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March 31, 2015

Thomas Abrams, M.D.
Director
Office of Prescription Drug Promotion
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 3203
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Abrams,

Public Citizen, a consumer advocacy group with more than 350,000 members and supporters nationwide, is writing today urging you to stop the apparently violative off-label promotional statements in the direct-to-consumer (DTC) advertisements of five prescription drugs approved for the treatment of Type 2 diabetes. The drugs are Farxiga (dapagliflozin), Jardiance (empagliflozin), Invokana (canagliflozin),¹ Victoza (liraglutide)² and Bydureon (extended-release exenatide), and the promotional materials in question are included in Appendix 1 to this letter.

This request comes in the context of a drastic reduction in recent years in the number of violative DTC and physician-targeted prescription drug ads cited by the FDA in Warning and Untitled letters sent to pharmaceutical companies. Between 1997 and 2001, the earliest five-year period for which data are publicly available, the agency sent an average of 111 such letters per year, while an average of only 29 letters per year were sent during the most recent five-year period, 2010 through 2014 (see Appendix 2).

The ads, which appear in print magazines as well as on the drugs' official promotional websites, all contain statements describing the alleged weight-reducing properties of the medications. However, none of the drugs is approved for weight loss and, despite the presence of disclaimers that the medications are not weight-loss drugs, the implication is clearly that weight loss is an additional potential benefit of the drugs. The deliberate placement of the claims in such close proximity to the drugs' approved indications serves to reinforce this impression.

¹ Unlike the other, consumer-directed advertisements, the advertisement in question for Invokana appeared in a physician-targeted publication, *Internal Medicine News*. However, because this advertisement could potentially be accessed by patients as well as physicians, we included it in this letter.

² The formulation of liraglutide branded as Victoza is approved only for the treatment of type 2 diabetes and has never been approved for the treatment of obesity. A higher-dose formulation of liraglutide was recently approved under the brand name Saxenda for the treatment of obesity.

In the case of Farxiga and Invokana, blood pressure reduction also is touted as a potential benefit. This is an especially egregious “benefit” claim, as hypotension is listed as an adverse effect in the medications’ labels, owing to the diuretic effect and possible volume depletion inherent in the drugs’ mechanism of action.^{3,4} Both the weight-loss and blood-pressure-reduction claims also were made in a recently aired TV commercial for Farxiga.⁵

These five drugs have been approved solely to lower hemoglobin A1C levels in patients with Type 2 diabetes, but the advertisements presented in this letter clearly convey the false perception to patients and doctors that the drugs have been deemed safe and effective for weight loss and/or reducing blood pressure. In addition, all five drugs have serious toxicities, including hypotension, urinary tract infections, yeast infections (Farxiga, Jardiance, and Invokana), bladder cancer (Farxiga), pancreatitis, thyroid C-cell tumors (Victoza and Bydureon), and renal impairment (all five drugs).⁶ By inflating the drugs’ perceived benefits, the advertisements dangerously skew the risk-benefit calculations made by physicians and patients in deciding whether to initiate or continue these therapies. This is especially likely to occur with a weight-loss claim targeted at overweight and obese Type 2 diabetics struggling with both their disease and their weight.

These advertisements prompt the following questions:

1. Has the Food and Drug Administration (FDA) reviewed and approved the advertisements presented in Appendix 1 prior to, or since, their release? If not, what is the agency’s position on the weight-loss claims, as well as the blood-pressure-reduction claims for Farxiga and Invokana, made in the advertisements? If the agency did review and approve the advertisements, what was its rationale for allowing the inclusion of the weight-loss and blood-pressure-reduction claims?
2. Has the FDA approved similar off-label efficacy claims in other DTC advertisements? If so, did these approvals result from a formal policy allowing such off-label efficacy claims in pharmaceutical DTC advertisements?

