DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993-0002

TRANSMITTED BY FACSIMILE

Sapan A. Shah, Ph.D.
President and Chief Executive Officer
Shionogi USA, Inc.
100 Campus Drive
Florham Park, NJ 07932

RE: NDA # 50-685, 50-686
Cedax® (ceftibuten capsules and ceftibuten for oral suspension)
MACMIS ID # 16900

WARNING LETTER

Dear Dr. Shah:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a Professional NDC Sheet, Direct Mail (CED-PLT-001-01) and a Cardinal Health NDC Sheet, Direct Mail (CED07-PLT-002-00) (direct mailers) for Cedax® (ceftibuten capsules and ceftibuten for oral suspension) (Cedax) submitted by Shionogi USA, Inc. (Shionogi) under cover of Form FDA-2253. The direct mailers are misleading because they omit and minimize important risks associated with use of Cedax, broaden its indication, and contain misleading claims. Thus, the direct mailers misbrand the drug in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(ii), (e)(5), (e)(6)(i). These violations are concerning from a public health perspective because they suggest that the product is both safer and effective in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience.

Background

According to its approved product labeling (PI) (in pertinent part, emphasis original):

> CEDAX (ceftibutin) 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 *Streptococcus 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.

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.

Cedax is also associated with a number of risks, including the following bolded Warnings (emphasis original):

WARNINGS

BEFORE THERAPY WITH THE CEDAX PRODUCT IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFTIBUTEN, OTHER CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO THE CEDAX PRODUCT OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ceftibuten, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Additionally, the PI reports that the most common adverse reactions in adults were nausea (4%), headache (3%), diarrhea (3%), dyspepsia (2%), dizziness (1%), abdominal pain (1%), and vomiting (1%), and the most common adverse reactions in pediatric patients were diarrhea (4%), vomiting (2%), abdominal pain (2%), and loose stools (2%).

Furthermore, the **CLINICAL PHARMACOLOGY** section of the PI states (in pertinent part, emphasis original):

Tissue Penetration:
Bronchial secretions: In a study of 15 adults administered a single 400-mg dose of ceftibuten and scheduled to undergo bronchoscopy, the mean concentrations in

epithelial lining fluid and bronchial mucosa were 15% and 37%, respectively, of the plasma concentrations.
[…]
Middle-ear fluid (MEF): In a study of 12 pediatric patients administered 9 mg/kg, ceftibuten MEF area under the curve (AUC) averaged approximately 70% of the plasma AUC.
[…]
Microbiology:
[…]
Ceftibuten is stable in the presence of most plasmid-mediated beta-lactamases, but it is not stable in the presence of chromosomally-mediated cephalosporinases produced in organisms such as *Bacteroides*, *Citrobacter*, *Enterobacter*, *Morganella*, and *Serratia* . . . . ceftibuten should not be used against strains resistant to beta-lactams due to general mechanisms such as permeability or penicillin-binding protein changes like penicillin-resistant *S. pneumoniae*.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. The direct mailers are misleading because they present numerous efficacy claims for Cedax but fail to reveal material risk information associated with use of the drug. For example, the direct mailers include the following efficacy claims:

- "Convenient once-a-day dosing . . ."
- "High penetration into the middle ear fluid and bronchial secretions"
- "Enhanced stability against beta-lactamase-producing pathogens"

However, the only risk disclosure presented for Cedax is the following statement: "Low incidence of diarrhea (only 4% in children)." The mailers fail to present any of the other risks reflected in the PI, including the bolded Warning regarding serious hypersensitivity reactions. Furthermore, this statement in the piece, which is itself framed as a positive claim ("Low incidence…"), is presented under a bullet titled "Excellent tolerability" and along with another positive claim about the drug, "Less than a 1% discontinuation rate due to adverse events in children." The totality of these omissions and representations creates the misleading impression that Cedax is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Broadening of Indication/Omission of Indication

The direct mailers are misleading because they suggest that Cedax is effective in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience. Specifically, the direct mailers include claims suggesting efficacy of the drug as an anti-infective, such as:

- "High penetration into the middle ear fluid and bronchial secretions"
- "Enhanced stability against beta-lactamase-producing pathogens"

