responds to your citizen petition dated April 19, 2012 (Petition). You request that the Food and Drug Administration (FDA or the Agency) immediately remove from the market the diabetes drug Victoza (liraglutide) because the known increased risks of thyroid cancer and pancreatitis, both of which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits.

You also make the following arguments in support of your request that FDA remove Victoza from the market:

- Victoza provides neither unique nor significant advantages, but only a complex collection of toxicities (Petition at 38).
- The potential for serious harm requires immediate withdrawal by FDA to avoid putting more patients at risk (Id.).
- The clinical safety review for the Victoza new drug application (NDA) listed 18 safety concerns with Victoza (Petition at 12-23).
- There are six serious safety issues with Victoza, any one of which should have precluded approval of Victoza (Petition at 28-34).
- Safety reviewers (clinical and pharmacology/toxicology) for the Victoza NDA thought that Victoza had too many safety issues to warrant approval (Petition at 23-24).

You also request that FDA require a pregnancy registry for Victoza to enable the Agency to track potential effects on human reproduction (Petition at 37). You state there is a potential for serious adverse effects on pregnancy, and in support of your request, you cite data on fetal malformations seen in animals exposed to Victoza (Id.).

FDA has carefully considered the information submitted in the Petition, the comments submitted to the docket, and other relevant data identified by the Agency. Based on our review of this information, and for the reasons explained below, your requests are denied. However, as with all FDA-approved products, we will continue to monitor and review available safety information related to Victoza and take any further action as appropriate.

I. BACKGROUND

A. Victoza (Liraglutide)

Novo Nordisk, Inc., is the holder of NDA 22-341 for Victoza (liraglutide [rDNA origin] injection), which the FDA approved on January 25, 2010. Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.¹ Victoza is the second drug approved in this class of drugs known as GLP-1 receptor agonists, with the first being exenatide.² Victoza is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise.

Victoza's active ingredient is liraglutide, which is an analog of human GLP-1 and, like native GLP-1, activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, G_s, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations.³ This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia.⁴ Victoza also causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Native GLP-1 has a half-life of 1.5 to 2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV and neutral endopeptidases. Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration.⁵

1. Postapproval Requirements and Requests for the Sponsor

The January 25, 2010 approval letter for Victoza imposed postapproval requirements on the sponsor, including a Risk Evaluation and Mitigation Strategy (REMS) and postmarketing studies and trials required under the Food and Drug Administration Amendments Act of 2007 (FDAAA) (codified in section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)). In the approval letter, the Agency also requested, in addition to the required reporting requirements for an approved NDA (21 CFR 314.80 and 314.81), that the sponsor submit, for a period of two years, all cases of pancreatitis as

¹ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf.

² See <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

³ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf.

⁴ Id.

⁵ Victoza is administered as a subcutaneous injection because it is a peptide that would break down in the stomach if administered orally (Petition at 2).

15-day alert reports and provide analyses of clinical trial and post-marketing reports of pancreatitis as adverse events of special interest in periodic safety update reports.⁶

The REMS was required to ensure that the benefits of the drug outweigh the potential serious risk of medullary thyroid carcinoma and acute pancreatitis, including necrotizing pancreatitis. The REMS included a Medication Guide to highlight information regarding the risks of thyroid tumors, including cancer, and information regarding pancreatitis. The REMS also included a communication plan consisting of a Dear Healthcare Provider (DHCP) letter, a Direct Mail letter requirement, and distribution of a Highlighted Information for Prescribers (HIP) sheet, all of which addressed the potential risk of medullary thyroid tumors, the risk of acute pancreatitis, and appropriate patient selection.

In May 2011, FDA required revisions to the communications plan because the REMS assessment showed that the REMS was not meeting its goal of educating health care providers about the potential risks associated with the use of Victoza. Accordingly, the communications plan was revised to modify the reminder *Dear Healthcare Provider* letter, which was required to be sent to the primary care physician audience within 60 days of approval of the REMS modification. It also revised the *Direct Mail* letter, which was required to be sent to all prescribers of Victoza on an annual basis for three years following approval of the REMS modification. We continue to review the sponsor's assessments of the REMS communications plan.

The FDAAA-mandated postmarketing requirements (PMRs) in the January 25, 2010 approval letter include studies on thyroid C-cell tumors, pancreatitis, medullary thyroid carcinoma, major adverse cardiovascular events (MACE), hypersensitivity, and overall malignant neoplasms.

2. *Supplements and Safety Analyses*

Since the initial approval of Victoza, the sponsor has submitted four labeling supplements and three efficacy supplements that included new clinical trial data. In 2012 and 2013, FDA approved the four labeling supplements that the sponsor submitted based on post-marketing safety surveillance of spontaneous reports regarding dehydration and renal failure,⁷ risk of urticaria,⁸ reports of rash and pruritus,⁹ and reports of pancreatitis.¹⁰

⁶ See FDA approval letter at Drugs@FDA, Jan. 25, 2010, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022341s000ltr.pdf.

⁷ See FDA approval letter at Drugs@FDA, May 18, 2011, at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/022341Orig1s004ltr.pdf.

⁸ See FDA approval letter at Drugs@FDA, Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2012/022341s007.s009.s013ltr.pdf.

⁹ See FDA approval letter at Drugs@FDA, Dec. 13, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2012/022341Orig1s017ltr.pdf.

¹⁰ See FDA approval letter at Drugs@FDA, Apr. 16, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/022341Orig1s018ltr.pdf.

In 2012, FDA approved the efficacy supplements, which resulted in updates to the labeling for Victoza to reflect safety and efficacy data from clinical studies submitted after approval.¹¹ With the approval of the efficacy supplements, FDA initiated additional reporting requests related to pancreatitis.¹²

In 2012, FDA also completed a cumulative review of postmarketing safety data (a 915 Safety Review)¹³ for Victoza submitted to the FDA since approval on January 25, 2010.¹⁴ The actions taken and ongoing surveillance activities resulting from this review include:

- The WARNINGS AND PRECAUTIONS and CONTRAINDICATIONS sections of the labeling for Victoza were updated in April 2012 to include additional information about serious hypersensitivity reactions, including anaphylaxis.
- The INDICATIONS AND USAGE section of the labeling for Victoza was updated in April 2012 to include additional information about pancreatitis. FDA is continuing to evaluate pancreatitis to determine if further regulatory action is required.
- The DOSAGE AND ADMINISTRATION section of the labeling for Victoza was updated in April 2012 to include additional information about resuming Victoza after a dose is missed.
- FDA is continuing to evaluate the patient instructions for use about improper pen storage, wrong injection technique, and device malfunctions.

We have undertaken additional review of these items, modified labeling to include information in the Warnings and Precautions and Adverse Reactions sections about post-marketing reports of pancreatitis, modified the Instructions for Use section to mitigate dosing and administration errors, and requested additional adverse event reporting information for pancreatitis and hypersensitivity reactions to address these safety concerns.

¹¹ See FDA approval letter at Drugs@FDA, Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/appltr/2012/022341s007.s009.s013ltr.pdf.

¹² Id.

¹³ Section 915 of FDAAA, Postmarketing Drug Safety Information for Patients and Providers, created section 505(r) of the Federal Food, Drug, and Cosmetic Act that includes a requirement for FDA to prepare summary safety analyses of adverse drug reaction reports for recently approved drugs (505(r)(2)(D)) ("915 Safety Review"). Such analyses must be prepared by 18 months after approval of a drug or after its use by 10,000 individuals—whichever is later—and must identify any new risks not previously identified, potential new risks, or known risks reported in unusual number.

¹⁴ See FDA website on Postmarket Drug and Biologic Safety Evaluations, available at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm#Postmarketing_Summaries.

B. Statutory Framework

1. NDA Approval Standards

The Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act) and FDA regulations require that an applicant seeking to market a new drug submit an NDA or abbreviated new drug application (ANDA). NDAs are submitted under section 505(b)(1) of the FD&C Act (21 U.S.C. 355(b)(1)) and approved under section 505(c) of the FD&C Act. NDAs contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought. NDA applicants must, among other things, describe the benefits and risks of the drug, including a discussion of why the benefits exceed the risks under the conditions of use stated in the labeling (21 CFR 314.50(d)(5)(viii)). Furthermore, applicants must not only provide substantial evidence of effectiveness for claimed indications in their applications, but also provide evidence to support the approved dosage and administration for the drug (21 CFR 314.50(d)(5)(v)). As stated in section 505(d) of the FD&C Act, “substantial evidence” means:

evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

2. Standard for Withdrawal of NDA Approval

Section 505(e) of the FD&C Act establishes the circumstances under which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA or ANDA. With respect to safety concerns, the Agency will withdraw approval of a drug product if it finds either of the following:

that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved

or

that new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown

to be safe for use under the conditions of use upon the basis of which the application was approved.¹⁵

With respect to effectiveness, the Agency will withdraw approval of a drug if it finds “that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.”¹⁶

II. DISCUSSION

In the Petition, you ask FDA to remove the diabetes drug Victoza from the market (Petition at 1). You state that the known increased risks of thyroid cancer and pancreatitis, which occurred in people enrolled in preapproval clinical trials, outweigh any documented clinical benefits (Id.). You also state that because Victoza provides neither unique nor significant advantages, but only a complex collection of toxicities, it should be removed from the market (Petition at 38). You say that the potential for serious harm requires immediate withdrawal by FDA to avoid putting more patients at risk (Id.).

In support of your request, you: (1) identify multiple safety concerns and issues associated with the use of Victoza; (2) cite FDA reviews for the Victoza NDA and reference statements made by FDA reviewers prior to the approval of Victoza; (3) reference FDA’s warnings on pancreatitis, thyroid C-cell tumors, and worsening renal function associated with the use of Victoza issued between January 2010 and June 2011, and (4) provide an analysis of your findings from the Adverse Event Reporting System (AERS) database from February 2010 through September 2011 on adverse events reported to the Agency by people using Victoza.

For the reasons discussed below, we have determined, based on the information available to us at this time, that initiating the withdrawal of the marketing approval of Victoza is not warranted. The safety concerns you raise in the Petition were appropriately and thoroughly considered at the time of initial approval of the Victoza NDA. Since approval, there have been no new safety findings from FDA’s ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of Victoza so as to necessitate the removal of Victoza from the market. Moreover, FDA has required a REMS, modifications to the REMS, and changes to the FDA-approved prescribing information which address a number of the safety concerns itemized in the Petition. FDA has requested additional reporting requirements from the sponsor and will continue to monitor and review available safety information related to Victoza, taking any further action as appropriate.

¹⁵ Section 505(e)(1) and (2) of the FD&C Act; see also 21 CFR 314.150(a)(2)(i) and (ii). In addition, the Agency can suspend approval immediately if it finds that there is an imminent hazard to the public health (section 505(e) of the FD&C Act).