We urge you to immediately issue Warning Letters requiring the manufacturers to withdraw these and any other advertisements containing similar off-label promotional statements. Unfortunately, as mentioned above, we must note here that the FDA’s enforcement of misleading drug marketing (both DTC and physician-targeted materials) has fallen far short in recent years. In 2014, only 10 Warning and Untitled letters were issued to pharmaceutical companies for violative DTC and physician-targeted prescription drug ads, the fewest number since at least 1997. This was the culmination of a steady decline in such letters during Margaret

³ Farxiga Label (revised August 2014). Food and Drug Administration-Approved Drug Products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed March 13, 2015.

⁴ Invokana Label (revised March 2015). Food and Drug Administration-Approved Drug Products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed March 24, 2015.

⁵ Ispot.tv. Farxiga TV Spot, ‘All Walks of Life.’ <http://www.ispot.tv/ad/7NDH/farxiga-all-walks-of-life>. Accessed March 13, 2015.

⁶ Food and Drug Administration. Most recent available FDA-approved labels (Farxiga 08/14; Jardiance 08/14; Invokana 03/15; Victoza 04/13; Bydureon 05/14) downloaded from: FDA-Approved Drug Products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Accessed March 10, 2015.

Hamburg's tenure, from a high of just 51 in 2010 to 31 in 2011, 28 in 2012, and 24 in 2013 (see Appendix 2).

The FDA's dismal record on issuing Warning and Untitled letters heightens the importance of other enforcement avenues. In order to deter the release of similarly violative DTC ads in the future, we urge you to, for the first time ever, use the authority granted to you by the 2007 Food and Drug Administration Amendments Act to issue civil monetary penalties to the manufacturers responsible for the ads in this document.⁷ As of January 27, 2015, not a single such penalty has been assessed.⁸

We look forward to a prompt response to our questions and to the implementation of our recommended actions.

Thank you for your attention to this important public health matter.

Sincerely,

Sammy Almashat, M.D., M.P.H.
Researcher

Sidney Wolfe, M.D.
Founder and Senior Advisor

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

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

⁷ Food and Drug Administration Amendments Act. Section 503B(f)(4). <http://www.gpo.gov/fdsys/pkg/PLAW-110publ85/pdf/PLAW-110publ85.pdf>. Accessed March 11, 2015.

⁸ Personal communication, on January 27, 2015, with Jean-Ah Kang of the Food and Drug Administration's Office of Prescription Drug Promotion.

Appendix 1. Promotional Materials (red arrows indicate unapproved benefits statements)

Farxiga (dapagliflozin) official promotional website (Accessed March 13, 2015):

The screenshot shows the Farxiga website interface. At the top, there is a navigation bar with links for 'Important Safety Information', 'Indication', 'Prescribing Information', and 'Medication Guide'. A search bar is present. Below the navigation, there are several buttons: 'Home', 'Considering FARRXIGA', 'Taking FARRXIGA', 'FARRXIGA Side Effects', 'Managing Type 2 Diabetes', and 'Savings and Support Info'. The main content area features a large image of three women walking on a beach. A red arrow points to a quote: "FARRXIGA helped improve my A1C. It also helped lower my weight." Below this, there is a 'FREE Offer' section stating 'Patients may get FARRXIGA for FREE.*' and a 'Start the Conversation' section. On the right side, there are three vertical panels with icons and text: 'Get Information and Support', 'Start the Conversation', and 'FREE Offer'. Below the main content, there is an 'Important Safety Information' section with several paragraphs of text. A red arrow points to a specific bullet point under 'Serious side effects can happen in people who take FARRXIGA, including:': 'Dehydration (the loss of body water and salt) which may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension).'

www.farxiga.com

Farxiga two-page advertising spread, as seen in the October 13, 2014, issue of *TIME* magazine. Image below (identical to the *TIME* spread) taken from the AdPharm Blog.

<https://adpharm.net/blog/2014/10/usa-farxiga-high-blood-sugar/>. Accessed March 13, 2015.

