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

Dear Dr. Woodcock,

This letter constitutes a response to the Food and Drug Administration's (FDA's) recent denial[1] of Public Citizen's 2012 petition to ban the diabetes drug liraglutide due to several serious safety concerns. We believe these concerns outweigh any of liraglutide's marginal benefits, which are limited to the surrogate endpoint of lowering blood sugar.[2] Public Citizen is extremely troubled by FDA's decision to deny our petition and keep liraglutide on the market. Given the range of known safer, alternative pharmacologic and nondrug treatments for diabetes, this decision to allow continued sales of liraglutide will unnecessarily continue to expose hundreds of thousands of patients to the drug's serious risks. This letter addresses one of the risks discussed in our petition, the potential for liraglutide to cause acute pancreatitis, in light of substantial evidence that has accumulated since the petition was filed.

Public Citizen has today published on its website (and attached herein) our analysis of MedWatch reports of acute pancreatitis occurring during treatment with liraglutide. The reports had been submitted to the FDA's Adverse Event Reporting System (AERS) in the first two years following the drug's approval in 2010. While previous studies have analyzed only the electronically available AERS data summaries on pancreatitis with liraglutide and other incretin mimetics,[3,4,5] none have previously examined the full MedWatch reports themselves, making it

[1] Food and Drug Administration. Denial of Public Citizen petition to ban liraglutide. March 25, 2014. http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf. Accessed May 20, 2014.
[2] Public Citizen. Petition to ban diabetes drug liraglutide (Victoza). April 19, 2012. http://www.citizen.org/hrg2020. Accessed May 20, 2014.
[3] Butler PC, Elashoff M, Elashoff R, Gale EA. A critical analysis of the clinical use of incretin-based therapies: Are the GLP-1 therapies safe? *Diabetes Care.* 2013;36:2118-2125.
[4] Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterol.* 2011;141:150-156.
[5] Institute for Safe Medication Practices. Perspectives on GLP-1 Agents for Diabetes. *QuarterWatch.* April 18, 2013 — Partial Data from 2012 Quarter 3. http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf. Accessed April 17, 2014.

difficult for the researchers who conducted these earlier studies to discern whether other potential causes of pancreatitis were involved.

To assess the likelihood that liraglutide caused the acute pancreatitis events described in the MedWatch reports, we used the well-accepted Naranjo adverse drug reaction probability scale. The 10-item Naranjo questionnaire, published in 1981, provides a systematic method for determining the likelihood of a causal relationship between a medication and an adverse event in a given patient.[6] At least 45 studies published between January 1, 2013 and May 26, 2014 have used the Naranjo scale to assess for causality of various drugs in adverse drug reactions.[7]

Our analysis found 278 cases of acute pancreatitis reported to the FDA between February 2010 and December 2011 in which liraglutide was listed as the primary suspect drug. Sixty percent of the cases (164 cases) required hospitalization, and two patients died from complications of acute pancreatitis. Using the Naranjo causality criteria, we classified liraglutide as the "probable" causative agent in 51 cases, including 12 for which we deemed a causal link to be highly probable. In addition, one positive rechallenge was classified as a "definite" case of liraglutide-induced acute pancreatitis. To our knowledge, this is the first reported case of a positive rechallenge of acute pancreatitis with liraglutide.

In addition, we reviewed several other studies, including one randomized, controlled trial, published since our 2012 petition. The studies, like our attached analysis, strongly suggest a causal link between the incretin mimetic class of diabetes drugs (to which liraglutide belongs) and acute pancreatitis. None of these studies apparently were reviewed in the agency's rejection of our petition:

1. **An analysis of the French Pharmacovigilance Database found that the side effect of acute and chronic pancreatitis is unique to the incretin mimetic class of diabetes medications.**[8] This study found a reporting odds ratio (ROR) of acute and chronic pancreatitis with incretin mimetics of 14.86 (95% confidence interval [CI]: 9.24-23.92) after adjusting for multiple potential confounders, with no significantly increased signal for pancreatitis seen with any non-incretin diabetes drugs. As is the case with reports to the FDA's AERS database (see Figure 2 in our attached report and the analysis by the Institute for Safe Medication Practices[9]), the adjusted risk of acute and chronic pancreatitis[10] was considerably higher with the GLP-1 agonists liraglutide and exenatide (adjusted ROR: 29.36 [95% CI: 16.02-53.81]) than with DPP-4 inhibitors (adjusted ROR: 12.08 [95% CI: 7.30-20.00]).