¹⁶ Section 505(e)(3) of the FD&C Act; see also 21 CFR 314.150(a)(2)(iii).

We discuss in greater detail below the concerns you raise related to the topics of (1) the effects of Victoza, (2) the rodent carcinogenicity studies, (3) the safety concerns and issues addressed in the NDA, (4) the risk-benefit analysis, (5) other potential indications raised in the Petition, and (6) labeling and safety alerts.

A. Effects of Victoza

1. Gastrointestinal Effects

In the Petition, you state that the actions of Victoza on the gastrointestinal tract include significant adverse impacts on patients, including nausea (up to 35 percent of subjects), vomiting, diarrhea, dyspepsia, and constipation (Petition at 3 and note 5).

We agree that the most common adverse effects seen in patients treated with Victoza, as well as for other approved GLP-1 analogs, are gastrointestinal in origin. GLP-1 analogs, including Victoza, slow gastric emptying in patients in dose-related fashion, which is likely an important mechanism contributing to the action of this class of drugs in reducing postprandial hyperglycemia.¹⁷ Overall, however, the adverse gastrointestinal effects appear to be monitorable, self-limited, and rarely associated with any serious adverse events.

Patients who experience intolerable gastrointestinal adverse events appear to be more likely to discontinue Victoza therapy — with nausea and vomiting being the most common adverse reactions leading to withdrawal for Victoza-treated patients. In rare postmarketing cases, nausea and vomiting appear to be associated with dehydration progressing to renal failure sometimes requiring hemodialysis. On May 18, 2011, FDA approved changes to Victoza's labeling to include information on these postmarketing reports and directed practitioners to use caution when initiating or escalating doses of Victoza in patients with renal impairment.¹⁸

In addition, FDA continues to closely monitor for postmarketing reports of renal impairment associated with the use of Victoza through routine pharmacovigilance and postmarketing required trials. See section II.C.5 of this response for a more detailed discussion on the safety concerns of renal toxicity and renal impairment associated with Victoza use.

In the Petition, you also summarize the findings of the clinical safety review for the Victoza NDA that discuss the gastrointestinal effects of Victoza use (Petition at 20). These are findings that the Agency carefully considered during the NDA review. We believe that you do not raise any new safety concerns related to this issue.

¹⁷ See labeling for Victoza at Drugs@FDA, at 16-17, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022341s004lbl.pdf.

¹⁸ Id.

2. Other Effects of Victoza

In addition to the effects of Victoza on the gastrointestinal tract, which we address above, you also discuss in the Petition the effects of Victoza on blood cells, the cardiovascular system, the kidneys, the pancreas, radiolabeled drug levels in rat tissues, and reproductive toxicity (Petition at 2-12).

In general, we find that your statements on the first 12 pages of the Petition regarding the effects of Victoza on blood cells, the cardiovascular system, the kidneys, the pancreas, radiolabeled drug levels in rat tissues, and reproductive toxicity accurately reflect information from your referenced sources, with the following exceptions:

- With respect to the kidneys, your statement that radioactivity peaked in kidneys 7 days after a single dose of radioactive Victoza in rats is incorrect. In terms of the timing of drug levels in the kidneys, the kidney to plasma ratio of radioactivity peaked 7 days after dosing, but the concentration of radioactivity in the kidneys peaked 24 hours after dosing.
- With respect to the pancreas, although you are correct that focal inflammation in the pancreas of Victoza-treated female rats may be consistent with pancreatitis, in the 2-year carcinogenicity study, pancreatitis did not occur and survival was unaffected by Victoza treatment in female rats. Furthermore, required postmarketing studies evaluating the effects of 3 months of Victoza treatment on the exocrine pancreas in a rat model of insulin-resistant type 2 diabetes mellitus showed Victoza did not induce changes in the pancreas consistent with pancreatitis.¹⁹

Thus, we do not have evidence from animal studies of drug-induced adverse effects on the pancreas, nor do we have definitive evidence of a causal relationship between GLP-1-based therapies and pancreatitis.

B. Rodent Carcinogenicity Studies

In the Petition, you state that the major safety issue with Victoza came from rodent carcinogenicity studies, where statistically significant drug-related increases in thyroid tumors occurred in two species (mice and rats) and both genders (male and female) at drug exposures similar to those seen in patients taking the maximum recommended human dose of 1.8 milligrams (mg)/day (Petition at 7).

We agree that the rodent carcinogenicity studies raised a safety concern. GLP-1 receptor agonists that cause sustained GLP-1 receptor activation *in vivo* are expected to induce thyroid C-cell tumors in mice and rats. The approved label for Victoza includes a boxed warning about the risk of thyroid C-cell tumors based on results from carcinogenicity

¹⁹ See FDA May 18, 2011 approval letter, *supra* note 7; see also *Am J Physiol Endocrinol Metab*, 303:E253-E264, 10.1152/ajpendo.00182.2012.

studies of Victoza in mice and rats and the unknown human relevance of liraglutide-induced C-cell tumors in mice and rats.²⁰

In addition, we required the applicant to conduct certain postmarketing studies to assess the signal of a serious risk of medullary thyroid carcinoma.²¹ Specifically, four of the seven required postmarketing studies (two nonclinical and two clinical studies) further evaluate the risk of Victoza-induced thyroid tumors.²² The four required studies were:

1. a 2-year study in mice to determine if 26 weeks of Victoza treatment increases the lifetime risk of thyroid C-cell tumors;
2. a 13-week mouse study to determine if Victoza-induced focal C-cell hyperplasia depends on a thyroid glucagon-like peptide-1 (GLP-1) receptor and rearranged-during-transfection (RET) proto-oncogene activation;
3. a 5-year prospective epidemiological study using a large health care claims database to determine the incidence of thyroid cancer among patients with type 2 diabetes exposed to Victoza and patients with type 2 diabetes not exposed to Victoza; and
4. a medullary thyroid carcinoma case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States to identify any increase related to the introduction of Victoza in the market place.

The two-year and 13-week mouse studies have been completed, and the other two are ongoing. Tertiary review of the 2 year mouse study by CDER's Executive Carcinogenicity Assessment Committee (ECAC) concluded that due to the low incidence of proliferative C-cell lesions in thyroid in male and female high dose recovery group mice and in concurrent control group male mice, a clear relationship to liraglutide treatment was not established for proliferative C-cell lesions in high dose recovery groups. No changes were recommended to the approved label for Victoza based on results from the 2-year mouse study. The 13-week study in wild-type mice and mice lacking a functional GLP-1 receptor showed liraglutide-induced thyroid C-cell hyperplasia was GLP-1 receptor-dependent, but there was no evidence liraglutide activated the RET protooncogene in mouse C-cells, a protooncogene often activated in

²⁰ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf. The approved label for Bydureon, an extended release formulation exenatide, a short acting GLP-1 receptor agonist, also contains a boxed warning about the risk of C-cell tumors. See labeling for Bydureon at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbl.pdf

²¹ See FDA Jan. 25, 2010 approval letter, *supra* note 6.

²² See <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>. FDA is authorized to mandate these studies under section 505(o)(3)(A) of the FD&C Act, as added by FDAAA.

proliferative thyroid C-cell lesions in humans, including C-cell hyperplasia and medullary thyroid cancer.²³

Moreover, another one of the seven required postmarketing studies evaluates the effect of Victoza on potential biomarkers of medullary thyroid carcinoma and the effects of Victoza on neoplasms. This study is a randomized, double-blind controlled trial evaluating the effect of Victoza injection on the incidence of major adverse cardiovascular events in patients with type 2 diabetes mellitus. This study is ongoing. In addition, the sponsor's REMS assessment plan is required to include an assessment of healthcare providers' awareness of the potential risk for medullary thyroid cancer and an evaluation of healthcare providers' identification and treatment of medullary thyroid carcinoma after the initiation of Victoza.²⁴ The concern about cardiovascular events and the other safety concerns you raise in the Petition are addressed in more detail below.

In sum, while we agree with the safety concerns regarding the risk of Victoza-induced thyroid tumors, we continue to believe that the benefits of the drug outweigh its risks. We will continue to monitor the results of the studies to determine whether further action is appropriate.

C. The Victoza NDA — Safety Concerns and Issues Addressed

In the Petition, you state that FDA's clinical safety review for the Victoza NDA listed 18 safety concerns with Victoza (Petition at 12). The Petition lists what you state are the most serious safety concerns, including thyroid carcinogenicity/thyroid C-cell tumors, calcitonin levels, medullary thyroid carcinoma, papillary thyroid cancer, human C-cell hyperplasia, major adverse cardiovascular events, pancreatitis and pancreatic cancer, thyroid neoplasm adverse events and serious adverse events of neoplasms, renal toxicity and renal impairment, hypersensitivity reactions, serious hypoglycemic events, injection-site reactions, increased heart rate, pregnancy, and gastrointestinal effects.²⁵ Gastrointestinal effects are discussed in section II.A.1 of this response, and we address the remaining safety concerns below.

²³ Results from the 13 week mouse study were published in March 2012. See Madsen et al, *Endocrinology*. 2012 Mar;153(3):1538-47, PMID: 22234463.

²⁴ See FDA Jan. 25, 2010 approval letter at 7, *supra* note 6.

²⁵ Petition at 12-23. In general, your statements regarding these concerns are factually correct because they are mostly taken verbatim from FDA reviews (except for the discussion on calcitonin levels). However, you appear to have selectively included only information that supports your arguments and have taken certain FDA statements out of context, resulting in your statements often being incomplete and misleading.

1. Thyroid Carcinogenicity/Thyroid C-cell Tumors

In the Petition, you state that Victoza is a drug that, in both mice and rats, had a stronger thyroid cancer signal than ever seen before for any drug, including exenatide (Petition at 28).

We disagree. We believe that it is unknown whether there is an association between Victoza treatment and thyroid C-cell tumors in humans. Moreover, while the articles and cases you reference in the Petition do raise concerns regarding a possible connection between Victoza and thyrotoxicity (medullary thyroid carcinoma, papillary cell carcinoma, C-cell hyperplasia), the lack of data from adequate human studies and animal studies (including both rodents and primates) prevents a clear association between a thyrotoxic risk to humans and Victoza treatment. Further studies are needed and are underway to investigate the actions of GLP-1 agonists like Victoza on each subtype of thyroid cancer.