The image shows a two-page advertising spread for Farxiga. The left page features a photograph of a smiling couple in a car. Below the photo, there is text titled 'WHAT IS FARRXIGA™ (dapagliflozin)?' and 'IMPORTANT SAFETY INFORMATION'. The right page has a headline 'Do you have high blood sugar? Ask your doctor about FARRXIGA.' followed by a paragraph of text. Below this, there are three blue boxes with white text: 'Lower A1C*', 'Lose Weight*', and 'Lower Blood Pressure*'. A red arrow points to the 'Lower Blood Pressure*' box. Below these boxes, there is text about 'FARRXIGA is not a weight-loss or blood-pressure drug.' and 'IMPORTANT SAFETY INFORMATION (cont.)'. At the bottom of the right page, there is a section titled 'FARRXIGA AT NO COST TO YOU' and the Farxiga logo. The AstraZeneca logo is at the bottom right of the entire spread.

Jardiance (empagliflozin) advertisement in the March 16, 2015 issue of *TIME* magazine.

HEY, ADULTS WITH TYPE 2 DIABETES!

**YOUR A1C
CALLED
IT WANTS TO GET DOWN**

JARDIANCE is a prescription medicine used with diet and exercise that helps lower blood sugar and A1C. And even though it's not for weight loss, it could help you lose a few pounds, too. ←

JARDIANCE is not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine).

Ask your doctor if you can get down with JARDIANCE and visit **MeetJARDIANCE.com**

Jardiance[®] 
(empagliflozin) tablets
10 mg/25 mg

For more information about JARDIANCE, talk to your doctor and see the Patient Information on the adjacent page.

Invokana (canagliflozin) advertisement in the February 15, 2015 (Vol. 48, No. 3) issue of Internal Medicine News.

GREATER REDUCTIONS in A1C²

INVOKANA® 300 mg demonstrated greater reductions in A1C vs Januvia® 100 mg

at 52 weeks in patients inadequately controlled on metformin + a sulfonylurea²

Adjusted Mean Change in A1C From Baseline (%)

Group	Mean baseline (%)	Adjusted Mean Change (%)
Januvia® (sitagliptin) 100 mg + metformin and a sulfonylurea (n=378)	8.13%	-0.66%
INVOKANA® 300 mg + metformin and a sulfonylurea (n=377)	8.12%	-1.03%
Difference		-0.37% difference*

*95% CI: -0.50, -0.25; P<0.05.

Secondary endpoint: **GREATER REDUCTIONS in body weight^{2†}**

Difference from Januvia® 100 mg: **-2.8%**; P<0.001

Incidence of hypoglycemia²

INVOKANA® 300 mg: **43.2%**; Januvia® 100 mg: **40.7%**
The incidence of hypoglycemia increases when used in combination with insulin or an insulin secretagogue.

INVOKANA® is not indicated for weight loss or as an antihypertensive treatment.

[†]Adjusted mean change from baseline.
Indicated trademarks are registered trademarks of their respective owners.

