DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Tracy Acker, Pharm.D.
Director, Regulatory Affairs
Supernus Pharmaceuticals, Inc.
1550 East Gude Drive
Rockville, MD 20850

RE: NDA 202810
Oxtellar XR (oxcarbazepine) extended-release tablet, for oral use
MA 179

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Key Opinion Leader Spanish video (video) (SPN.OXT.2015-0104)[1] for Oxtellar XR (oxcarbazepine) extended-release tablet, for oral use (Oxtellar XR) submitted by Supernus Pharmaceuticals, Inc. (Supernus) on November 19, 2015 under cover of Form FDA 2253. The video makes false or misleading claims and/or representations about the risks associated with Oxtellar XR. Thus, the video misbrands Oxtellar XR within the meaning of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); *cf.* 21 CFR 202.1(e)(5); (e)(6). The video also provides evidence that Oxtellar XR is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Oxtellar XR misbranded or otherwise makes its distribution violative. 21 U.S.C. 355(a); 352(f); 331(a), (d); *see* 21 CFR 201.5; 201.100; 201.115. These violations are concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Oxtellar XR and suggest a use for which the labeling does not provide adequate directions for safe and effective use of the product.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Oxtellar XR.[2]

According to the FDA-approved product labeling (PI)[3], Oxtellar XR is indicated for adjunctive therapy of partial seizures in adults and in children 6 years to 17 years of age.

[1] This letter replaces the letter issued on October 17, 2016. The video is recorded in Spanish and was initially submitted with an incorrect version of a transcript, which included an English translation. A corrected transcript and English translation were submitted by Supernus on October 18, 2016.
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.
[3] The version of the Oxtellar XR PI that was approved when the piece was disseminated and the version referred to in this letter is dated October 2012. However, a new version of the PI was approved in December 2015.

Oxtellar XR is contraindicated in patients with a known hypersensitivity to oxcarbazepine or to any of its components. Oxtellar XR is associated with serious risks. The PI contains warnings and precautions regarding hyponatremia, anaphylactic reactions and angioedema, hypersensitivity reactions in patients with hypersensitivity to carbamazepine, serious dermatologic reactions, suicidal behavior and ideation, withdrawal of anti-epileptic drugs (AEDs), multi-organ hypersensitivity, hematologic reactions, risk of seizures in the pregnant patient, and changes in laboratory tests. The most common adverse reactions associated with Oxtellar XR are dizziness, somnolence, headache, balance disorder, tremor, vomiting, diplopia, asthenia, and fatigue.

Lack of Adequate Directions for Use

The video presentation about Oxtellar XR begins immediately with the following statements from Key Opinion Leader and Supernus (b) (4), Dr. Jesus Eric Piña-Garza (emphasis added):

- "Oxtellar XR is a medication that I frequently add to other medications when the epilepsy is not controlled or the person is having side effects." [Bite 1]

- "Oxcarbazepine XR has helped me treat my patients improve the level of convulsive control." [Bite 2]

Use of the general terms "epilepsy" and "convulsive" in discussing the drug suggests that Oxtellar XR is intended for use in treating epilepsy, including seizure types other than partial seizures. However, as described in the INDICATIONS AND USAGE section of the PI, "Oxtellar XR is indicated as adjunctive therapy of partial seizures in adults and in children 6 years to 17 years of age." Therefore, the video presentation provides evidence that Oxtellar XR is intended for use in treating all seizure types, which is a use for which it lacks approval and for which its labeling does not provide adequate directions. We acknowledge that the correct indication appears following his presentation in scrolling text and a voiceover; however, placement of the indication following Dr. Piña-Garza's presentation does not negate the earlier statements. The presentation also misleadingly suggests that Oxtellar XR is approved for the treatment of all seizure types, when this is not the case, and that Oxtellar is safe and effective for the treatment of seizures other than partial seizures, when you have not provided support for that suggestion.

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 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 opening segment of the video consists of the presentation by Dr. Piña-Garza, in which he conveys benefit claims but fails to disclose any specific risks associated with the drug during his segment of the video. As described in the WARNINGS AND PRECAUTIONS section of the PI, Oxtellar XR is associated with several serious, potentially life-threatening

risks and numerous adverse reactions. The presentation of risks associated with Oxtellar XR is relegated to the end of the video after Dr. Piña-Garza's presentation, where it is unlikely to draw the viewer's attention, as it is displayed in scrolling text with a voiceover. This overall presentation misleadingly minimizes the risks associated with Oxtellar XR because it fails to convey risk information with a prominence reasonably comparable to the claims of effectiveness. The presentation in the video is especially problematic from a public health perspective given the serious and potentially life-threatening risks associated with the drug.

Conclusion and Requested Action

For the reasons discussed above, the video misbrands Oxtellar XR within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a); 321(n); 331(a); *cf.* 21 CFR 202.1(e)(5); (e)(6). The video also provides evidence that Oxtellar XR is intended for a new use for which it lacks approval, and for which its labeling does not provide adequate directions for use, which also renders Oxtellar XR misbranded or otherwise makes its distribution violative. 21 U.S.C. 355(a); 352(f); 331(a), (d); *see* 21 CFR 201.5; 201.100; 201.115.

OPDP requests that Supernus immediately cease violating the FD&C Act, as described above. Please submit a written response to this letter on or before November 14, 2016, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Oxtellar XR that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

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 179 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. OPDP reminds you that only written communications are considered official.

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

Sincerely,

{See appended electronic signature page}

Dhara Shah, PharmD
Regulatory Review Officer
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD, RAC
Team Leader
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DHARA SHAH
10/31/2016

MATHILDA K FIENKENG
10/31/2016