You also state that “FDA was willing to overrule the conclusions of its own pharmacologists and medical safety officer and disregard this information” and “FDA and sponsors do their utmost to find reasons why the results do not apply to humans” (Petition at 28). These statements are speculative and are not supported by FDA’s analysis of the Victoza NDA as described in the FDA reviewers’ memoranda.²⁶

Specifically, you state that all three safety reviewers (clinical and pharmacology/toxicology) thought that Victoza had too many safety issues to warrant approval (Petition at 23). You state that FDA pharmacology reviewers concluded, prior to Victoza’s approval, that it was not approvable due to its induction of thyroid C-cell tumors in animals at drug exposures similar to drug exposures seen in people taking the drug (Petition at 1). We disagree with this statement. While Victoza induced thyroid C-cell tumors in mice and rats at clinically relevant drug exposures, the reviews state that the reason the pharmacology reviewers, Drs. Parola and Davis-Bruno, did not recommend approval was because the human relevance of liraglutide-induced rodent C-cell tumors was unknown, and the mechanistic studies performed by the applicant did not mitigate this risk.²⁷ Ultimately, it was determined that additional preclinical data would not resolve the uncertainty of the relevance of rodent C-cell tumor findings in humans, at least in the short term.²⁸ However, because the malignant tumors themselves in rodents

²⁶ See Drug Approval Package for Victoza, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000TOC.cfm.

²⁷ See Dr. Anthony Parola, Pharmacology/Toxicology Review and Evaluation, at 3, July 10, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf. In agreement with Dr. Parola’s rationale for recommending against approval, Dr. Davis-Bruno stated: “The nonclinical deficiency lies in the inability to dismiss the rodent carcinogenicity findings as rodent specific and therefore of human relevance until proven otherwise by supportive studies of the sponsor’s design and at their discretion.” See Dr. Karen Davis-Bruno, July 13, 2009 Memorandum at 2, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf.

²⁸ See Dr. Curtis Rosebraugh, Summary Basis for Regulatory Action, Jan. 25, 2010, at 14, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf.

were very few in number, were not detected until treatment of over 50% of the animal's lifespan, did not occur in both sexes, and occurred only at levels that were several-fold above human exposures, it was determined that this factor should not preclude approval of Victoza.²⁹ But, to further study this concern, the sponsor was required to conduct longer term post-marketing studies on the incidence of thyroid cancer and medullary thyroid carcinoma in patients using Victoza.³⁰

Although you do not discuss the issue further, this point on the unknown human relevance is reflected later in the Petition when you state the following regarding the primary Pharmacology and Toxicology review:

This reviewer's [Dr. Parola's] conclusion of "not approvable" was related to unresolved toxicology issues, most importantly the unknown relevance to humans of the liraglutide-induced thyroid C-cell tumors seen in rats and mice at clinically relevant exposures. The reviewer was also concerned by the use of lower concentrations of liraglutide in nonclinical formulations in repeat-dose studies that might have underestimated exposure.³¹

As indicated above, we agree with the first statement that the most important unresolved toxicology issue was the unknown human relevance of liraglutide-induced thyroid C-cell tumors in rats and mice at clinically relevant exposure. We do not agree, however, with your second statement. The reviewer's concern about the dosing formulation was that the lower concentration of Victoza in the dosing formulation used in nonclinical studies compared to the marketed formulation may have underestimated local toxicity due to the high concentration of drug at or near the injection site. Liraglutide-induced thyroid C-cell tumors in rodents are related to systemic drug exposure, which was adequately evaluated in rodent carcinogenicity studies.

In the Petition, you also cite Dr. Paul Brown's memorandum,³² in which he states that the tumor findings "are significant enough to warrant further evaluation of risk" (Petition at 23). You also quote his statements in which he notes that ECAC agreed that the applicant had not shown convincingly that the tumor findings were irrelevant to humans and that "it appears possible that at least a segment of the population could be at increased risk" (Id.). Dr. Brown's review summarized the carcinogenicity issue described in detail in the primary and secondary pharmacology and toxicology reviews. He did not provide a definitive recommendation for or against approval, but rather provided several options for how the application might be handled and what additional information might be helpful in further assessing the risk.³³

²⁹ Id.

³⁰ See FDA Jan. 25, 2010 approval letter, *supra* note 6.

³¹ Petition at 23 (you also reference Dr. Karen Davis-Bruno's agreement with Dr. Parola's assessment).

³² Petition at 23 and note 69.

³³ See Dr. Paul Brown, Tertiary Pharmacology/Toxicology Review, May 23, 2008, at 3, available at

In the Petition, you also state that FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) agreed that it could not rule out the thyroid as a possible target organ for neoplasm induction in people.³⁴ You state that 12 committee members, including both thyroid cancer experts, voted "no" on the question of whether the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans" (Petition at 1). The Agency considered the EMDAC vote and comments and concluded that this safety issue could be addressed through labeling. The Agency also required postmarketing studies to assess the signal of a serious risk, as discussed in more detail in section II.F.1 of this response.

In the Petition, you also state that Dr. Rosebraugh found the lack of thyroid C-cell lesions in monkeys reassuring, even though monkeys were treated for only 5 percent of their life span and the numbers tested were very small (Petition at 26 and note 80). You then state that because the power to detect cancer in the monkey toxicity studies was much lower than the rodent studies, a negative response is not meaningful (Id.). We believe you have mischaracterized Dr. Rosebraugh's review when you describe his finding as "reassuring." In his review, Dr. Rosebraugh states that the results of the monkey study must be viewed with caution as GLP-1 receptors also have not been demonstrated in monkey thyroid tissue, and there were a limited number of animals, limited life-time exposure and immunogenic response in monkeys that may have neutralized the effects in monkeys.³⁵

You also state that Dr. Rosebraugh, to justify his recommendation, used the argument that FDA has previously approved a drug that caused cancer in carcinogenicity studies (pioglitazone; bladder cancer), a drug that "continues to receive support by practicing physicians" (Petition at 26). Your phrasing, once again, mischaracterizes Dr. Rosebraugh's review, which is actually emphasizing the distinction between these two drugs. His review on this point states:

Medullary thyroid carcinoma is a very rare tumor with approximately 600 cases per year. Since this is a very rare occurrence, it is highly unlikely that any clinical trial will ever answer the question of whether liraglutide increases the risk of this cancer. I also note that we do not have a signal of malignancy in the database, unlike other drugs such as pioglitazone where despite only having a relative small exposure, there was a signal for bladder cancer in the application database and again in one published clinical trial, yet it continues to receive support by practicing physicians.³⁶

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf; see also Dr. Rosebraugh's Summary, Jan. 25, 2010, at 6, *supra* note 28.

³⁴ The April 2, 2009, EDMAC meeting focused on Victoza's cardiovascular safety and the thyroid C-cell tumor data. The EDMAC was asked to vote on specific questions pertaining to these issues.

³⁵ See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 8, *supra* note 28.

³⁶ Id. at 14.

With respect to the points you make on the data from the literature regarding evidence of GLP-1 binding to human thyroid tissue (Petition at 29), the rationale for FDA's opinions and decisions are discussed in the pharmacology/toxicology review.³⁷ Specifically, the article by Körner et al. (Petition, note 94) was referenced in the pharmacology/toxicology review, and the articles referenced in Petition notes 95, 96, and 97 were published in 2011 and 2012, after Victoza was approved.

In the Petition, you also state that based on data generated by your Health Research Group analyzing cases from the FDA Adverse Event Reporting System (FAERS) database, "it appears that the two FDA-approved GLP-1 agonists (liraglutide and exenatide) share the property of increasing cancer risk" (Petition at 30). This conclusion is not supported by the data presented because reporting bias may account for your findings. See section II.F.2 of this response, which discusses the limitations of the FAERS database.

In addition, Dr. Mahoney's statements regarding thyroid C-cell tumors that you cite in the Petition are direct quotes from the clinical safety review and include the primary recommendations of the original clinical safety review of Victoza (Petition at 24). All of the findings and recommendations were carefully considered during the NDA review. You do not raise any new safety issues or concerns regarding thyroid C-cell tumors.

In sum, the risk of potential Victoza-associated thyroid toxicity is presently addressed by product labeling and a REMS. As discussed above, the approved labeling for Victoza includes a boxed warning on the risk of thyroid C-cell tumors based on results from carcinogenicity studies of Victoza in mice and rats, and the unknown human relevance of liraglutide-induced C-cell tumors in mice and rats.³⁸ We believe the current boxed warning for Victoza is adequate, and the Agency will continue to monitor for any adverse reports of rare thyroid cancers. In the following sections, we discuss in more detail the additional points you raise in the Petition related to thyroid carcinogenicity and toxicity.

a. Calcitonin Levels

In the Petition, you state that calcitonin is a 32 amino acid polypeptide synthesized mainly in thyroid C-cells and its accurate measurement is an important screening tool for thyroid C-cell tumors because they secrete calcitonin at above normal levels (Petition at 12).

We agree that the significance of calcitonin levels in relation to Victoza use is calcitonin's utility in detecting thyroid C-cell tumors or medullary thyroid cancer. We

³⁷ See Pharmacology/Toxicology Reviews, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000TOC.cfm.

³⁸ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

disagree, however, with your statement that it is impossible to know what those calcitonin levels actually were in the subjects enrolled in the Victoza clinical trials (Petition at 12-13). In support of your statement, you say that there was no description or validation of the calcitonin assay used and that the assay used in the trials may have underestimated the risk for patients by showing that calcitonin values falling into the “gray area” between 10 and 20 nanograms per liters (ng/L) can vary by assay. Despite the reference you provide in the Petition (Petition at 13, note 35), we disagree that the assay sensitivity is of significant concern in assessing calcitonin values in patients taking Victoza. Calcitonin values in the range of 10 ng/L to 20 ng/L are not very useful in predicting medullary thyroid cancer. Data suggest that the concern for medullary thyroid cancer does not become material until values reach much higher levels. Thus, depending on the case-series, calcitonin values exceeding 30 to 50 ng/L increase the likelihood of medullary thyroid cancer, and values exceeding 100 ng/L are highly predictive of cancer.³⁹ Accordingly, we do not believe that the cutoff value of calcitonin for which you have expressed concern is clinically significant in terms of predicting medullary thyroid cancer. Therefore, the point you make on assay sensitivity is moot. Moreover, we note that in the Victoza NDA, there were few patients with calcitonin values greater than 20 ng/L.⁴⁰ Thus, calcitonin values in the “gray area” did not substantially contribute to the clinical safety profile of Victoza.

In support of your statement, you also state that there was no presentation of individual arithmetic data (as opposed to log transformation of data to produce geometric means) (Petition at 13). We disagree. In the original clinical safety review, the clinical safety reviewer carefully considered not only analyses of central tendency (i.e., median/mean) as you discuss (Petition at 15), but also outlier analyses that included critical review of data from individual subjects with higher calcitonin values.⁴¹ These outlier analyses were not affected by lack of presentation of individual arithmetic data (i.e., the statistical methodology) because review of these data was based on careful consideration of individual patient narratives and laboratory data.⁴²

You state that in spite of the use of the sponsor’s inappropriate use of geometric means for presenting the data on calcitonin levels, the clinical reviewer was able to discover that, by weeks 26 and 28, there was a dose-dependent increase in the percent of women who had a shift in their calcitonin levels from below the lower limit of quantitation to within the range of quantitation while receiving Victoza (Petition at 15). You also quote Dr. Mahoney’s finding that “[t]he percentage of women who exhibited this shift [in

³⁹ Iacobone M et al. Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002; 26:886-890.

