CEDAX* Capsules/Powder for Oral Suspension

FOR ORAL ADMINISTRATION

DESCRIPTION

Ceftibuten dihydrate is semisynthetic third generation cephalosporin antibiotic for oral administration. Its chemical formula is: (+)-(6R, 7R)-7-[(z)-2-(2-amino-4-thiazolyl) -4-carboxycrotonamido] -8-oxo-5thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, dihydrate. It occurs as both the cis- and trans- forms. Molecular weight = 446.43.

Each CEDAX* Capsule contains 200mg or 400mg ceftibuten. The inactive ingredients in CEDAX capsules are microcrystalline cellulose, sodium starch glycolate and magnesium stearate. The gelatine capsule contains titanium dioxide as a colouring agent.

Each bottle of CEDAX* Powder for Oral Suspension contains sufficient powder to deliver 90mg or 180mg per 5ml dose following reconstitution. CEDAX* Powder is cherry flavoured and contains xanthan gum, sucrose, simethicone, silicon dioxide, titanium dioxide, polysorbate 80 and sodium benzoate as inactive ingredients.

ACTIONS

As with most beta-lactam antibiotics, the bactericidal activity of ceftibuten results from the inhibition of bacterial cell wall synthesis. Due to its chemical structure, ceftibuten is highly stable to beta-lactamases. Many beta-lactamase-producing micro-organisms, which are resistant to penicillins or other cephalosporins, may be inhibited by ceftibuten.

Ceftibuten-*trans*, formed by isomerization of ceftibuten (*cis* form), has only one-fourth to one-eighth the activity of ceftibuten.

Microbiology: Ceftibuten is highly stable toward plasmid-mediated penicillinases and cephalosporinases. However, it is not stable to some cephalosporinases that are chromosomally mediated in organisms such as Citrobacter, Enterobacter and Bacteroides. As with 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 proteins (PBP) like penicillin-resistant *S.pneumoniae*. Ceftibuten binds preferentially to PBP-3 of *E.coli* resulting in the formation of filamentous forms at 1/4 to 1/2 the minimum inhibitory concentration (MIC) and lysis at two times the MIC. The minimum bactericidal concentration (MBC) for ampicillin-sensitive and -resistant *E.coli* is nearly equal to the MIC.

Ceftibuten has demonstrated activity in vitro and in clinical infections against most strains of the following micro-organisms:

Gram-positive micro-organisms: *Streptococcus pyogenes, Streptococcus pneumoniae* (excluding penicillin-resistant strains);

Gram-negative micro-organisms: *Haemophilus influenzae* (both beta-lactamase positive and negative strains); *Haemophilus parainfluenzae* (beta-lactamase positive and negative); *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive); *Escherichia coli; Klebsiella* spp. (including *K.pneumoniae and K. oxytoca*); indole-positive Proteus (including *P.vulgaris*) as well as other species of Proteeae, ie, Providencia; *P.mirabillis; Enterobacter* spp. (including *E.cloacae* and *E. aerogenes*); *Salmonella* spp.; *Shigella* spp.

Ceftibuten has demonstrated in vitro activity against most strains of the following micro-organisms; however, clinical efficacy has not been established:

Gram-positive micro-organisms: Group C and Group G streptococci.

Gram-negative micro-organisms: Brucella, Neisseria, *Aeromonas hydrophilia. Yersinia enterocolitica, Providencia rettgeri., Providencia stuartii* and strains of Citrobacter, Morganella and Serratia that do not hyperproduce chromosomal cephalosporinases.

Ceftibuten is inactive against staphylococci, enterococci, *Acinetobacter, Listeria, Flavobacterium,* and *Pseudomonas* spp. Ceftibuten shows little activity against most anaerobes, including most species of Bacteroides. Ceftibuten-*trans* is inactive microbiologically in vitro and in vivo against these same strains.

Susceptibility Testing: *Diffusion technique:* Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. Ceftibuten is tested by the disc method for susceptibility testing described by Bauer AW, et al: Am J Clinical Pathology 1966; 45 ; 493, The National Committee for Clinical Laboratory Standards, Approved Standard: April 1990 and Federal Register 1974: 39 (May 30): 19182-19184. Interpretation of probable susceptibility involves correlation of the diameters obtained in the disc test with the ceftibuten MIC.

Laboratory results of testing using a single disc containing 30 µg ceftibuten should be interpreted according to the following criteria: a zone diameter ≥21mm is Susceptible (S); 18-20mm. Moderately Susceptible (MS): ≤17mm. Resistant (R). For Haemophilus, a zone >28 mm indicates susceptibility. Pneumococcal isolates with oxacillin zone sizes of >20 mm are susceptible to penicillin and can be considered susceptible to ceftibuten.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" indicates that inhibitory concentrations of the antibiotic may well be achieved if high dosage is used or if the infection is confined to tissues and fluids (eg urine) in which high antibiotic concentrations are attained. A report of "Resistant" indicates that the achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected. Standard procedures require the use of laboratory control micro-organisms. The 30µg disc should give a zone diameter of 29-35mm for *E.coli* ATCC 25922 and 29-35 mm for H. influenzae ATCC 49247.