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[6] Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.
[7] Medline search on May 26, 2014, for articles concerning the Naranjo scale with search terms of "Naranjo" and "adverse drug reaction."
[8] Faillie JL, Babai S, Crépin S, et al. Pancreatitis associated with the use of GLP-1 analogs and DPP-4 inhibitors: a case/non-case study from the French Pharmacovigilance Database. *Acta Diabetol*. 2014;51:491-497.
[9] Institute for Safe Medication Practices. Perspectives on GLP-1 Agents for Diabetes. *QuarterWatch*. April 18, 2013 — Partial Data from 2012 Quarter 3. http://www.ismp.org/quarterwatch/pdfs/2012Q3.pdf. Accessed April 17, 2014.
[10] In this analysis of GLP-1 agonists vs. DPP-4 inhibitors, 12 of the 147 total cases represented cases of "serious elevations of pancreatic enzymes", not formal diagnoses of acute or chronic pancreatitis.

2. **A recently completed randomized, controlled trial of weight loss in more than 3,700 non-diabetic obese and overweight subjects (the SCALE trial) found that a daily dose of 3.0 mg of liraglutide tripled the risk of acute pancreatitis over 56 weeks of use.**[11] Novo Nordisk, the manufacturer of liraglutide,[12,13] and the FDA[14] have both claimed that the high background rate of pancreatitis in diabetes patients makes difficult, or even precludes, a determination of causality between liraglutide and acute pancreatitis. In a letter to the FDA responding to Public Citizen's 2012 petition to ban liraglutide, Novo Nordisk stated the following: "If the Petition's argument – that Victoza accounts for the episodes of pancreatitis in the [pre-approval] LEAD trials – is defensible, then one test of its veracity would be a large-scale study of Victoza in patients without diabetes. *If such a study showed increased rates of pancreatitis, then it would lend credence to the Petition's argument* [emphasis added]."[15]

   While we, of course, do not agree with this reasoning, the findings of the SCALE randomized controlled trial, *which excluded subjects with Type 1 or 2 diabetes* or a prior history of acute or chronic pancreatitis, demonstrated that liraglutide therapy resulted in a threefold increase in the rate of acute pancreatitis (3 vs. 1 events per 1,000 patient-years of exposure in liraglutide- and placebo-treated subjects, respectively).

   These findings strikingly parallel the pooled results of the pre-approval randomized, controlled clinical trials for liraglutide in Type 2 diabetic subjects, cited in our petition, in which liraglutide resulted in a 3.7-fold increase in acute and chronic pancreatitis events (2.2 vs. 0.6 cases per 1,000 patient-years in liraglutide-treated and control subjects, respectively).[16]

3. **Two recently published randomized trials of alogliptin[17] and saxagliptin,[18] which were not powered to detect a significant difference in pancreatitis rates, showed a numerical increase in acute pancreatitis in drug-treated subjects.** The alogliptin

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[11] Pi-Sunyer X, Astrup A, Fujioka K, et al. Efficacy and safety of liraglutide 3.0 mg for weight management in overweight and obese adults: the SCALE obesity and prediabetes, a randomized, double-blind and placebo-controlled trial. Abstract #700. American Association of Clinical Endocrinologists 23rd Annual Scientific and Clinical Congress. http://am.aace.com/sites/all/files/Abstract-Book.pdf. Accessed May 20, 2014.

[12] Moses A. Novo Nordisk replies to BMJ investigation on incretins and pancreatic damage. BMJ. 2013 Jul 10;347:f4386.

[13] Novo Nordisk. Response of Novo Nordisk, Inc. to Public Citizen's Petition to Withdraw Victoza from the Market. August 24, 2012. http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0404-0003. Accessed June 3, 2014.

[14] Food and Drug Administration. Denial of Public Citizen petition to ban liraglutide. March 25, 2014. http://www.citizen.org/documents/2020_FDA%20Final%20Response%20to%20Petition.pdf. Accessed May 20, 2014.

[15] Novo Nordisk. Response of Novo Nordisk, Inc. to Public Citizen's Petition to Withdraw Victoza from the Market. August 24, 2012. http://www.regulations.gov/#!documentDetail;D=FDA-2012-P-0404-0003. Accessed June 3, 2014.

[16] Food and Drug Administration. Liraglutide clinical safety review. Silver Spring: FDA/CDER; July 2009. PDF p. 58. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000medr_P2.pdf. Accessed April 8, 2014.

[17] White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med.* 2013;369:1327-1335.