Secondary endpoint: **GREATER REDUCTIONS in systolic blood pressure^{3†}**

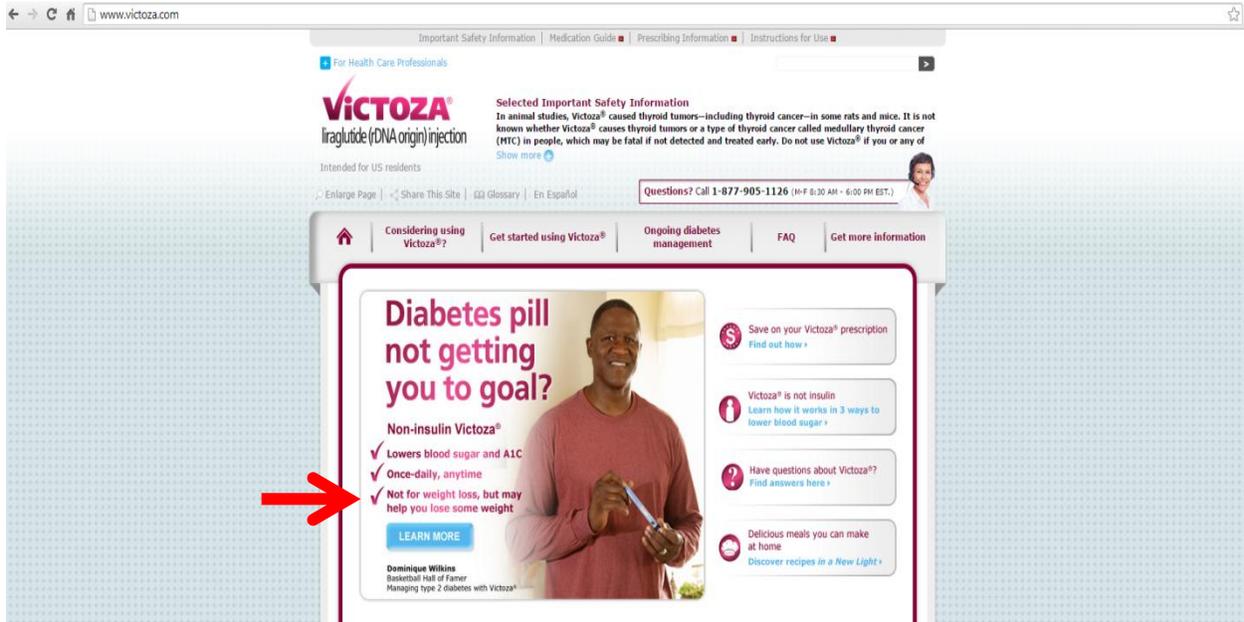
Difference from Januvia® 100 mg: **-5.9 mm Hg**; P<0.001

Adverse events (AEs)³

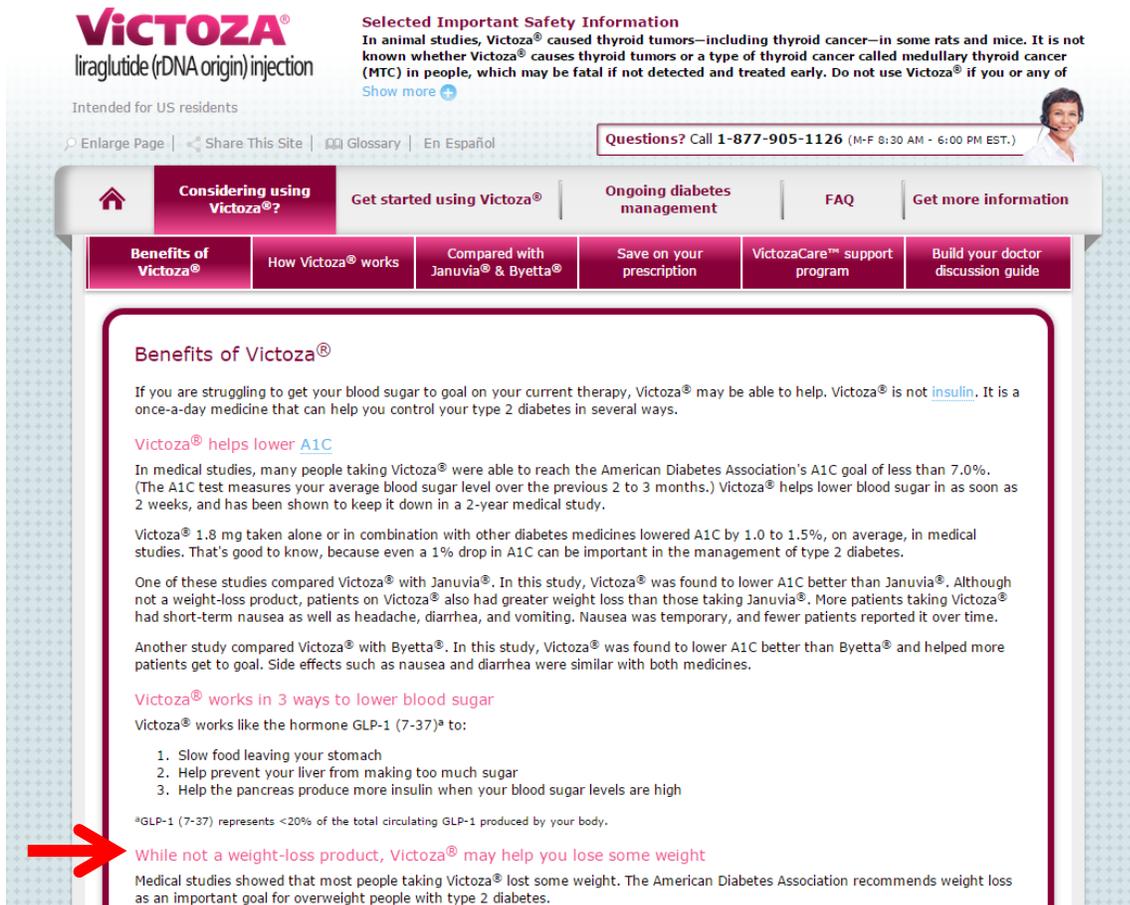
Incidences of AEs were similar between groups except for:
Male/female genital mycotic infection, INVOKANA® 300 mg: **9.2%/15.3%**; Januvia® 100 mg: **0.5%/4.3%**
Increased urine frequency/volume, INVOKANA® 300 mg: **1.6%/0.8%**; Januvia® 100 mg: **1.3%/0%**