The 30µg ceftibuten disc should be used for all in vitro testing of isolates. The class disc (Cephalothin) for cephalosporin susceptibility testing is not appropriate because of spectrum differences with ceftibuten.

Dilution technique: A recommended procedure for dilution susceptibility testing for ceftibuten is that of the National Committee for Clinical Laboratory Standards. Approved Standard: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Mueller-Hinton agar or cation-adjusted Mueller-Hinton broth is the recommended media for commonly isolated, rapidly growing pathogens and *Haemophilus* spp. Blood and blood constituents may be added for testing certain streptococci.

Micro-organisms may be considered susceptible to ceftibuten if the MIC value for ceftibuten is ≤8 µg/ml and resistant if the MIC is ≥32 µg/ml. Micro-organisms having an MIC of 16 µg/ml are moderately susceptible.

As with standard diffusion methods, dilution procedures require the use of laboratory control micro-organisms. Standard ceftibuten powder should give MIC values in range of 0.125-0.5 µg/ml for *E.coli* ATCC 25922 and ≥32 µg/ml for *S.aureus* ATCC 29213 and 0.25-1.0 mcg/ml for H. influenzae ATCC 49247.

INDICATIONS AND USAGE

CEDAX* is indicated in the treatment of the following infections when caused by strains of susceptible micro-organisms:

- Upper respiratory tract infections, including the following specific infections: pharyngitis, tonsillitis, and scarlet fever in adults and/or children; acute sinusitis in adults; otitis media in children.
- Lower respiratory tract infections in adults, including acute bronchitis, acute exacerbations of chronic bronchitis and acute pneumonia in patients appropriately considered for oral therapy, ie, those with primarily community-acquired infections.
- Urinary tract infections in adults and children, both complicated and uncomplicated infections.
- Enteritis and gastroenteritis in children caused by Salmonella, Shigella or *E.coli.* CEDAX* has not demonstrated activity against species of Campylobacter or Yersinia.

DOSAGE AND ADMINISTRATION

As with other oral antibiotics, duration of treatment generally ranges from five to ten days. For treatment of infections due to *Streptococcus pyogenes*, a therapeutic dose of CEDAX* should be administered for at least 10 days.

Adults: The recommended dose of CEDAX* is 400mg daily. CEDAX* Capsules may be taken without regard to mealtime. For treatment in the following indications this may be administered as 400 mg once daily: acute bacterial sinusitis, acute bronchitis, acute exacerbations of chronic bronchitis, and complicated or uncomplicated urinary tract infections.

For the treatment of community-acquired pneumonia in patients in whom oral therapy is appropriate, the recommended dose is 200mg every 12 hours.

Adult patients with renal impairment: CEDAX* pharmacokinetics are not affected sufficiently to require dosage modification unless creatinine clearance values are lower than 50ml/min. If creatinine clearance is from 49 to 30 ml/min, the daily dose should be decreased to 200mg. With creatinine clearance values of 29 to 5ml/min, the recommended daily dose is 100mg.

If alteration of dosing frequency is preferred, a 400mg dose of CEDAX* may be administered every 48 hours (every 2 days) to a patient with a creatinine clearance of 30-49 ml/min, and every 96 hours (every 4 days) if creatinine clearance is 5-29ml/min.

In patients undergoing hemodialysis two or three times weekly, a single dose of CEDAX* 400mg may be administered at the end of each hemodialysis session.

Children: The recommended dose is 9 mg/kg/day (maximum of 400mg daily) of the oral suspension. This may be administered as a single daily dose for treatment in the following indications: pharyngitis with or without tonsillitis, acute otitis media with effusion, and complicated or uncomplicated urinary tract infections.

For the treatment of acute bacterial enteritis in children, the total daily dosage may be administered in two divided doses of 4.5mg/kg every 12 hours.

Children weighing more than 45kg or older than 10 years may receive the recommended adult dose.

CEDAX* Suspension may be taken approximately one or two hours before or after mealtime. Shake bottle well before measuring each dose.

CEDAX POWDER FOR ORAL SUSPENSION

Directions for Preparation of Suspension

Tap bottle to thoroughly loosen the powder contents, then prepare suspension as directed. **Pharmacist:** Add the specified volume of water in two divided portions. Shake bottle vigorously after each addition of water to wet and suspend the powder thoroughly. **Consumer:** If precise measure of water is not possible, use the fill line on the label as guide. Add water one-half way to the fill line and shake bottle vigorously to wet the powder thoroughly. Then add water to fill line. Shake bottle again and check that final volume of suspension is at fill line.

Refrigerate the suspension at 2° to 8°C for up to 14 days.

DRUG INTERACTIONS

Drug interaction studies have been conducted with CEDAX* and each of the following: high-dose aluminium-magnesium hydroxide antacid, ranitidine, and single dose intravenous theophylline. No significant drug interaction occurred. The effect of CEDAX* on the plasma levels or pharmacokinetics of theophylline administered orally is not known. No other significant drug interactions have been reported to date.

Drug/food interaction: Food taken concomitantly does not interfere with the efficacy of CEDAX* Capsules. However, the rate and the extent of absorption of CEDAX* from Suspension may be affected by concomitant food intake.

