DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Firoozeh Patel, President and CEO
Spriaso, LLC
3199 Oakcliff Drive
Salt Lake City, UT 84124

RE: NDA 206323
TUXARIN ER™ (codeine phosphate and chlorpheniramine maleate) extended release tablets, CIII
MA 1

WARNING LETTER

Dear Ms. Patel:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a webpage titled "Product Pipeline: Tuxarin ER"[1] for the approved product TUXARIN ER™ (codeine phosphate and chlorpheniramine maleate) extended release tablets, CIII (Tuxarin ER) on the website for Spriaso, LLC (Spriaso). This webpage makes false or misleading claims and/or representations about the risks associated with Tuxarin ER, and inadequately communicates the full indication for the drug. As a result, Tuxarin ER is misbranded under the Federal Food, Drug and Cosmetic Act (FD&C Act). 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(3)(ii); (e)(5). Among other acts, the FD&C Act prohibits distribution of a misbranded drug. *See generally* 21 USC 331. Spriaso also did not comply with 21 CFR 314.81(b)(3)(i). This webpage is concerning from a public health perspective because it creates a misleading impression about the safety and approved indication for Tuxarin ER.

Background

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

According to its FDA-approved product labeling (PI)[3] (emphasis in original):

[1] Tuxarin ER Product Pipeline webpage at http://spriasollc.com/Pipeline_Tuxarin.aspx (last accessed December 13, 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 Tuxarin ER PI referred to in this letter is dated August 25, 2016.

TUXARIN ER is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

Important Limitations of Use
Not indicated for pediatric patients under 18 years of age

Tuxarin ER contains codeine phosphate, an opiate agonist antitussive. This product is associated with a number of serious risks. The PI for the drug contains a boxed warning regarding respiratory depression and death which have occurred in children who received codeine following tonsillectomy and/or adenoidectomy. Tuxarin ER is contraindicated in postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy, and in patients with known hypersensitivity to codeine, chlorpheniramine, or any of the product's components. The PI also contains warnings and precautions regarding death related to ultra-rapid metabolism of codeine to morphine, respiratory depression, drug dependence, head injury and increased intracranial pressure, activities requiring mental alertness, obstructive bowel disease, acute abdominal conditions, and use in special risk populations. In addition, the PI indicates that common adverse reactions associated with Tuxarin ER include nausea and vomiting, constipation, abdominal distension, abdominal pain, blurred vision, diplopia, visual disturbances, confusion, dizziness, depression, drowsiness, sedation, headache, euphoria, facial dyskinesia, feeling faint, lightheadedness, general feeling of discomfort or illness, excitability, nervousness, agitation, restlessness, somnolence, insomnia, dyskinesia, irritability, and tremor.

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 webpage makes representations and/or suggestions about Tuxarin ER such as the following:

- "First Long Acting Tablet, Schedule III, Codeine Antitussive Combination with Chlorpheniramine Antihistamine"

- "No spills or taste issues"

However, the webpage fails to communicate **any** risk information about the product. By omitting the risks associated with Tuxarin ER, including serious and potentially fatal risks, the webpage 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.

Furthermore, the webpage contains the following claims:

- "Minimize serious risk of over dosing"

- "Issues with Hydrocodone and Chlorpheniramine commercial products
    - Current market is dominated by liquids prone to serious risk of dosing errors."

- "Issues with Promethazine (antihistamine) plus Codeine commercial products.
    - Current market is dominated by short acting liquids that are prone to dosing errors.
    - FDA requires boxed warning added to all promethazine containing products
    - Unlike promethazine no known serious safety issues with Chlorpheniramine"

These claims are misleading because they suggest that Tuxarin ER is safer than its competitors based on differences in dosage formulations and the safety profiles of individual ingredients. No references were cited in support of these claims and we are not aware of evidence to support the suggestion that Tuxarin ER is safer than its competitors because of its tablet formulation or because it is not associated with "dosing errors" or "serious safety issues." On the contrary, according to the WARNINGS AND PRECAUTIONS section of the PI for Tuxarin ER, overdose of codeine has been associated with fatal respiratory depression. This section of the Tuxarin ER PI also discusses several serious safety issues such as the risk of death related to ultra-rapid metabolism of codeine to morphine, dose-related respiratory depression, and drug dependence. Furthermore, similar to the products containing promethazine referred to in the claims above, the PI for Tuxarin ER also contains a boxed warning as discussed in the Background section above. Comparing the safety profile of a single ingredient in a combination product to another single ingredient in a competitor combination product (i.e., promethazine versus chlorpheniramine) is misleading as it fails to take into consideration the overall safety profile of the entire combination product.

Such statements raise considerable public health concerns and are particularly alarming with respect to an opiate agonist product, as these controlled substances can lead to overdose, dependence, abuse, and death.

Inadequate Communication of Indication

The webpage contains claims such as the following:

- "First Long Acting Tablet, Schedule III, Codeine Antitussive Combination with Chlorpheniramine Antihistamine"

- "Chlorpheniramine . . . helps to dry your runny nose, provide relief for sneezing, itchy and watery eyes, and itching of the nose, throat, and roof of the mouth, and calm the cough."

- "Chlorpheniramine is most widely used antihistamine to manage cough and cold symptoms."

These claims are misleading because they fail to adequately communicate the full approved indication for Tuxarin ER. Specifically, the INDICATIONS AND USAGE section of the PI states the following (bolded and underlined emphasis in original; italic font emphasis added):

TUXARIN ER is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold *in adults 18 years of age and older*.

Important Limitations of Use
Not indicated for pediatric patients under 18 years of age

By failing to adequately disclose this information, the webpage creates the misleading impression that the drug is approved for use in patients of all ages. This is particularly concerning given that Tuxarin ER has a boxed warning and a contraindication regarding use in children, neither of which is disclosed on the webpage as discussed above.

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 webpage 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, Tuxarin ER is misbranded under the FD&C Act. 21 U.S.C. 352(a), (n); 321(n). *See* 21 CFR 202.1(e)(3)(ii); (e)(5). Furthermore, Spriaso did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Spriaso immediately cease misbranding Tuxarin ER. Please submit a written response to this letter on or before December 28, 2016, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Tuxarin ER that contain presentations such as those described above and explaining your plan for discontinuing use of such materials.

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 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 1 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 Tuxarin ER complies 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
Director, Division of Advertising and
Promotion Review 2
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T DEAN
12/13/2016