⁴⁰ See Dr. Mary Parks, Summary Review for Regulatory Action, Jan. 22, 2010, at 30, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000sumr.pdf.

⁴¹ See Clinical Safety Reviews, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P1.pdf.

⁴² Id.

calcitonin levels] was numerically higher for each of the liraglutide dose groups than for either placebo or active comparator” (Petition at 15 and note 37). However, later in the Petition on the issue of C-cell tumor risk, you also quote Dr. Parks’ opinion that the calcitonin analyses were exploratory and clinical relevance was “highly questionable” (Petition at 27). You suggest she felt that the gastrointestinal symptoms could have influenced the investigators to suspect that these subjects were taking Victoza and resulted in more monitoring of them since investigators would be more concerned that someone taking Victoza was at more risk for C-cell tumors (Petition at 27 and note 91). Rather than focusing on selected quotes, the more comprehensive discussion of the risks and benefits in the review should be considered. For example, the following excerpt from Dr. Parks’ memorandum puts these statements in context:

Dr. Mahoney presented the percentage of patients who had any upward shift in calcitonin levels from baseline to Weeks 26/28 in the 5 Phase 3 trials. She noted a dose-dependent increase in women but not in men, although the highest percentage of upward shift occurred at the 1.8 mg dose in both genders (Table 7.1.3.3.2.4.2 of Dr. Mahoney’s review). Similar trends of increasing calcitonin levels in the liraglutide groups versus comparators are noted in different analyses, including a repeated measures analysis performed by the applicant. In this analysis (See Table 7.1.3.3.2.4.5 from Dr. Mahoney’s review), the LS Mean calcitonins were higher in the liraglutide groups than active control or placebo at Week 12, and higher than placebo at Week 26. The relative difference between liraglutide and the comparators were accompanied by significant p-values at Week 12. At Week 24, the relative differences between the 3 liraglutide doses and placebo were significant, as was the difference between active control and placebo ($p < 0.05$). Not only should these analyses be considered exploratory, but the clinical relevance of these findings is highly questionable given that the majority of mean calcitonins are below 1.0 ng/L with a few hovering around 1.0 ng/L, within the normal reference range for both genders.⁴³

In the Petition, you reference Dr. Rosebraugh’s review of the Victoza NDA on the issue of thyroid cancer and calcitonin levels (Petition at 25). You state that Dr. Rosebraugh disregarded the calcitonin level shift upward with an increased dose of Victoza.⁴⁴ We believe that these selected comments from his review should be considered in context. As stated in Dr. Rosebraugh’s review, he did not disregard upward shifts, but placed them in the context of the values never exceeding normal and probably being within the range that may be expected for the variability of a test being used close to the level of quantification (LOQ). A more detailed discussion of this point is set forth in Dr. Rosebraugh’s review.⁴⁵

⁴³ See Dr. Parks’ Summary, Jan. 22, 2010, at 29, *supra* note 40.

⁴⁴ Petition at 25. In the Petition, you also state that Dr. Rosebraugh objected to routine screening of calcitonin or ultrasonography in patients who would be treated with Victoza (Petition at 25). We still do not believe that ultrasonography screening should be required as it could lead to unnecessary thyroidectomies.

⁴⁵ See Dr. Rosebraugh’s Summary, Jan. 25, 2010, *supra* note 28.

You also say that “[t]he FDA Liraglutide Cross-Discipline Team leader had stated that ‘patients in all treatment arms [in the liraglutide clinical trials] underwent routine calcitonin measurements.’ As a result, ‘almost all of these cancers ... were discovered at surgery that was prompted by routine protocol-specified calcitonin or ultrasound screening.’ Yet liraglutide was approved with no requirement for health professionals to monitor calcitonin” (Petition at 30). We believe this statement is misleading. The cancers discussed here were not medullary thyroid cancers, but rather were non-C-cell thyroid cancers for which calcitonin measurement is not useful. Therefore, for the reasons explained above, we do not share your concerns with the data regarding calcitonin levels, which the Agency carefully considered in its review of the Victoza NDA.⁴⁶

b. Thyroid Carcinoma/Medullary Thyroid Cancer

In the Petition, you state that medullary thyroid carcinoma (a form of thyroid cancer that originates in the C-cells) was diagnosed in a single comparator-treated subject, who evidently had this condition prior to enrollment.⁴⁷

While your statement is factually correct, this case occurred in a comparator-treated patient (i.e., the patient was not receiving Victoza therapy) and was presumably present pre-treatment because the baseline calcitonin level exceeded 100 ng/L. As noted, depending on the case-series, calcitonin values exceeding 30 to 50 ng/L increase the likelihood of medullary thyroid cancer, and values exceeding 100 ng/L are highly predictive of cancer.⁴⁸

You also state that Dr. Rosebraugh “took comfort” from knowing that the rodent malignant tumors were “very few in number,” in spite of the fact that, for a very rare tumor, the presence of a few tumors is an important signal (Petition at 25 and note 78). The following excerpt regarding this issue from Dr. Rosebraugh’s review places your representation of this statement in proper context:

⁴⁶ You state that in June 2011, FDA issued an alert and the sponsor issued a “Dear Healthcare Provider” (DHCP) letter warning of the risk of C-cell tumors in patients using Victoza, but note that there is still nothing in the Victoza labeling regarding the monitoring of calcitonin levels in patients treated with this drug (Petition at 30). However, in this case, FDA did not issue a safety alert. When a DHCP letter is issued, a copy is sent to MedWatch, and MedWatch posts the letter. This posting reflected the additional DHCP letter we required after the January 2011 REMS assessment.

⁴⁷ Petition at 18. You also state that Dr. Rosebraugh disregarded the four-fold excess of thyroid tumors in liraglutide-treated subjects (Petition at 25). We did not disregard this finding, but rather we considered it in the proper context that the concern with Victoza use was its unknown potential in regard to medullary thyroid cancer. The imbalance of reports of thyroid cancer noted in the clinical trials that you are referring to was for papillary thyroid cancer, and is a different type of cancer than medullary thyroid cancer.

⁴⁸ Iacobone M et al., Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002; 26:886-890.

I am struck that the actual malignant tumors themselves (as opposed to non-malignant tumors or focal hyperplasia) in rodents were very few in number, were not detected until treatment of over 50% of the animal's lifespan, did not occur in both sexes, and occurred only at levels that were several-fold above human exposures.⁴⁹

In the Petition, you also say that Dr. Rosebraugh was incorrect in stating that “even the rodent models did not have carcinomas above baseline rates at doses approximating human exposure” (Petition at 25). You state that “in fact, male rats had statistically increased levels of thyroid carcinomas at 0.5 times the expected human exposure and female rats had statistically increased levels of thyroid carcinomas at twice the expected human exposure, rates higher than both concurrent and historical controls” (Id., referencing Table 6). We disagree with your assessment of Dr. Rosebraugh's statement.⁵⁰ His statement was in regard to powering a clinical study and effect size that may be expected if Victoza truly did cause medullary thyroid cancer based on animal studies. However, because of the small increase of medullary thyroid cancer demonstrated in the animal studies, it would probably be infeasible to conduct a trial should Victoza have a carcinogenic effect. In the Petition, you speculate that increased frequency as seen in rats and mice may make such a trial feasible. We do not think, however, it is possible to conduct a clinical trial as the tumors are too rare, which would require a trial of infeasible size. Below is the comment from Dr. Rosebraugh's review, which explains this point.

Dr. Joffe has a very thorough review of the likelihood that additional clinical data would feasibly define human risk. As the table below from his review (page 59) demonstrates, given the rarity of the tumor, there would have to be at a minimum 100-fold increase in the incidence of the cancer for detection. This seems highly unlikely (even the rodent models did not have carcinomas above baseline rates at doses approximating human exposures) and also indicates that this is not likely a question to be answered by a clinical trial.⁵¹

Rodent studies would include mice (which clearly did not have a statistical or baseline rate increase at clinically relevant exposures) and rats. Table 7 from the Petition (Petition at 9) demonstrates that “statistical significance” for carcinoma incidence is only achieved in male rats receiving 0.75 mg/kg (kilogram), which translates to 8X human exposure. Female rats did not have “statistical significance” for carcinoma incidence at any dose.

Dr. Rosebraugh concluded the following regarding the animal signal for carcinoma:

⁴⁹ See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 14, *supra* note 28.

⁵⁰ We also believe you may be confusing several topics with your assertion regarding “statistically increased levels of thyroid carcinomas.” You appear to be confusing comparing carcinoma rates and adenoma rates (non-cancerous but considered by some to be pre-cancerous) and combining carcinoma and adenoma.

⁵¹ See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 11, *supra* note 28.

I am also cognizant that this is not the first time the agency has had to face an issue where a drug has caused cancer in both sexes of two different rodent species. Rat or/and mouse studies for statins were noted to cause liver carcinoma with various agents. Simvastatin, an early but not the first in class statin, caused hepatic carcinoma in mice (4-8x human exposure-both sexes) and rats (15-25x human exposure-both sexes) at human exposure multiples similar to those seen for MTC [medullary thyroid cancer] in rodents with liraglutide. I also note that lovastatin, the first approved statin caused liver carcinoma in both sexes in mice, but only in male rats, yet this seemingly safer pre-clinical profile finding did not preclude the approval of simvastatin which seemed to have a stronger signal causing hepatic carcinoma in rats in both sexes. While we approved these medications and were willing to tolerate the unknown risk because of the clinical benefit we felt they may have, it wasn't until years later that the mechanism was defined to demonstrate that this effect did not have relevance to humans.⁵²

In sum, as reflected in Dr. Rosebraugh's review, it was determined that, although preclinical rodent studies demonstrated C-cell tumor findings in rodents at clinically relevant doses, additional preclinical data would not resolve the uncertainty of the relevance of rodent C-cell tumor findings to humans. And, moreover, given the rarity of medullary thyroid cancer, it was unlikely that any clinical trial would be able to determine whether Victoza increased the risk of this cancer.⁵³

c. Papillary Thyroid Cancer/Human C-Cell Hyperplasia

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss papillary thyroid cancer and human C-cell hyperplasia (Petition at 16-18 and notes 38-42). These are findings that we carefully considered during the NDA review. You do not raise any new safety concerns related to these issues.⁵⁴

2. *Major Adverse Cardiovascular Events (MACE)*

In the Petition, you state that an inadequately evaluated risk for MACE was cited in the Victoza NDA and is one of six serious safety issues that should have precluded approval of Victoza (Petition at 28). You also state that Victoza could increase major cardiovascular adverse events to which diabetics are already at an increased risk (Petition at 30). In support of your position, you cite statements made by members of EMDAC for Victoza that raised concerns about the cardiovascular risk of Victoza (Petition at 19 and notes 46-50). You also reference statements made by reviewers in recommending for or against approval of the Victoza NDA related to the cardiovascular risks (Petition at 24 and 27).

