DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Michele Yelmene
Vice President, Regulatory and Quality Assurance
Xeris Pharmaceuticals, Inc.
180 N LaSalle Street, Suite 1600
Chicago, IL 60601

RE: NDA 212097
GVOKE™ (glucagon) injection, for subcutaneous use
MA 43

Dear Ms. Yelmene:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer broadcast television advertisement (TV ad) entitled "Gvoke PFS TV Commercial (:60)" [US-GVKPFS-19-00061(v1)] for GVOKE™ (glucagon) injection, for subcutaneous use (Gvoke) submitted by Xeris Pharmaceuticals, Inc. (Xeris) under cover of Form FDA 2253. This TV ad makes false or misleading claims and representations about the risks associated with and efficacy of Gvoke. Thus, the TV ad misbrands Gvoke within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(n); 331(a); 321(n). *See* 21 CFR 202.1(e)(5). These violations are concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Gvoke, a drug that is used for the treatment of severe hypoglycemia and is also associated with several serious and life-threatening risks, including the risk of hypersensitivity reactions that patients have experienced from a previous exposure to other formulations of glucagon.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Gvoke.[1] According to the FDA-approved product labeling (PI):

> GVOKE is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes ages 2 years and above.

This product is associated with a number of serious risks. Gvoke is contraindicated in patients with pheochromocytoma, insulinoma, and in patients with a known hypersensitivity to glucagon or to any of the excipients in Gvoke. The PI also contains warnings and precautions regarding catecholamine release in patients with pheochromocytoma, hypoglycemia in patients with insulinoma, hypersensitivity and allergic reactions, lack of efficacy in patients

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

with decreased hepatic glycogen, necrolytic migratory erythema, and hypoglycemia in patients with glucagonoma. The most common adverse reactions reported with Gvoke were nausea, vomiting, injection site edema raised 1 mm or greater, and headache in adults; and nausea, hypoglycemia, vomiting, headache, abdominal pain, hyperglycemia, injection site discomfort and reaction, and urticaria in pediatric patients.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The TV ad is misleading because it includes efficacy claims for Gvoke but fails to include important risk information associated with the drug. For example, the TV ad fails to include the contraindication in patients with a known hypersensitivity to glucagon or to any of the excipients in Gvoke. In addition, the TV ad fails to include information regarding the warning and precaution for hypersensitivity and allergic reactions. Specifically, the WARNINGS AND PRECAUTIONS and the PATIENT COUNSELING INFORMATION sections of the PI state the following (underlined emphasis added; bolded emphasis original):

> **5.3 Hypersensitivity and Allergic Reactions**
> Allergic reactions have been reported with glucagon, these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. . . .
>
> **17 PATIENT COUNSELING INFORMATION**
> . . . .
> Serious Hypersensitivity
> Inform patients that allergic reactions can occur with GVOKE. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions [*see Warnings and Precautions (5.3)].*

Moreover, although the TV ad includes the contraindications for pheochromocytoma and insulinoma, the TV ad fails to include material facts about the consequences that may result from the use of the drug. According to the WARNINGS AND PRECAUTIONS section of the PI, Gvoke may stimulate the release of catecholamines from a pheochromocytoma and cause a dramatic increase in blood pressure and may stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. By omitting these serious risks associated with Gvoke and material facts pertaining to these risks for Gvoke, the TV ad misleadingly suggests that Gvoke is safer than has been demonstrated.

False or Misleading Claims about Efficacy

Promotional materials misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure

to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The TV ad includes the claims, “Easy to use. Easy to know you did it right. Pretty easy, huh?” These claims misleadingly suggest that the Gvoke pre-filled syringe can be easily used and individuals can confidently recognize that they have correctly administered the product. However, with regard to ease of use, FDA notes that the DOSAGE AND ADMINISTRATION section of the PI and the Instructions for Use describe multiple steps involved in the preparation and administration of the Gvoke pre-filled syringe and recommends that users become familiar with these instructions before an emergency happens. In addition, FDA notes that there is no signal to the user to know whether they “did it right.” The multiple steps involved in the administration of Gvoke and the lack of a signal to indicate that the product was administered correctly reflect the complexity of use of Gvoke in an emergency situation. Thus, the misleading claims regarding ease of use and knowing “you did it right” are concerning from a public health perspective, especially in light of risks associated with prolonged hypoglycemia. No references are cited to support the above-referenced claims, and FDA is not aware of data to support them. If you have data to support these claims, please submit them to FDA for review.

Omission of Material Fact

The TV ad presents the following claims:

- VOICEOVER (VO): “If you have diabetes and take insulin, you know low blood sugar can be scary. You might start to sweat, panic, worry you might pass out. You may even feel like you’re falling.”

These claims are misleading and minimize the seriousness of the condition because they include some of the early, mild symptoms of hypoglycemia but fail to present the symptoms of severe hypoglycemia for which Gvoke is indicated. Specifically, the Instructions for Use states, “If not treated, the patient may progress to severe hypoglycemia which can include: confusion, seizures, unconsciousness, death.”

In addition, the TV ad includes the claim, “I can be used even before passing out.” However, the TV ad fails to provide any information regarding the circumstances when it is appropriate to administer Gvoke and the need for administration by others. For example, the Gvoke Instructions for Use indicate that Gvoke is not intended for mild cases in which eating or drinking sugar is possible. Specifically, the Instructions for Use states, “The GVOKE PFS may have been prescribed so that relatives, close friends and caregivers can give the injection if you become hypoglycemic (severe low blood sugar) and are unable to take sugar by mouth.” Further, the DOSAGE and ADMINISTRATION section of the PI specifically states, “Because severe hypoglycemia requires the help of others to recover, instruct the patient to inform those around them about GVOKE and its Instructions for Use.”

By omitting material information about the seriousness of the condition, the circumstances when it is appropriate to administer Gvoke, and the need for administration by others, the TV ad creates a misleading impression about the administration of Gvoke. This is particularly concerning from a public health perspective as this product is for use in an emergency and

may need to be administered by relatives, close friends or caregivers if the patient, for example, becomes unconscious.

Conclusion and Requested Action

For the reasons discussed above, the TV ad misbrands Gvoke within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(n); 331(a); 321(n). *See* 21 CFR 202.1(e)(5).

OPDP requests that Xeris immediately cease violating the FD&C Act, as discussed above. Please submit a written response to this letter on or before August 28, 2020, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Gvoke that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. If you believe that your product is not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 43 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Gvoke comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Samantha Bryant, PharmD, BCPS
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

{See appended electronic signature page}

Melinda McLawhorn, PharmD, MPH, BCPS, RAC
Team Leader
Division of Advertising & Promotion Review 2
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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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