Learn more and register for updates at INVOKANAhcp.com

Victoza (liraglutide) official promotional website (Accessed March 13, 2015):



www.victoza.com



<http://www.victoza.com/considering/benefits>

Bydureon (extended-release exenatide) official promotional website (Accessed March 13, 2015):

<https://www.bydureon.com/considering-bydureon.html>

Once-weekly **BYDUREON**[®]
 exenatide extended-release for
 injectable suspension
 This site is intended for US Consumers

Important Safety Information | Approved Uses | Prescribing Information including **Boxed WARNING** | Medication Guide | Instructions for Use

Go to Healthcare Professional Site REGISTER »

Considering BYDUREON Using BYDUREON BYDUREON Side Effects Managing Type 2 Diabetes Savings and Support Info

Considering BYDUREON

Grilling up fish for dinner
 Casting for the big one
 Hitting the driving range

Nature walks with Rita
 Growing vegetables
 Cooking a seafood stew

Waxing my classic car
 My half hour on the treadmill
 Maintaining the garden

Considering BYDUREON

Type 2 diabetes can be frustrating. Sometimes, no matter how hard you try, you just don't see the results. Your needs change over time and the medicine that worked before may not be enough now. You may need to take your treatment plan in another direction.

It may be time to talk to your doctor about BYDUREON. BYDUREON is an injectable prescription medicine used just once a week that may help improve blood sugar in adults with type 2 diabetes when used along with diet and exercise. BYDUREON may be able to help you reach the blood sugar goal you have agreed on with your doctor.

Take a closer look at BYDUREON

- The first once-weekly, non-insulin injection
- Clinically proven to significantly lower A1C and help with weight loss*
BYDUREON is not a weight-loss drug. Individual results may vary.
- Can be used at any time of day, with or without meals

*In a 24-week study, adults with type 2 diabetes taking BYDUREON 2 mg with diet and exercise alone or with other diabetes pills, lowered A1C by an average of 1.6% (starting at 8.5%) and additionally reduced weight by an average of 5 pounds (starting at 214 pounds). BYDUREON is not a weight-loss drug. Individual results may vary.