⁵² Id. at 15.

⁵³ Id. at 14.

⁵⁴ Your discussions on calcitonin values are not relevant to the discussion on papillary thyroid cancer (Petition at 16).

As explained below, we disagree that the concerns regarding MACE should have precluded approval of Victoza.

In the Petition, you cite Dr. Mahoney's clinical safety review as not recommending approval of Victoza at this time, in part because there was "inadequate data to assess the risk of MACE in humans" (Petition at 24 and note 70). Dr. Mahoney's statements are direct quotes from the clinical safety review and include the primary recommendations of the original clinical safety review of Victoza (Petition at 24). All of the findings and recommendations were carefully considered during the NDA review. You do not raise any new safety issues or concerns regarding MACE.

You also state that Dr. Rosebraugh was reassured from the analysis of the data available that Victoza "will not have a negative cardiovascular impact" (Petition at 24). You say that Dr. Rosebraugh's opinion contradicted that of FDA's clinical safety reviewer, Dr. Mahoney, who had noted that the studies had not been designed to be combined for meta-analysis, the studies were done without prospectively designed adjudication of cardiovascular events, and patients were specifically excluded from clinical trials.⁵⁵ We note that the opinions of the reviewers are described in the respective reviews and all such opinions and other factors are considered in reaching the overall decision to approve a drug. With respect to your reference to Dr. Mahoney's statement that the studies had not been designed to be combined for meta-analysis, Dr. Rosebraugh also made observation in his review regarding the limitations of the data, the reasons behind the limitations, and his conclusions.⁵⁶

We recommend that Dr. Rosebraugh's review of Victoza be considered in its entirety, in particular, the points he makes on the issue of cardiovascular safety. In his review, Dr. Rosebraugh points out that while it was already known that sulfonylurea drugs may increase cardiovascular mortality, there were increasing concerns that other antidiabetic drugs may also increase cardiovascular events.⁵⁷ As a consequence, in December 2008, FDA issued a guidance that recommends that glycemic control agents for type 2 diabetes coming before the Agency should have some type of screening preapproval cardiovascular assessment (step one), with further, definitive postapproval testing (step two) when indicated by the results of the preapproval assessment (the diabetes cardiovascular guidance). The diabetes cardiovascular guidance details these assessments.⁵⁸ As part of the Victoza NDA review, it was determined that although

⁵⁵ Petition at 24-25. You state that Dr. Rosebraugh based his conclusions, in part, on the vote of EDMAC, which thought that there were enough cardiovascular safety data to allow marketing, even though both cardiologists on the committee and the biostatistician on the committee disagreed (Id.). We emphasize that comments from all panel members are considered in the deliberations.

⁵⁶ See Dr. Rosebraugh's Summary, Jan. 25, 2010, at 12, *supra* note 28.

⁵⁷ Id. at 2.

⁵⁸ Guidance for industry on *Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, December 2008, Clinical/Medical.

Victoza was not in total alignment with the requirements of the diabetes cardiovascular guidance, Victoza seemed to, in spirit, fulfill the “step-one” screening preapproval cardiovascular assessment and gave some reassurance that Victoza would not have a negative cardiovascular impact (where for every analysis conducted there was not an excess risk observed in which the confidence interval excluded 1.0). The Victoza NDA was presented at a subsequent EDMAC meeting where the majority of the panel voted that Victoza had fulfilled the step-one requirements, which allowed Victoza to be marketed while awaiting the results of a definitive study. We also refer you to Dr. Parks’ review, which has a comprehensive discussion on the cardiovascular safety evaluation of Victoza.⁵⁹

You reference certain comments made in Dr. Parks’ review related to this issue. You say that Dr. Parks pointed out that the diabetes cardiovascular guidance is just that, a guidance and not a regulatory requirement. You quote Dr. Parks as stating, “[i]n my opinion, this NDA has sufficiently demonstrated an acceptable CV [cardiovascular] risk profile premarketing” (Petition at 27 and note 90). However, the Petition does not explain the basis for Dr. Parks’ statements. She explains that it would have been an *unjust* requirement on FDA’s part to mandate that the three NDAs [which included Victoza] under review during this time period comply with every aspect of this new guidance. The Phase 2 and 3 trials designed to support the approval of these drugs were completed prior to December 2008, and these programs were conducted and submitted to the FDA in advance of the issuance of the guidance.

We also note that the two-sentence summary in the Petition does not fully reflect Dr. Parks’ four-page assessment of the cardiovascular risks and how she weighed the cardiovascular safety data in her final recommendation for approval. We refer you to Dr. Parks’ review for a more detailed discussion on this issue and on the limitations of applying the diabetes cardiovascular guidance to the Victoza NDA review.⁶⁰

Dr. Parks’ review goes further to summarize the findings from FDA’s analyses of an agreed-upon collection of cardiovascular endpoints referred to as FDA Custom MACE endpoints. Tables 8.1 and 8.2 of her memo summarize these analyses, and these tables are followed by a more lengthy discussion of her interpretation of the findings, which ultimately led to her statement you quote in the Petition.⁶¹

In addition, as indicated in Dr. Joffe’s review, he concurred with the majority vote of the EDMAC panel that Victoza had fulfilled the spirit of the diabetes cardiovascular guidance.⁶² He also noted that there were too few placebo comparator events to permit a

⁵⁹ See Dr. Parks’ Summary, Jan. 22, 2010, at 24-27, *supra* note 40.

⁶⁰ Id. at 24-25.

⁶¹ Id. at 25-28.

⁶² See Dr. Hylton Joffe, Cross-Discipline Team Leader Review, Oct. 14, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000crossr.pdf; see also Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes,

meaningful comparison to placebo and stated that a definitive cardiovascular safety trial should be required.⁶³ Thus, it was determined that there were enough cardiovascular data to approve Victoza, but that postmarketing cardiovascular studies may be required.

Currently, a trial is underway that is examining the long-term effect of Victoza on cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke as primary outcomes based on an FDA requirement for a cardiovascular outcomes trial for all new antidiabetic agents.⁶⁴ This is a multinational, multicenter, randomized, double-blind, placebo-controlled phase 3 efficacy/safety study that began recruiting patients with type 2 diabetes mellitus in 2010. These patients are being randomized to receive Victoza or placebo in a 1:1 ratio and will be monitored for a period of 5 years to determine the cardiovascular safety of long-term treatment with Victoza.

In addition, a small phase 2 trial is planned to investigate the effect of Victoza on cardiac function in type 2 diabetes mellitus patients with co-morbid congestive heart failure.⁶⁵ This randomized study will compare left ventricle function and functional reserve capacity with tissue Doppler echocardiography in a longitudinal manner over an 18-week period comparing two groups: (1) Victoza and metformin; and (2) glimepiride and metformin.

In sum, you do not raise in the Petition any new safety issues or concerns regarding cardiovascular risks associated with the use of Victoza. We will monitor the results of the studies on this issue and take further action if appropriate.

3. *Pancreatitis and Pancreatic Cancer*

a. Pancreatitis

In the Petition, you quote findings from the clinical safety review for the Victoza NDA regarding the risk of pancreatitis associated with the use of Victoza (Petition at 20-21 and note 54). The Agency carefully considered these findings during the NDA review. You do not raise any new safety concerns related to this issue. We note that at the time of initial approval of Victoza, the risk of pancreatitis was addressed in physician and patient labeling and a required communication plan as part of a REMS.⁶⁶ The Agency also

December 2008, Clinical/Medical, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>.

⁶³ See Dr. Joffe's Review, Oct. 14, 2009, *supra* note 62.

⁶⁴ Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – a long term evaluation (LEADER). See <http://www.clinicaltrials.gov/ct2/show/NCT01179048>.

⁶⁵ Liraglutide and heart failure in type 2 diabetes, <http://www.clinicaltrials.gov/ct2/show/NCT01425580>.

⁶⁶ See FDA May 18, 2011 approval letter, *supra* note 7; see also section II.F of this response for a more detailed discussion of the actions FDA has taken to address the safety concerns of Victoza. In addition, the incidence of pancreatitis in Victoza-treated patients versus comparators is being assessed in the LEADER

required postmarketing studies to assess the signal of a serious risk of acute pancreatitis, including necrotizing pancreatitis. In addition, we requested 15-day alert and special interest reports for cases of pancreatitis.

In support of your position that use of Victoza increases the risk of pancreatitis, you cite data from the Victoza NDA, including statements made by Dr. Rosebraugh concerning pancreatitis. You also reference scientific literature, including two human case studies. You reference your research in FDA's AERS database for the period from February 2010 through September 31, 2011 (Petition at 30-31). And, you cite FDA's June 13, 2011, warning to health care professionals to be alert to the risks of acute pancreatitis associated with the use of Victoza (Petition at 32 and note 110).

You say that there was a 3.7-fold increased risk of pancreatitis in subjects taking Victoza compared to the risk in those using comparator drugs during the randomized clinical trials of Victoza (Petition at 30). You also state that toxicity to the pancreas was also seen in preclinical studies in rats, mice, and monkeys (Id.).

Prior to the January 2010 approval of Victoza, a signal for an increased risk of pancreatitis had been observed in post-marketing adverse event reporting for two approved GLP-1 based drugs (Byetta [exenatide] and Januvia [sitagliptin]). Therefore, pancreatitis was considered an adverse event of special interest in the Victoza NDA review.

Non-clinical studies conducted with liraglutide did not demonstrate evidence of overt pancreatic toxicity or pancreatitis in standard toxicology studies, nor in rats and mice treated for up to 2 years (life-span), including doses that greatly exceeded clinical exposure.

A numeric imbalance in cases of pancreatitis, not favoring Victoza, was observed in the pre-approval clinical trials. The significance of this finding is unclear given the small numbers (7 cases, or 2.2 cases per 1000 patient-years, among Victoza-treated patients and 1 case, or 0.6 cases per 1000 patient-years, among comparator-treated patients); however, this imbalance was noted in the WARNINGS AND PRECAUTIONS section of product labeling at the time of approval. In addition, a REMS was required at the time of approval, including a required communication plan, to ensure that the benefits of Victoza outweighed the serious risk of pancreatitis. A REMS assessment plan, including an assessment of health care providers' awareness of the need for prompt evaluation of patients who develop symptoms suggestive of pancreatitis and an evaluation of health care providers' identification and treatment of acute pancreatitis after initiation of Victoza, also was required.⁶⁷ With the Victoza approval, FDA also required a nonclinical

postmarketing required study. Although the LEADER study is primarily designed to evaluate cardiovascular events, LEADER is assessing multiple safety issues of interest, including pancreatitis. See <http://www.clinicaltrials.gov/ct2/show/NCT01179048>.