Drug/laboratory test interactions: No known chemical or laboratory test interactions have been noted with CEDAX*. A false positive direct Coombs test has been reported during the use of other cephalosporins. However, the results of assays using red cells of healthy persons to test whether CEDAX* would cause direct Coombs in vitro reactions showed no positive reactions even at concentrations as high as 40 mg/ml.

ADVERSE EFFECTS

In clinical trials in approximately 3000 patients, CEDAX* was generally safe and well tolerated with the majority of observed adverse events being moderate and transient in nature and rare to very rare in frequency. The most frequently reported adverse events were gastrointestinal, including nausea (≤3%) and diarrhoea (3%), and headache (2%).

Rarely reported adverse events included dyspepsia, gastritis, vomiting, abdominal pain and dizziness, and serum sickness-like disorders. Very rarely, *Clostridium difficile* was associated with moderate to severe diarrhoea. Convulsions, were also reported very rarely, but were not definitely attributed to therapy. Most adverse events responded to symptomatic treatment or ceased upon discontinuation of CEDAX* therapy.

CEPHALOSPORIN CLASS-RELATED ADVERSE EVENTS

In addition to the adverse events listed above in patients treated with CEDAX*, the following adverse reations and altered laboratory tests have been reported for the cephalosporin antibiotic class but have not been observed to date with CEDAX*.

Adverse Reactions: Allergic reactions, including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, severe diarrhea and antibiotic-associated colitis, superinfection, renal dysfunction, toxic nephropathy, aplastic anemia, hemolyic anemia and hemorrhage. **Abnormal Laboratory Tests:** Elevated bilirubin, positive direct Coombs test, glycosuria, ketonuria, pancytopenia, neutropenia and agranulocytosis.

Clinical laboratory abnormalities, including haemoglobin decreases, leukopenia, eosinophilia and thrombocytosis were reported very rarely. Also reported very rarely were transient elevations in AST (SGOT), ALT (SGPT), and LDH. Rarely, these were considered possibly associated with CEDAX* therapy.

CONTRAINDICATIONS

CEDAX* is contraindicated in patients with known allergy to cephalosporins or to any components of CEDAX*

PRECAUTIONS

The dosing of CEDAX* may require adjustment in patients with marked renal insufficiency as well as patients undergoing dialysis.

CEDAX* is readily dialysable. Dialysis patients should be monitored carefully, and administration of CEDAX* should be timed to occur immediately following dialysis.

CEDAX* should be prescribed with caution in individuals with a history of complicated gastrointestinal disease, particularly chronic colitis.

Cephalosporin antibiotics should be administered with extreme caution to patients with known or suspected allergy to penicillins. Approximately 5% of patients with documented penicillin allergy experience cross-reactivity to the cephalosporin antibiotics. Serious acute hypersensitivity reactions (anaphylaxis) have been reported also in individuals receiving both penicillins and cephalosporins, and cross-hyperreactivity with anaphylaxis has been known to occur. If an allergic reaction to CEDAX* occurs, discontinue use and administer appropriate therapy. Serious anaphylaxis requires appropriate emergency treatment as indicated clinically, ie adrenaline, intravenous fluids, airway management and oxygen administration, antihistamines, corticosteroids, other pressor amines and vigilant observation.

During therapy with broad-spectrum antibiotics like CEDAX* alteration of the intestinal flora may result in antibiotic-associated diarrhoea, including pseudomembranous colitis due to *Clostridium difficile* toxin. Patients may experience moderate to severe or life-threatening diarrhoea, with or without dehydration, either during or after treatment with the associated antibiotic. It is important to consider this diagnosis in any patient noted to have persistent diarrhoea while taking any broad-spectrum antibiotic like CEDAX*.

Paediatric use: Safety and efficacy of CEDAX* in infants less than six months of age have not been established.

Usage during pregnancy and lactation: There are no adequate and controlled studies in pregnant women or during labour and delivery. Because animal reproduction studies are not always predictive of human response, administration of CEDAX* during such clinical situations should be weighed in terms of potential risk and benefit to both mother and foetus.

CEDAX* has not been detected in the milk of nursing mothers.

OVERDOSAGE.

No toxic manifestations have been seen following accidental overdosage with CEDAX*. Gastric lavage may be indicated, otherwise no specific antidote exists. Significant quantities of CEDAX* can be removed from the circulation by haemodialysis. Effective removal by peritoneal dialysis has not been determined.

In healthy adult volunteers receiving single doses of up to 2g of CEDAX*, no serious adverse reactions were observed and all clinical and laboratory findings were within normal range.

How supplied:

CEDAX 400:	Boxes of 5 and 10 capsules of 400mg in strips
CEDAX Suspension:	Bottle containing 90mg/5ml ceftibuten after reconstitution. 30 and 60ml.
	Bottle containing 180mg/5ml ceftibuten after reconstitution. 30 and 60ml.

Storage:

Store between 2° and 25°C. Following reconstitution of the suspension, both the 90mg/5ml and the 180mg/5ml formulations can be stored for 14 days under refrigeration, 2° to 8°C.

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