DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Brian Dorsey
Senior Vice President, Pharmaceutical Development & Operations
Pernix Therapeutics Holdings, Inc.
440 Stevens Avenue, Suite 200
Solana Beach, CA 92075

RE: NDA 050685, 050686
CEDAX® (ceftibuten) Capsules and Oral Suspension
MA #241, #211

Dear Mr. Dorsey:

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 Pernix Therapeutics Holdings, Inc.'s (Pernix) webpage[1] for CEDAX® (ceftibuten capsules and ceftibuten for oral suspension) (Cedax) titled, "Cedax." The webpage is false or misleading because it omits risks and material facts associated with use of Cedax. Thus, the webpage misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and makes its distribution violative of the FD&C Act, 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(5). Pernix also did not comply with 21 CFR 314.81(b)(3)(i).

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Cedax.[2] According to its FDA-approved product labeling (PI):

> CEDAX (ceftibuten) is indicated for the treatment of individuals with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below.
>
> **Acute Bacterial Exacerbations of Chronic Bronchitis** due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Strepococcus pneumoniae* (penicillin-susceptible strains only).
>
> **NOTE:** In acute bacterial exacerbations of chronic bronchitis clinical trials where *Moraxella catarrhalis* was isolated from infected sputum at baseline, ceftibuten clinical efficacy was 22% less than control.

[1] http://pernixtx.com/cedax (last accessed June 28, 2013)
[2] 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.

Acute Bacterial Otitis Media due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Streptococcus pyogenes.*

NOTE: Although ceftibuten used empirically was equivalent to comparators in the treatment of clinically and/or microbiologically documented acute otitis media, the efficacy against *Streptococcus pneumoniae* was 23% less than control. Therefore, ceftibuten should be given empirically **only** when adequate antimicrobial coverage against *Streptococcus pneumoniae* has been previously administered.

Pharyngitis and Tonsillitis due to *Streptococcus pyogenes.*

NOTE: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. Ceftibuten is generally effective in the eradication of *Streptococcus pyogenes* from the oropharynx; however, data establishing the efficacy of the CEDAX product for the prophylaxis of subsequent rheumatic fever are not available.

Cedax is contraindicated in patients with known allergy to the cephalosporin group of antibiotics. The PI for Cedax includes warnings regarding serious acute hypersensitivity reactions and pseudomembranous colitis, and precautions regarding the emergence and overgrowth of resistant organisms, dosage adjustment in patients with renal insufficiency, and caution in patients with a history of gastrointestinal disease. The most common adverse reactions in adults were nausea, headache, diarrhea, dyspepsia, dizziness, abdominal pain, and vomiting, and the most common adverse reactions in pediatric patients were diarrhea, vomiting, abdominal pain, and loose stools.

Omission of Risk Information/Omission of Material Facts

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The webpage contains several efficacy claims for Cedax, but fails to communicate **any** risk information associated with the use of the drug. By omitting the serious risks associated with Cedax, the webpage misleadingly suggests that Cedax is safer than has been demonstrated. We acknowledge that the webpage includes a link to the Full Prescribing Information. However, this does not mitigate the complete omission of important risk information from the webpage.

In addition, the webpage presents the claim quoted below (emphasis original), in conjunction with the images of children who clearly appear to be under 12 years of age:

CEDAX IS A THIRD GENERATION ORAL CEPHALOSPORIN INDICATED FOR THE TREATMENT OF MILD TO MODERATE:

- **Acute Bacterial Exacerbations of Chronic Bronchitis** due to *Haemophilus influenzae* (including β-lactamase-producing strains), *Moraxella catarrhalis* (including β-lactamase-producing strains), or *Strepococcus pneumoniae* (penicillin-susceptible strains only).

The website thus associates this indication with the images of children who are clearly under 12 years of age but misleadingly omits material facts about the instructions for use of the product in this population. Specifically, the website does not reveal that the PI only provides dosage information for the treatment of acute bacterial exacerbations of chronic bronchitis in patients 12 years of age and older.

The webpage also omits important dosage and administration recommendations for Cedax. Specifically, the webpage provides the dosage recommendation, "9 mg/kg," in conjunction with the images of children, but misleadingly fails to provide material information related to the use of Cedax in children. With respect to the dosing in pediatric patients with pharyngitis, tonsillitis, or acute bacterial otitis media, the DOSAGE AND ADMINISTRATION section of the PI states, "**Pediatric patients weighing more than 45 kg should receive the maximum daily dose of 400 mg**" (emphasis original), and the recommended dose frequency and duration is once a day for 10 days. Additionally, the PI states, "**Cedax Oral Suspension must be administered at least 2 hours before or 1 hour after a meal**" (emphasis original).

Furthermore, this webpage misleadingly omits important material information regarding pathogen coverage and the use of Cedax, as identified in the "NOTE" portions of the INDICATIONS AND USAGE section of the PI. For example, but not limited to, the website describes how Cedax is indicated for acute bacterial otitis media but does not disclose that efficacy against the pathogen *Streptococcus pneumonia* was 23% less than control, as described in the "NOTE" portions of the INDICATIONS AND USAGE section of the PI.

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 Cedax webpage was not submitted to OPDP under cover of Form FDA-2253 at the time of initial publication as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Cedax 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, Pernix did not comply with 21 CFR 314.81(b)(3)(i).

OPDP requests that Pernix immediately cease misbranding Cedax. Please submit a written response to this letter on or before January 7, 2014, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Cedax that contain presentations such as those described above, and explaining your plan for discontinuing use of such 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 or 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 the MA #241 and #211 in addition to the NDA numbers 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 distribution of Cedax complies with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jessica M. Fox, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion

{See appended electronic signature page}

Samuel M. Skariah, PharmD
Team Leader
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/

JESSICA M FOX
12/20/2013

SAMUEL M SKARIAH
12/20/2013