⁶⁷ See FDA Jan. 25, 2010 approval letter, *supra* note 6.

postmarketing study on pancreatitis, which has been completed.⁶⁸ This study evaluated the effects of 3 months of liraglutide treatment on the exocrine pancreas in a rat model of insulin-resistant type 2 diabetes mellitus, and showed liraglutide did not induce changes in the pancreas consistent with pancreatitis.

Public communications announcing the approval of Victoza cautioned patients and prescribers about a potential increased risk of pancreatitis associated with the use of Victoza.⁶⁹

In the Petition, you also say that Dr. Rosebraugh stated in his review that even if one assumes that this class of drugs does cause pancreatitis, FDA would not remove them from the market, but instead would “encourage awareness and early diagnosis” (Petition at 26). You also quote Dr. Rosebraugh as saying “I do not think that we have evidence that liraglutide is any worse [an] offender in this regard than the other agents” (Id. and note 83). Dr. Rosebraugh did make these statements, but not without also expressing his concerns regarding pancreatitis. In his review, Dr. Rosebraugh states:

For the GLP-1 analogues, it is particularly important that clinicians have heightened awareness of the possibility of pancreatitis as these drugs are associated with high rates of nausea and vomiting, which may mask the diagnosis of pancreatitis if physicians are not vigilant in regard to a complete differential diagnosis.

Liraglutide has increased my concern in this regard, as they have a numeric imbalance of pancreatitis cases. . . . There were too few cases of pancreatitis in the safety database, and this small number of events is too fragile to determine if there is any causative effect, or to determine if there is a greater risk of pancreatitis with liraglutide compared to other diabetic drugs that work through the incretin system. However, given our prior concerns with drugs in this class and the new animal data reported in the literature that I mentioned earlier, this cannot be minimized or dismissed. I believe that future trials should include prospective evaluation for pancreatitis with amylase/lipase measurement routinely and also for cases where subjects have nausea and vomiting that occurs outside of routine measurements. . . . Our concern regarding pancreatitis, and the findings from the liraglutide database, should be relayed in the label.⁷⁰

FDA has continued to update the label appropriately as new safety data emerges. On November 28, 2012, the applicant submitted a prior approval supplement to update the WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections of the labeling to include additional information about pancreatitis based on spontaneous

⁶⁸ Id. at 4.

⁶⁹ See REMS available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000rems.pdf; see also FDA News Release, *FDA Approves New Treatment for Type 2 Diabetes*, Jan. 25, 2010, available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm198638.htm>.

⁷⁰ See Dr. Rosebraugh’s Summary, Jan. 25, 2010, at 13, *supra* note 28.

adverse event reports. This supplement was approved on April 16, 2013. The WARNINGS AND PRECAUTIONS section of the Victoza labeling now includes the following language:

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza. After initiation of Victoza, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, Victoza should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, Victoza should not be restarted. Consider antidiabetic therapies other than Victoza in patients with a history of pancreatitis.⁷¹

This language is consistent with the labeling for the other approved GLP-1 receptor agonists, Byetta⁷² and Bydureon.⁷³

The two case reports referenced in the Petition may point to a role by Victoza in contributing to pancreatitis based on the time of presentation of pancreatitis; however, both cases are confounded by the patients' medical histories and the use of concomitant medications. A postmarketing case report also lists several confounding factors that do not present a clear picture with regard to Victoza and pancreatitis.⁷⁴ There are inherent limitations to the evaluation of spontaneous adverse event reporting of pancreatitis with anti-diabetic drugs because of the high background rate of pancreatitis in the diabetic population, and because the disease (diabetes) and its comorbidities (obesity; concomitant medications) contribute to the adverse event. These factors preclude a determination of causality.

There was no evidence at the time of approval of Victoza, and there has been no compelling new evidence provided, that supports that either pancreatitis is so serious in proportion to potential benefit that it is essential that it be considered in assessing the risks and benefits of using the drug, or that pancreatitis could be prevented or reduced in frequency or severity by appropriate use of the drug. However, the Agency will continue

⁷¹ See labeling for Victoza approved on Apr. 16, 2013, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

⁷² See labeling for Byetta, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021773s029s030lbl.pdf.

⁷³ See labeling for Bydureon, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbl.pdf.

⁷⁴ Famularo G, Gasbarrone L, Minisola G. Pancreatitis during treatment with liraglutide. *JOP*. 2012; 13:540-541.

to evaluate pancreatitis associated with Victoza use to determine if further regulatory action is required.⁷⁵

b. Pancreatic Cancer

The Petition states that Victoza increases the risk of pancreatic cancer and cites AERS data to support this finding. Pancreatic cancer is characterized by the National Cancer Institute as a common cancer, i.e., occurring at a rate of greater than 35,000 new cases per year.⁷⁶ Analysis of drug-related risk utilizing FAERS data does not provide strong evidence of risk when the adverse event (i.e., pancreatic cancer) occurs commonly in the background untreated population and has a long latency period. Any causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time.

In our review of 49 unique cases recovered from FAERS we found no new evidence regarding the risk of pancreatic carcinoma in association with the use of Victoza that would support any changes to the current approved labeling. Therefore, any suspicion of causal association between exposure to Victoza and pancreatic cancer is indeterminate at this time. We will continue to monitor and to review available safety information related to pancreatic cancer in patients who are receiving Victoza.

4. Thyroid Neoplasm and Other Serious Adverse Events of Neoplasm

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss various types of thyroid neoplasm adverse events (Petition at 17-18 and note 42). These are findings that the Agency carefully considered during the NDA review. You do not raise any new safety concerns related to this issue.

In the Petition, you also cite the clinical safety review on the rates of serious adverse events of neoplasm (Petition at 21 and note 55) and state that “the clinical reviewer found a rate for all serious neoplastic events of 12.3 per 1,000 patient years in liraglutide-treated subjects versus 8.1 events per 1,000 patient years in control subjects with no particular cancer-cell type predominating” (Id.). You say that a possible explanation for this difference in neoplastic events was thought to lie in epidemiologic data that suggested an association between higher insulin levels and increased malignancy risk (Petition at 21 and note 56).

As noted in the clinical safety review, “[t]here have been recent concerns, based on epidemiologic data (some of which are conflicting), of a possible association between insulin and increased risk of malignancy. Liraglutide causes an increase in insulin levels.

⁷⁵ See FDA’s Web site on Postmarket Drug and Biologic Safety Evaluations, available at http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/ucm204091.htm#Postmarketing_Summaries.

⁷⁶ Common Cancer Types, National Cancer Institute, available at <http://www.cancer.gov/cancertopics/types/commoncancers>.

This risk should be further assessed in future trials of liraglutide.”⁷⁷ The review also stated that this issue, similar to many of these safety issues “while potentially important, can be addressed through labeling and/or future studies, and do not rise to the level of approvability issues.”⁷⁸ We also note that the incidence of malignancy in Victoza-treated patients versus comparators is being assessed in postmarketing studies.

In the Petition, you also indicate that if an individual has a preexisting lesion, treatment with GLP-1 receptor agonists may result in an increase in neoplasms (Petition at 33). Based on the data currently available, we disagree. As noted in the reviews for the Victoza NDA:

[M]ost of the events in Table 8, including the neoplasm events, were reported in only one liraglutide-treated patient and the lack of similar reported events in the comparator group may simply be related to the liraglutide group being nearly two times larger than the comparator group. Furthermore, as noted by Dr. Mahoney, 9 of the 17 serious malignant neoplasms in the liraglutide group in the original NDA and 2 of the 6 serious malignant neoplasms in the comparator group occurred within the first 6 months of treatment with study medication. This timeframe is unlikely to reflect drug-related carcinogenesis, even if the drug is a tumor promoter. When these 11 patients are excluded, the frequency of serious malignant neoplasms in the original NDA is 3.6 events per 1000 patient-years with liraglutide vs. 3.5 events per 1000 patient-years with comparator.⁷⁹

In addition, the articles you cite in the Petition do not present any concrete data that would lead to a clear conclusion regarding a possible connection between Victoza and neoplastic events (Petition at 33, notes 118 and 119). You have cited literature that we believe is not applicable.⁸⁰ Moreover, as discussed above, spontaneous adverse event reports of common cancers do not provide supporting evidence for causality when the cancer is a relatively common occurrence in the population, and spontaneous reports are of limited value in determining drug-related causality when there is a long latency period for the event such as cancer. For the common cancers, no unusual presentation was noted in the cancer or in the population in which the cancers were reported. For those cancers

⁷⁷ See Dr. Karen Mahoney, Clinical Safety Review, Aug. 6, 2009, Part 2 at 233, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf.

⁷⁸ Id.

⁷⁹ See Dr. Hylton Joffe, Cross-Discipline Team Leader Review, Dec. 3, 2009, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000crossr.pdf

⁸⁰ The review article referenced in note 118 includes both clinical and nonclinical information regarding insulin and IGF-1, which links obesity to an increased risk of cancer, i.e., the article does not apply to GLP-1 agonist therapies, and the article reference in note 119 is a published study showing exogenous and endogenous GLP-2 enhances colon carcinogenesis, but the study did not evaluate the effects of GLP-1 or GLP-1 receptor agonists (Petition at 33, notes 118 and 119).

described as rare (<35,000 cases/year in all ages),⁸¹ there was a relatively short exposure time to Victoza prior to the diagnosis of cancer.

Thus, for the reasons explained above, we disagree with your statement that concerns regarding serious neoplastic events, including pancreatic cancer, should have precluded approval of Victoza (Petition at 28). We do believe, however, that given the lack of adequate data with regard to any possible neoplastic events as a result of the use of Victoza, further vigilance and monitoring for rare cancers is warranted. As with all FDA-approved products, FDA will continue to monitor and review available safety information related to Victoza, including postmarketing reports of neoplastic events, through routine pharmacovigilance, the ongoing cardiovascular outcomes trial, and through the medullary thyroid registry.

5. Renal Toxicity/Renal Impairment

In the Petition, you indicate that use of Victoza may result in renal toxicity (Petition at 33-34). You also cite from the literature a single case of tubular necrosis potentially associated with the use of Victoza (Petition at 33-34).

As you note, “[i]n May 2011, as a result of postmarketing reports, the FDA required the addition of a new warning to the label for Victoza, stating that health care professionals and subjects need to be alert to signs of ‘acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis.’”⁸² As part of our review of the labeling supplement, which included a review of the postmarketing data, we also concluded that the Victoza labeling should include language on the postmarketing reports of dehydration, including reports of altered renal function, which are associated with the use of Victoza. In FDA’s view, this labeling update was appropriate to address the safety issues regarding renal impairment.

