

**TRANSMITTED BY FACSIMILE**

John Keller, PhD, President and CEO  
Shionogi Inc.  
300 Campus Drive  
Florham Park, NJ 07932

**RE: NDA 022129**  
ULESFIA<sup>®</sup> (benzyl alcohol) lotion, for topical use  
MA 187

**WARNING LETTER**

Dear Dr. Keller:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a "Patient Co-Pay Assistance Voucher" (ULE304014) (voucher) for ULESFIA<sup>®</sup> (benzyl alcohol) lotion, for topical use (Ulesfia).<sup>1</sup> This voucher is false or misleading because it omits important risk information associated with the use of Ulesfia and omits material facts. Thus the voucher misbrands Ulesfia 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), (n); 321(n); 331(a). See 21 CFR 202.1(e)(5). Shionogi Inc. (Shionogi)<sup>2</sup> also did not comply with 21 CFR 314.81(b)(3)(i). These violations are concerning from a public health perspective because they create a misleading impression about the safety and effectiveness of Ulesfia.

**Background**

Below are the indication and summary of the most serious and most common risks associated with the use of Ulesfia.<sup>3</sup> According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (emphasis in original):

ULESFIA<sup>®</sup> Lotion is indicated for the topical treatment of head lice infestation in patients 6 months of age and older.

**Limitation of Use**

<sup>1</sup> Available at <http://www.ulesfialotion.com/pdf/Ulesfia-Voucher.pdf> (last accessed March, 29, 2016)

<sup>2</sup> Shionogi Inc. transferred the reporting responsibilities for Ulesfia to Concordia Pharmaceuticals Inc. (Concordia). Concordia has an Exclusive Distribution Agreement with Lachlan Pharma Holdings for the distribution of Ulesfia in the United States under an agreement with Zylera Pharmaceuticals, LLC.

<sup>3</sup> 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.

ULESFIA<sup>®</sup> Lotion does not have ovocidal activity.

### **Adjunctive Measures**

ULESFIA<sup>®</sup> Lotion should be used in the context of an overall lice management program:

- Wash (in hot water) or dry-clean all recently worn clothing, hats, used bedding, and towels.
- Wash personal care items such as combs, brushes and hair clips in hot water.
- A fine-tooth comb or special nit comb may be used to remove dead lice and nits.

The PI for Ulesfia contains warnings and precautions regarding neonatal toxicity, eye irritation, contact dermatitis, and use in children. The most common adverse reactions associated with Ulesfia during clinical trials were ocular irritation, application site irritation, and application site anesthesia and hypoesthesia.

### **Omission of Risk Information**

Promotional materials are misleading if they fail to reveal facts that are 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 voucher makes representations and/or suggestions about the efficacy of Ulesfia such as the following:

- “Ulesifa – the #1 prescribed branded Rx treatment for head lice”
- “Ulesfia is benzyl alcohol 5%, this is a non-neurotoxic formulation, and is not a pesticide and is the #1 prescribed branded Rx product for the treatment of head lice.”
- “Ulesfia should be used as part of an overall head lice management program” in conjunction with a list of steps that can be taken to help prevent the control and spread of head lice.

However, the voucher fails to communicate **any** risk information. We note that the statements “For more information on Ulesfia, please visit [www.ulesfialotion.com](http://www.ulesfialotion.com)” and “For more information, please refer to the package insert for full prescribing details or visit [www.ulesfialotion.com](http://www.ulesfialotion.com)” are included on the voucher. However, these statements do not mitigate the omission of risk information from the voucher. By omitting the risks associated with Ulesfia, the voucher fails to provide material information about the consequences that may result from the use of the drug and creates a misleading impression about the drug’s safety.

### **Omission of Material Facts/Inadequate Communication of Indication**

As already noted, the voucher makes representations about the use of Ulesfia for the treatment of head lice infestation, but it is misleading because it fails to communicate material information regarding the FDA-approved indication for Ulesfia. Specifically, it omits the following material information from the INDICATIONS AND USAGE section of the PI (emphasis original):

### **Limitation of Use**

ULESFIA<sup>®</sup> Lotion does not have ovocidal activity.

Additionally, the voucher is misleading because it fails to adequately communicate that Ulesfia is indicated only for patients 6 months of age and older. We acknowledge that the “**Dear Pharmacists**” section on the bottom of the back page of the voucher contains the statement, “Ulesfia . . . is indicated for patient[s] 6 month of age and older” (emphasis original). However, this does not mitigate the misleading impression.

### **Failure to Submit Under Form FDA-2253**

FDA regulations require companies to submit any labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) and is required to include a copy of the product’s current professional labeling. A copy of the voucher was not submitted to OPDP under cover of Form FDA-2253 at the time of initial dissemination as required by 21 CFR 314.81(b)(3)(i).

### **Conclusion and Requested Action**

For the reasons discussed above, the voucher misbrands Ulesfia within the meaning of the FD&C Act, and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). See 21 CFR 202.1(e)(5). Furthermore, Shionogi also did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Shionogi immediately cease misbranding Ulesfia and/or cease introducing the misbranded drug into interstate commerce. Please submit a written response to this letter on or before April 13, 2016, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Ulesfia that contain statements such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Ulesfia. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

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 at (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 187 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 Warning 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 Ulesfia comply with each applicable requirement of the FD&C Act and FDA implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA  
Division Director  
Office of Prescription Drug Promotion

cc: Erin O'Neil, CPA, CA, CFA, and Chief Operating Officer  
Concordia Pharmaceuticals Inc.  
Attn: Mandy Dorsey, US Regulatory Affairs  
Mapi USA, Inc. [US Agent for Concordia Pharmaceuticals Inc.]  
2343 Alexandria Drive, Suite 100, Lexington, KY 40504

Robert C. Moscato, Jr.  
Chief Executive Officer  
Zylera Pharmaceuticals, LLC  
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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.**  
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/s/  
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ROBERT T DEAN  
03/29/2016