CEDAX®
(ceftibuten capsules/
oral suspension)

Sciele Pharma, Inc.
A SHIONOGI COMPANY

IMPORTANT CORRECTION OF DRUG INFORMATION

February 9, 2009

Dear Healthcare Provider:

This letter is sent to you at the request of the U.S. Food and Drug Administration (FDA). The FDA's Division of Drug Marketing, Advertising, and Communications (DDMAC) notified Shionogi USA, Inc. (Shionogi) that two direct mailers for Cedax® (ceftibuten capsules/oral suspension) were false or misleading because they omitted and minimized risks associated with Cedax therapy, broadened the indication for the drug, and contained misleading claims, and that therefore these promotional materials were in violation of the Federal Food, Drug, and Cosmetic Act.

Specifically, the direct mailers omitted most of the risks associated with use of Cedax, including the bolded WARNING from the approved product labeling regarding serious hypersensitivity reactions and other adverse events associated with the product. Additionally, the direct mailers included claims suggesting efficacy of the drug as an anti-infective and enhanced stability against beta-lactamase producing pathogens, but omitted the full approved indications for Cedax, including important limitations to the indications as reflected in special "NOTES." Thus, the FDA states that the direct mailers misleadingly suggested that Cedax is effective for the treatment of a broader range of infections, and for a wider range of pathogens, including a wider range of beta-lactamase-producing pathogens, than has been demonstrated by substantial evidence or substantial clinical experience. Furthermore, the FDA states that the direct mailers contained a misleading claim regarding the "high" penetration of Cedax into middle ear fluid and bronchial secretions without revealing the specific degree of penetration, thereby overstating the efficacy of the product.

Sciele Pharma, Inc., the current marketer of Cedax, now takes this opportunity to provide you with the following important corrective information about Cedax and the risks associated with use of the drug.

Product Indications

Cedax is only 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 influenza* (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 *M. catarrhalis* was isolated from infected sputum at baseline, ceftibuten clinical efficacy was 22% less than control.

- **Acute Bacterial Otitis Media** due to *Haemophilus influenza* (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.

Safety Information

- **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.**

- The most common adverse events reported in US Clinical Trials in adult patients include nausea (4%), headache (3%), diarrhea (3%), dyspepsia (2%), dizziness (1%), abdominal pain (1%), vomiting (1%). The discontinuation rate in adult patients was 2%.

- The most common adverse events reported in US Clinical Trials in pediatric patients include diarrhea (4%), vomiting (2%), abdominal pain (2%), loose stools (2%). The incidence of diarrhea in pediatric patients ≤2 years old was 8% compared with 2% in pediatric patients >2 years old. The discontinuation rate in pediatric patients was <1%.

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*. Like other beta-lactam agents, 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*.

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.

See Attached Package Insert (Rev 04/08)

Sincerely,

Nicole D. Forman

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Sciele Pharma, Inc.

CEDAX®
(ceftibuten capsules/
oral suspension)

Dose	NDC
Cedax Capsules, 400 mg - 20 count	**45809-401-20**
Cedax Suspension, 90 mg/5ml - 60ml	**45809-801-60**
Cedax Suspension, 90 mg/5ml - 90ml	**45809-801-90**
Cedax Suspension, 90 mg/5ml - 120ml	**45809-801-12**

Inquiries should be referred to Sciele Pharma Inc. Medical Affairs – (800) 849-9707 ext. 1454