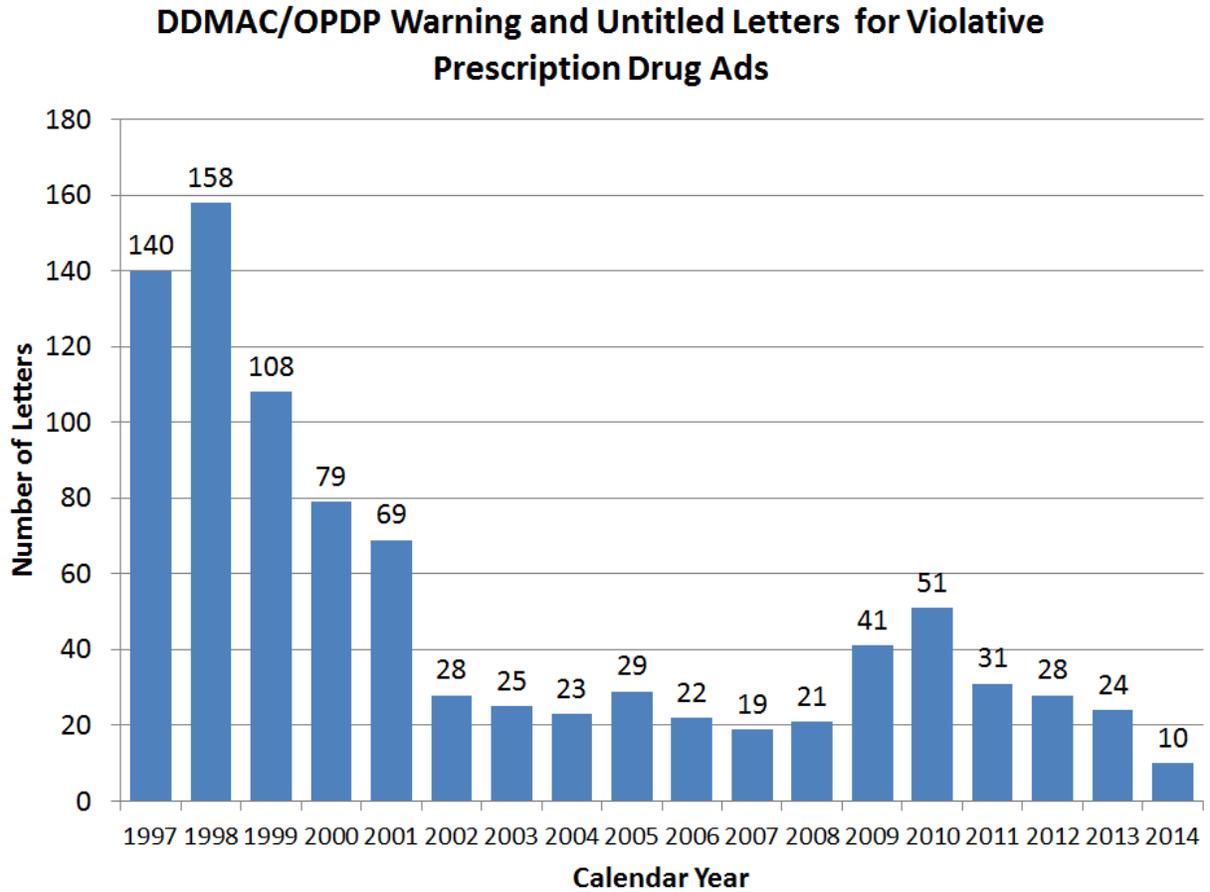
Start Saving Today!*
 Activate or request your BYDUREON SavingsRx Card here.
 *Eligibility Requirements and terms of use apply.
 GET STARTED

Are You Considering BYDUREON?
 Register to receive a FREE Information Kit* to help you talk to your doctor about BYDUREON.
 *Some restrictions apply.
 SIGN UP NOW

How BYDUREON May Help
 Learn how BYDUREON may help you improve your A1C.
 READ MORE

<https://www.bydureon.com/considering-bydureon.html>

Appendix 2. FDA Warning and Untitled Letters to Pharmaceutical Companies Over Violative Promotional Materials and Activities



* Includes both direct-to-consumer and physician-targeted advertisements. The Division of Drug Marketing and Communications (DDMAC) was redesignated the Office of Prescription Drug Promotion (OPDP) in 2011.

Source: Food and Drug Administration. Warning Letters and Notice of Violation Letters to Pharmaceutical Companies.
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm>.
 Accessed March 12, 2015.