However, the pieces fail to present the full indications for the product, including the specific infections for which the drug is indicated, namely acute bacterial otitis media and acute bacterial exacerbations of chronic bronchitis, and that Cedax is approved only for the treatment of mild-to-moderate infections. Therefore, the direct mailers misleadingly imply that Cedax is effective for the treatment of any middle ear or bronchial infection. The direct mailers also fail to reveal that Cedax is approved for use only against susceptible strains of designated microorganisms, and to identify the list of organisms for each indication (see Background section above), thus suggesting that Cedax is effective against a wider range of pathogens than has been demonstrated. Other important material limitations to pathogen coverage and the use of Cedax, as identified in the "NOTE" portions of the INDICATIONS AND USAGE section of the PI, are also misleadingly omitted from the pieces, contributing to the impression that the drug is useful in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience. For example, these notes reveal that ceftibuten clinical efficacy was 22% less than control in acute bacterial exacerbations of chronic bronchitis where *Moraxella catarrhalis* was isolated from infected sputum at baseline. The notes also reveal that ceftibuten should be given empirically for the treatment of acute bacterial otitis media only when adequate antimicrobial coverage against *Streptococcus pneumoniae* has been previously administered, since the efficacy of Cedax against *Streptococcus pneumoniae* was 23% less than control. The direct mailers misleadingly fail to include any of this material information about the drug's indication.

Furthermore, the claim that Cedax exhibits "Enhanced stability against beta-lactamase-producing pathogens," misleadingly suggests that Cedax is effective against all beta-lactamase-producing organisms when this is not the case. While Cedax is stable in the presence of most **plasmid-mediated** beta-lactamases, the PI states that it is not stable in the presence of **chromosomally-mediated** cephalosporinases produced in organisms such as *Bacteroides*, *Citrobacter*, *Enterobacter*, *Morganella*, and *Serratia*. In the absence of a disclosure of the drug's indications, including the specific infections and organisms for which the drug is approved, the claim suggests that Cedax exhibits enhanced stability and is effective against all beta-lactamase producing organisms and the infections they cause when this is not the case.

Misleading Claims

The direct mailers are misleading because they fail to reveal facts that are material in light of representations made in the pieces. Specifically, the pieces claim that Cedax is associated with "High penetration into the middle ear fluid and bronchial secretions," but fail to include any context to clarify the meaning of "high" penetration. With regard to middle ear fluid and bronchial penetration, the Cedax PI reports that mean concentrations of ceftibuten in epithelial lining fluid and bronchial mucosa in adults were only 15% and 37%, respectively, of the plasma concentrations, and ceftibuten middle ear fluid area under the curve (AUC) in pediatric patients averaged approximately 70% of the plasma AUC. Without information about the actual level of penetration, this claim of high penetration is thus misleading because it overstates the efficacy of the product. Specifically, the audience is not likely to interpret this claim, absent context, as meaning that mean concentrations of ceftibuten in epithelial lining fluid and bronchial mucosa in adults are 15% and 37%, respectively, of the plasma concentrations, and that ceftibuten middle ear fluid area under the curve (AUC) in

pediatric patients averaged approximately 70% of the plasma AUC, particularly given that some other antibiotics indicated for the treatment of the same infections can achieve tissue or fluid concentrations greater than plasma levels (e.g., 500% of plasma levels or greater).

Conclusion and Requested Action

For the reasons discussed above, the direct mailers misbrand Cedax in violation of the Act, 21 U.S.C. 352(a) & 321(n). *Cf*. 21 CFR 202.1(e)(3)(ii), (e)(5), (e)(6)(i).

DDMAC requests that Shionogi immediately cease the dissemination of violative promotional materials for Cedax such as those described above. Please submit a written response to this letter on or before December 1, 2008, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) in use for Cedax as of the date of this letter, identifying which of these materials contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Because the violations described above are serious, we request, further, that your submission include a 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. Please direct your response to me at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS ID #16900 in addition to the NDA numbers. We remind 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 Cedax comply with each applicable requirement of the 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}

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

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

/s/

Thomas Abrams

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