Based on the information currently available, it is not possible to reach any conclusions for Victoza with regard to direct renal toxicity. While we will continue to monitor and review available safety information related to Victoza, including any postmarketing reports of renal impairment, any possible relationship between the risk of renal toxicity and exposure to liraglutide is unknown presently and predisposing factors remain uncertain.

⁸¹ Common Cancer Types, National Cancer Institute, available at <http://www.cancer.gov/cancertopics/types/commoncancers>.

⁸² Petition at 22 and note 65. In the Petition, you state that most of these cases were in patients who had experienced nausea, vomiting, diarrhea or dehydration, and that “[s]ince these are common adverse events in patients taking liraglutide, it may make it difficult to promptly identify the cause” (Petition at 22). We note that the data on which the labeling updates were based were spontaneously reported postmarketing adverse event data for which it is often difficult to establish conclusively cause and effect. See section II.F.2 of this response for a more detailed discussion on the limitations of FAERS data.

In sum, the serious adverse event (renal failure) that appears to be associated with more severe gastrointestinal symptoms is appropriately addressed by physician and patient labeling and continues to be monitored in the postmarketing setting.

6. Hypersensitivity Reactions

In the Petition, you state that patients and their health care providers face unknown serious risks of hypersensitivity reactions with Victoza use — another safety issue you say should have precluded approval of the drug (Petition at 34). In support of your position, you cite a medical officer consultation report from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), which you state highlighted several safety concerns regarding the allergenicity of Victoza — noting that nearly 10 percent of liraglutide-treated subjects in the phase 3 clinical trials formed antidrug antibodies (ADA), half of which showed cross-reactivity with native GLP-1 (Petition at 34).

In the Petition, you also question whether the DPARP consultant's advice underlying the recommendation for a postmarketing study⁸³ is being followed under the 5-year epidemiological study FDA required that the applicant undertake in the approval letter for Victoza, and you express concern that the results of the study will not be known until 2016, if at all (Petition at 34). For these reasons, you state that unknown serious risks of hypersensitivity reactions remain with Victoza use (Petition at 34).

We do not believe that the risk of hypersensitivity reactions with Victoza use should have precluded approval of the drug. We have reviewed reports in the FAERS database and the medical literature for the serious hypersensitivity reactions associated with Victoza. The reports and medical literature describe a broad spectrum of hypersensitivity reactions associated with the use of Victoza. However, the majority of the cases lacked information typically needed to determine the strength of a causal relationship between a hypersensitivity event and a drug (e.g., time course to event, patient medical history, and/or concomitant medications). Also, there were no reported fatalities.

During the Victoza clinical development program, antidrug antibodies (ADA) to Victoza in patients receiving it were detected. In the four major phase 3 trials, neutralizing ADA developed in nearly 10 percent of study drug recipients with about half of these ADAs displaying cross reacting to native GLP-1. The presence of these antibodies did not appear to have a substantial impact on efficacy as there did not appear to be a treatment interaction between ADA positive status and change from baseline in hemoglobin A1c (HbA1c) at 26 weeks, the primary efficacy endpoint. In addition, neither development of neutralizing ADA to Victoza or ADA cross-reactivity with GLP-1 appeared to impact long-term glycemic control.

⁸³ In the Petition, you state that the consultant recommended a postmarketing study to address cutaneous and musculoskeletal manifestations. The consultant stated: "The outcome measures in this postmarketing immunogenicity study should also address these immune mechanisms, including appropriate historical and physical assessments of target body systems (e.g., cutaneous and musculoskeletal manifestations), measuring complement levels as an index of immune complex mediated disease, and screening hepatic transaminases and renal function tests in the setting of systemic inflammatory findings." (Petition at 34).

Moreover, there were no serious adverse events noted in relation to ADA formation, and the occurrence of hypersensitivity reactions was not associated with the presence of ADA. Although there was a trend toward increased frequency of infection and musculoskeletal disorders in the ADA positive patients, the differences were accounted for by small numerical increases in events.

Although the ADA formation did not appear to affect efficacy and no significant ADA-related safety signal was observed, the Agency has required the applicant to conduct a postmarketing clinical trial (LEADER) to, among other things, assess the long-term effects of Victoza on immunological reactions, including antibody formation, allergic reactions including those at injection sites, and immune-complex diseases as medical events of special interest.⁸⁴ Although the LEADER trial is primarily designed to evaluate cardiovascular events, we believe that due to the large trial population (9,000 subjects) and 5-year length of the study, it will provide a better assessment of the impact of ADAs on the safety and efficacy of Victoza by inclusion of appropriate evaluations for ADA.

Moreover, as a result of the temporal association between the initiation of Victoza and the onset of the reported hypersensitivity reactions, the biological plausibility of this exogenously administered protein in causing allergic reactions, and the potential for serious outcomes, FDA required the addition of *anaphylactic reactions* and *angioedema* to the WARNINGS AND PRECAUTIONS section and ADVERSE REACTIONS, *Postmarketing Experience* subsection of the Victoza labeling.⁸⁵ Also, as you state in the Petition, FDA included a statement in the Victoza labeling, under Adverse Reactions, that “Immunogenicity-related events, including urticaria, were more common among Victoza-treated patients (0.8%) than among comparator treated patients (0.4%) in clinical trials” (Petition at 34). In addition, in December 2012, FDA approved Victoza labeling changes to the prescribing information related to adverse reactions and postmarketing experience with the inclusion of two MedDRA preferred terms for allergic reaction: *rash* and *pruritus*.⁸⁶

7. Serious Hypoglycemic Events

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discusses the hypoglycemic events associated with Victoza use (Petition at 21 and note 59). These are findings that the Agency carefully considered during the NDA review.

⁸⁴ LEADER, *supra* note 65, <http://clinicaltrials.gov/ct2/show/NCT01179048>; see also FDA Jan. 25, 2010 approval letter, *supra* note 6.

⁸⁵ See labeling for Victoza at Drugs@FDA, approved Apr. 6, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s017lbl.pdf

⁸⁶ See FDA approval letter at Drugs@FDA, Dec. 13, 2012, available at http://www.accessdata.fda.gov/drugsatfda_docs/applletter/2012/022341Orig1s017ltr.pdf.

You do not raise any new safety concerns related to this issue. As the clinical reviewer noted, “the available evidence to date suggests that major hypoglycemia can occur with liraglutide, but this event is infrequent and most likely to occur with concomitant sulfonylurea use — a similar finding noted with other incretin-based therapies. The extenuating circumstances associated with isolated events of major hypoglycemia in the other treatment settings should be included in labeling.”⁸⁷ Accordingly, we believe the current labeling for Victoza appropriately contains language that states that serious hypoglycemia can occur when Victoza is used with an insulin secretagogue (e.g., a sulfonylurea) or insulin.⁸⁸

8. *Injection Site Reactions*

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss injection site reactions associated with Victoza use (Petition at 22 and note 60). The Agency carefully considered these findings during the NDA review.

You do not raise any new safety concerns related to this issue. The clinical reviewer explains that phase 3 trials included in the original NDA submission found the incidence of injection site reactions was 2.0 percent with liraglutide compared to 1.5 percent with placebo and 1.2 percent with active comparator.⁸⁹ The review notes that these differences were principally driven by the preferred terms of *injection site rash*, *injection site erythema*, and *injection site reaction*.⁹⁰ The clinical reviewer did not identify an association between anti-liraglutide antibody status and local injection site reactions. However, conclusions were limited by low event rates (most preferred terms related to injection site reactions occurred in 1 of 5 liraglutide-treated patients). There were four withdrawals due to injection site reactions in the major phase 3 trials included in the original NDA submission. None of these events was reported as serious.⁹¹

9. *Increased Heart Rate*

In the Petition, you summarize the findings of the clinical safety review for the Victoza NDA that discuss the increase in heart rate associated with Victoza use (Petition at 22 and note 61). The Agency carefully considered these findings during the NDA review.

You do not raise any new safety concerns related to this issue. We note that you do not cite in the Petition the subsequent review of this issue by FDA in Efficacy Supplements

⁸⁷ See Dr. Joffe Review, Dec. 3, 2009, at 44, *supra* note 79.

⁸⁸ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

⁸⁹ See Dr. Joffe Review, Dec. 3, 2009, at 48, *supra* note 79.

⁹⁰ *Id.*

⁹¹ *Id.*

(001, 007, and 009) submitted by the applicant, in which the clinical reviewers noted, once again, the small increase in heart rate. At this point, FDA concluded that although the significance of this finding was still unclear, labeling language regarding increased pulse should be included in the Victoza label. We approved this updated labeling language on April 6, 2012.⁹²

10. Pregnancy

In the Petition, you state your concerns with Victoza's effect on neonatal health and the potential for serious adverse effects in pregnancy (Petition at 22-23, and 37). You say that major fetal malformations were seen in animals exposed to extremely low levels of the drug (Petition at 37). You request that a pregnancy registry be established for Victoza to enable the Agency to track potential effects on human reproduction (Id.).

For the reasons explained below, we deny your request. Victoza is labeled as Pregnancy Category C based on animal data from reproductive and developmental toxicology studies conducted for drug approval in which some adverse fetal effects were noted. Pregnancy Category C is assigned to drugs if animal reproduction studies have demonstrated an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite potential risk. In the Petition, you note that fetal malformations were observed in rat and rabbit studies at exposures of Victoza that were less than the human therapeutic drug exposure from a 1.8 mg/day dose (Petition at 37). Although Victoza was associated with an increase in fetal malformations in rat and rabbit studies, Victoza did not increase the incidence of any specific fetal adverse developmental effect in a dose-dependent manner. The absence of a dose response for specific adverse fetal outcomes does not raise an increased concern for a selective effect of this drug on fetal development. Accordingly, the Victoza labeling also states that "Victoza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus" and that "Victoza has been shown to be teratogenic in rats and rabbits."⁹³ At the time of approval, there were no human data that, with the animal data noted above, signaled a safety concern that would warrant a post-marketing requirement for a pregnancy registry.

During the approval process, FDA may consider the establishment of a pregnancy exposure registry that will collect data to be analyzed in a required post-marketing study under FD&C Act section 505(o)(3) when, for example, there is a known serious risk of fetal harm or when signals of serious risk of fetal harm are detected from other information and data. This information and data could include information and data from animal reproductive/developmental studies, known structure-activity relationships, and known concerns from the pharmacological class. In addition, a pregnancy registry can

⁹² See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022341s007s009s013lbl.pdf.

⁹³ See labeling for Victoza at Drugs@FDA, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022341s018lbl.pdf.

also be required after approval for certain purposes, including those discussed above, if the Secretary becomes aware of new safety information, as defined in section 505-1(b) of the FD&C Act. A review of the safety data since the approval of Victoza has not revealed any new nonclinical or human data or information that FDA believes suggests the need for requiring a pregnancy registry under section 505(o)(3).