[18] Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med.* 2013;369:1317-1326.

study showed an approximately 50% increase in the rate of acute pancreatitis in the alogliptin arm (12/2,701 vs. 8/2,679 cases, respectively; p=0.50), while the saxagliptin trial demonstrated a near-doubling in "definite" cases in those given saxagliptin relative to controls (17/8,280 vs. 9/8,212, respectively; p=0.17). In a recent Perspective piece in *The New England Journal of Medicine*, the FDA and European Medicines Agency (EMA) suggested that these discrepant rates were inconsistent with a signal for pancreatitis.[19]

4. **A 2013 study by Butler et al. of deceased human organ donors compared pancreata of diabetic patients treated for a year or more with sitagliptin or exenatide to those of diabetic patients not treated with incretin mimetics as well as those of nondiabetics**.[20] The pancreata of those taking incretin mimetics were 40% larger than those of diabetic patients not on incretin mimetic therapy as a result of increased exocrine cell proliferation. Pancreatic exocrine cell proliferation and/or inflammation in response to incretin mimetic therapy has also been documented in mouse,[21] rat,[22] and monkey[23] pancreata.

   Two manufacturers of incretin mimetic drugs published rebuttals to the study by Butler et al., claiming that the small sample size and methodological issues precluded any definitive conclusions regarding a causal link between the drugs and the pathological findings.[24,25] However, to our knowledge, no incretin mimetic manufacturer — or anyone else — has attempted to conduct a similar study to refute these findings.[26] Thus, in the absence of such data, the Butler et al. study remains the only study of its kind investigating the effects of long-term incretin mimetic therapy on human pancreatic pathology.

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[19] Egan AG, Blind E, Dunder K, et al. Pancreatic safety of incretin-based drugs—FDA and EMA assessment. *N Engl J Med.* 2014;370:794-7.

[20] Butler AE, Campbell-Thompson M, Gurlo T, et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes.* 2013;62:2595-2604.

[21] Gier B, Matveyenko AV, Kirakossian D, et al. Chronic GLP-1 receptor activation by exendin-4 induces expansion of pancreatic duct glands in rats and accelerates formation of dysplastic lesions and chronic pancreatitis in the Kras (G12D) mouse model. *Diabetes.* 2012;61:1250-1262.

[22] Nachnani JS, Bulchandani DG, Nookala A, et al. Biochemical and histological effects of exendin-4 (exenatide) on the rat pancreas. *Diabetologia.* 2010;53:153-159.

[23] FDA. Liraglutide Pharmacology Review. FDA/CDER, Silver Spring; July 2009. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P1.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022341s000pharmr_P2.pdf. Accessed May 9, 2014.

[24] Engel SS, Golm GT, Lauring B. Comment on: Butler et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62(10):e18.

[25] Heine RJ, Fu H, Kendall DM, Moller DE. Comment on: Butler et al. Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes*. 2013;62(10):e16-17.

[26] A re-analysis of some of the data that formed the basis of the Butler et al. study was recently published (Diabetes Bonner-Weir S, In't Veld PA, Weir GC. Reanalysis of study of pancreatic effects of incretin therapy: methodological deficiencies. Obes Metab. 2014 Jan 8. doi: 10.1111/dom.12257. [Epub ahead of print]); however, no original studies, similar in design to the Butler et al. study, have been published.

The recent filing by Novo Nordisk of a new drug application for liraglutide for the treatment of obesity, based primarily on the SCALE trial, is extremely worrisome.[27] The 3.0 mg dose sought for approval as a weight loss drug is 1.7 times higher than the highest approved dose for the treatment of diabetes, despite the fact that hundreds of cases of acute pancreatitis have already been reported in patients using this and lower doses.[28] Novo Nordisk's application will be discussed at a September 11th meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, with a final Prescription Drugs User Fee Act (PDUFA) deadline for an approval decision set for October 20th.[29]

In 2013, 2.6 million prescriptions were filled for liraglutide, with 1 million of these representing new prescriptions.[30] If liraglutide is allowed to stay on the market and, in addition, approved to treat non-diabetic overweight and obese patients, the number of patients unnecessarily exposed to the drug's risks would dramatically increase.

Sincerely,

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Enclosure

cc: Margaret A. Hamburg, M.D., Commissioner, FDA
Jean-Marc Guettier, M.D., Director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research, FDA

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[27] Novo Nordisk. Company Announcement. Novo Nordisk files for regulatory approval of liraglutide 3 mg for the treatment of obesity. December 20, 2013. http://www.novonordisk.com/include/asp/exe_news_attachment.asp?sAttachmentGUID=4182bbe8-6101-4ad9-802b-7b83302f8169. Accessed May 22, 2014.
[28] Public Citizen. Acute pancreatitis with liraglutide. June 4, 2014. http://www.citizen.org/hrg2204.
[29] Trends-in-Medicine. Quick Takes. June 1, 2014. 2014 FDA Advisory Committees and Other Regulatory Meetings of Interest.
[30] IMS data for liraglutide prescriptions, 2013.