Monitoring adverse events from exposed Victoza pregnancies can be accomplished by annual review of the periodic safety update reports (PSURs) submitted by the applicant and review of adverse event reports submitted voluntarily to the FDA's Adverse Event Reporting System (FAERS). Although monitoring FAERS has its own limitations (see section II.F.2), if a signal of fetal toxicity were detected, the need for regulatory action could be assessed and, if deemed necessary, an observational study, such as a pregnancy registry, could be initiated to try to determine if Victoza exposure in pregnancy has human teratogenic effects.

In sum, among the 18 safety concerns you list for Victoza, you identify 6 of these concerns as safety issues that should have precluded approval of Victoza (Petition at 28). You list the following six safety issues: (1) thyroid carcinogenicity and other thyroid toxicity, (2) inadequately evaluated risk for major adverse cardiovascular events, (3) acute pancreatitis, (4) other serious neoplastic events, (5) renal toxicity, and (6) hypersensitivity reactions (Id.).

With the exception of renal toxicity,⁹⁴ all of these safety issues and concerns were identified at the time of the original NDA and were already considered in depth by FDA in coming to its conclusions on the overall risk-benefit assessment and approval of Victoza. As discussed above, these safety issues were carefully considered during the original NDA and were not overlooked or ignored during the review process. We disagree that any one of the six safety issues you list in the Petition should have precluded approval of Victoza. We also disagree that the safety concerns that you list in the Petition are grounds for immediate removal of Victoza from the market. We believe that the safety issues that you list in the Petition can be addressed through FDA-approved labeling and the approved REMS. We also have required the sponsor to undertake several FDAAA-mandated postmarketing studies and trials to assess the signals of serious risk. In addition, we have requested that the sponsor submit additional reports related to pancreatitis.

D. Risk-Benefit

On the issue of the risk-benefit analysis of Victoza, you state that Dr. Rosebraugh lists the benefits of Victoza as:

- less hypoglycemia,
- weight loss,

⁹⁴ In section II.C.5 of this response, we discuss the postmarketing reports on the renal safety findings for Victoza.

- comparable or even increased HbA1c reduction in comparison to results with other diabetes drugs, and
- the once-daily dosing schedule (Petition at 26-27 and note 85).

You also quote Dr. Rosebraugh as stating that, “[w]hile many sponsors may responsibly introduce a drug into marketing, theirs is a profit-based business and the pressures to generate revenue are strong. Also, with most classes of drugs, there are similar drugs in development from competitors which places even more pressure to generate profit before there is competition” (Petition at 27 and note 86). You state that such comments are expected from the sponsor or Wall Street, not the FDA (Petition at 27). Then you note that Dr. Rosebraugh recommended approval of Victoza.

Dr. Rosebraugh recommended approval of Victoza after consideration of all the reviews and factors present in the application process, as clearly reflected in his review.⁹⁵ We believe Dr. Rosebraugh’s comments should be considered in context. Dr. Rosebraugh’s review in its entirety provides a more comprehensive evaluation of the risk-benefit analysis of Victoza than is reflected in the selected statements in the Petition.

E. Other Potential Indications Raised in the Petition

1. Pediatric Trials

In the Petition, you state that there should not be studies for Victoza in the pediatric population because such pediatric trials expose children to a drug that FDA toxicology and clinical safety reviewers concluded should not even have been approved for adults because of unresolved safety issues.⁹⁶

Although we agreed to certain limitations on pediatric trials for Victoza, we do not agree with your assessment that no pediatric trials should be conducted. As noted in our review of the NDA:

Because of the thyroid C-cell tumor findings in rodents, the Division expressed concern with long-term exposure to liraglutide in children until more data are available. The carcinogenicity issue is less of a concern in the short-term pharmacokinetic/pharmacodynamic studies. Therefore, the Division and PeRC found it acceptable for the sponsor to proceed with the pharmacokinetic/pharmacodynamic study based on the current state-of-knowledge for liraglutide but agree that the action letter should specify the

⁹⁵ See Dr. Rosebraugh’s Summary, Jan. 25, 2010, *supra* note 28.

⁹⁶ Petition at 35. The Pediatric Research Equity Act (PREA) requires all applications (or supplements to an application) submitted under section 505 of the FD&C Act or section 351 of the Public Health Service Act (PHSA) (42 U.S.C. 262) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505B(a) of the FD&C Act (21 U.S.C. 355c(a))).

necessary needed data before the Division agrees with the conduct of longer-term studies in children.⁹⁷

In addition, the applicant requested and received a waiver for children <10 years old and a deferral for children ≥10 years old.⁹⁸ However, FDA did not believe a waiver for all children was justified; Victoza did not meet any of the three criteria of section 505B(a)(4)(A) of the FD&C Act that would justify a waiver for this older group of children.

The Victoza approval letter states that the Phase 3 study must not be initiated until at least 1 month after submission of the complete study report for postmarketing requirement 1583-5 (which was a 13-week mouse study to determine if liraglutide-induced focal C-cell hyperplasia depends on a thyroid GLP-1 receptor and rearranged-during-transfection (RET) proto-oncogene activation). FDA reviewed the applicant's submission of this postmarketing requirement and found it acceptable. Therefore, the pediatric phase 3 study has begun recruitment and currently is ongoing.

2. Antiobesity trials

In the Petition, you state that there is a concerted effort by Novo Nordisk to expand the indications for liraglutide. You state that recently published obesity trials funded by Novo Nordisk employed doses up to 3.0 mg/day — a dose 1.7 times higher than the maximum dose currently used for treatment of diabetes (Petition at 35). You also state that although there was a dose-dependent weight loss effect, there were also dose-dependent increases in gastrointestinal symptoms, especially nausea (Id.).

We cannot comment on your contention that Novo Nordisk is seeking to expand the indications for Victoza. As a general matter, it is FDA's intent to carefully review and consider any clinical data (including any adverse events) submitted to us in an NDA or supplement.

F. Labeling and Safety Alerts

1. Labeling

In the Petition, you state that you believe labeling changes are inadequate for Victoza and that labeling changes would merely delay the time until the drug must be withdrawn from the market, leaving an increasing number of patients at risk of serious harm (Petition at 36).

⁹⁷ See Dr. Joffe's Review, Dec. 3, 2009, at 55, *supra* note 79.

⁹⁸ Id. at 54. The Division and the Pediatric Review Committee (PeRC) agreed with the request, which is consistent with our approach to other non-insulin treatments for type 2 diabetes (there are too few children less than 10 years of age with type 2 diabetes; therefore, studies in this population are highly impractical) (Id.).

We disagree. The primary safety issues raised in the Petition are pancreatitis and thyroid cancer and, to a lesser extent, major adverse cardiovascular events (or MACE). At the time of initial approval of Victoza on January 25, 2010, these issues were addressed in physician labeling (including a Boxed Warning for the potential risk of medullary thyroid cancer), patient labeling, a REMS, and enhanced reporting on the part of the sponsor. Additionally, we required several FDAAA-mandated postmarketing studies and trials to assess the signals of serious risk. FDA continues to closely monitor this drug product to better understand the safety signals detected in the clinical development program, as well as monitor for potential new safety signals.

2. Safety Alerts/FAERS

In the Petition, you also state that FDA's safety alerts issued over Victoza's first year and half of marketing have not succeeded in preventing serious adverse reactions — as seen by the increase in adverse reactions in the continuing reports in the FDA's database — indicating that FDA's use of warnings is not sufficient protection (Petition at 36-37).

We disagree. The FAERS database has limitations, and it cannot be used to calculate the incidence of an adverse event in the U.S. population.

FAERS collects information about adverse events, medication errors, and product problems that were reported after the administration of approved drug and therapeutic biologic products. Specifically, applicants must report to FDA adverse drug experience information, as described in 21 CFR 314.80. The regulation defines "adverse drug experience" broadly as "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related...." 21 CFR 314.80(a). There is no certainty that the reported adverse events resulted from the use of the product of interest. For purposes of FAERS, FDA does not require that a causal relationship between a product and an event be demonstrated, and reports do not always contain sufficient detail to accurately evaluate an event. Furthermore, the quantity and quality of information in postmarketing adverse event reports is highly variable, and this further limits the ability to accurately determine whether or not the drug played a causal role in any particular case.

There are many factors that can influence whether or not an event will be reported — such as the time a product has been marketed and the publicity regarding an event. These influences may stimulate reporting in some instances but can inhibit reporting in others.

In considering the significance of adverse event reporting rates, it is worth noting that the reporting rates for any particular drug may not reflect actual adverse event incidence. In addition, the proportion of total incident cases that are reported is variable.

Despite the limitations of spontaneous reports and reporting rates, these data may contribute to the overall evaluation of drug safety because they emerge from real-life use of a drug. However, conclusions about the safety of a drug should not be based entirely on postmarketing adverse event reports and reporting rates, but rather, one should

consider the totality of evidence derived from premarketing studies, ongoing controlled clinical trials, and postmarketing safety data.

In the Petition, you also state that the increase in adverse event reports is due in part to the fact there is no easy way for either patients or practitioners to know whether the common gastrointestinal side effects are something to ignore or are indicative of serious toxicity that needs immediate attention (Petition at 36-37).

We disagree. Obesity and various gastrointestinal adverse events, such as pancreatitis (common with diabetics), can mask or confound symptoms associated with serious gastrointestinal toxicity. However, with awareness and close monitoring by physicians, possible adverse events related to the GLP-1 receptor agonist class can be diagnosed in a timely fashion and managed appropriately.

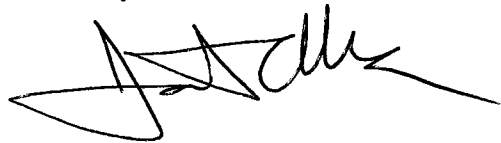
III. CONCLUSION

We have determined, based on the information available to us at this time, that initiating the withdrawal of the marketing approval of Victoza is not warranted. Also, as explained above in section II.C.10, we are denying your request that we require a pregnancy registry for Victoza.

The safety concerns you raise in the Petition were appropriately and thoroughly considered at the time of initial approval of the Victoza NDA. Since approval, there have been no new safety findings from FDA's ongoing surveillance, or raised in the Petition, that sufficiently alter the risk-benefit analysis of Victoza so as to necessitate the removal of Victoza from the market. Moreover, FDA has required a REMS, modifications to the REMS, and changes to the labeling which address a number of the safety concerns itemized in the Petition. We also have required FDAAA-mandated postmarketing studies and requested additional reports from the sponsor.

Accordingly, for the reasons described above, the Petition is denied. FDA will continue to monitor and review available safety information related to Victoza and take any further action as appropriate.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a stylized flourish extending to the right.

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