TRIOCEF
20 mg/mL (Oral Drops) & 100 mg/5 mL
Granules for Suspension
(Cefixime)

ANTIBACTERIAL
DESCRIPTION

FORMULATION
Each 5 mL (1 teaspoonful) of reconstituted suspension contains:
Cefixime .................................................. 100 mg

PHARMACOLOGY

Cefixime is a semi-synthetic third-generation cephalosporin beta-lactam antibiotic for oral administration. It is highly stable in the presence of beta-lactamase enzymes. Cefixime acts by binding to specific penicillin-binding proteins (PBP) located inside the bacterial cell wall, resulting in the inhibition of the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases may be susceptible to cefixime.

PHARMACOKINETICS

Absorption and Distribution
Cefixime (TRIOCEF) is about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food. The oral suspension produces average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal adult volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal adult volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal adult volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media. Crossover studies of tablet versus suspension have not been performed in children.

Serum protein binding of cefixime is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days.
Metabolism and Excretion

There is no evidence of metabolism of cefixime in vivo. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours but may range up to 9 hours in some normal volunteers.

Renal Impairment: In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21 to 60 mL/min.

Clinical Studies

Comparative clinical trials of otitis media were conducted in nearly 400 children between the ages of 6 months to 10 years. Streptococcus pneumoniae was isolated from 47% of the patients, Haemophilus influenzae from 34%, Moraxella.catarrhalis from 15% and S. pyogenes from 4%.

The overall response rate of Streptococcus pneumoniae to cefixime was approximately 10% lower and that of Haemophilus influenzae or Moraxella.catarrhalis approximately 7% higher (12% when beta-lactamase positive isolates of H. influenzae are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg twice a day or 8 mg/kg once a day, or with a comparator. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had Haemophilus influenzae resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.
INDICATIONS

Cefixime (TRIOCEF) is used in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

- uncomplicated urinary tract infections caused by *Escherichia coli* and *Proteus mirabilis*,
- otitis media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella catarrhalis* (most of which are beta-lactamase positive), and *S. pyogenes*,
- pharyngitis and tonsillitis caused by *S. pyogenes*,
- lower respiratory tract infections (acute bronchitis and acute exacerbations of chronic bronchitis) caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (beta-lactamase positive and negative strains), and
- uncomplicated gonorrhea (cervical/urethral) caused by *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains).
- typhoid fever caused by *Salmonella typhi*

DOSAGE AND ADMINISTRATION

The usual pediatric dose in children over 6 months and under 50 kg is 8 mg/kg/day. This dosage may be given as a single daily dose or 4 mg/kg may be given every 12 hours. In children with typhoid fever, 15-20 mg/kg BW can be given as a single dose or into two equal doses every 12 hours for 7 to 14 days. Maximum dose is 400 mg/day. Or as prescribed by the physician.

<table>
<thead>
<tr>
<th>AGE GROUP</th>
<th>Cefixime 100 mg/ 5mL suspension Dose in mL (tsp)</th>
<th>Given OD</th>
<th>Given every 12 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 to 11 mos</td>
<td>(-)</td>
<td>(-)</td>
<td></td>
</tr>
<tr>
<td>1 to 2 yrs</td>
<td>2.5 to 5 mL (½ to 1 tsp)</td>
<td>1.25 to 2.5 mL (¼ to ½ tsp)</td>
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</tr>
<tr>
<td>3 to 6 yrs</td>
<td>5 to 10 mL (1 to 2 tsp)</td>
<td>2.5 to 5 mL (½ to 1 tsp)</td>
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</tr>
<tr>
<td>7 to 12 yrs</td>
<td>10 to 15 mL (2 to 3 tsp)</td>
<td>5 mL to 7.5 mL (1 to 1 ½ tsp)</td>
<td></td>
</tr>
<tr>
<td>Children &gt; 12 yrs</td>
<td>20 mL (4 tsp)</td>
<td>10 mL (2 tsp)</td>
<td></td>
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<tr>
<td>old and Adults</td>
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DIRECTIONS FOR RECONSTITUTION

To reconstitute: Add 35 mL of water to make a 60 mL suspension.

Prior to reconstitution, tap the bottle several times to loosen granule contents. Add 35 mL of water in TWO PORTIONS to the dry mixture bottle. Shake well after each addition until the contents are evenly suspended.

CONTRAINDICATIONS

Cefixime (TRIOCEF) is contraindicated to patients with a history of hypersensitivity to penicillins or other cephalosporins. Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, IV fluids and IV antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.

WARNINGS AND PRECAUTIONS

_Clostridium difficile_ associated diarrhea (CDAD)

_Clostridium difficile_ associated diarrhea (CDAD) has also been reported with use of nearly all antibacterial agents, including cefixime, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of _C. difficile_. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against _C. difficile_ may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of _C. difficile_, and surgical evaluation should be instituted as clinically indicated.

Prothrombin activity

Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with kidney or liver impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous Vitamin K administered as indicated.
ADVERSE EFFECTS

Most adverse effects reported with cefixime were similar to those reported with other oral cephalosporins and were usually mild and transient in nature.

**Hypersensitivity Reactions:** Anaphylactic/anaphylactoid reactions, skin rashes, urticaria, fever, pruritus, arthralgia, angioedema, facial edema; erythema multiforme, SJS, toxic epidermal necrolysis, serum sickness-like reactions

**GI:** Diarrhea, loose or frequent stools, abdominal pain, anorexia, flatulence, dry mouth, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the clinical studies on cefixime.

**Hepatic:** Transient elevation of ALT, AST, alkaline phosphatase, hepatitis, and jaundice

**Renal:** Transient elevations in BUN or creatinine levels, and rarely, acute renal failure

**CNS:** Headache, dizziness, nervousness, insomnia, somnolence, malaise, fatigue, seizures

**Hematologic:** Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia; prolongation of prothrombin time was seen rarely.

**DRUG INTERACTIONS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Elevated carbamazepine levels have been reported when administered concomitantly with cefixime. Drug monitoring when these drugs are given together is advised.</td>
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<tr>
<td>Warfarin /other anticoagulants</td>
<td>Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is given concomitantly.</td>
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<tr>
<td>Probenecid</td>
<td>Concomitant administration of probenecid reportedly increases peak serum concentration and AUC of cefixime and decreases renal clearance and Vd of the drug.</td>
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<tr>
<td>Salicylates</td>
<td>Concomitant administration of 650 mg oral dose of aspirin and a 400 mg oral dose of cefixime in healthy adult men may result in a 20-25% decrease in peak serum concentration of cefixime and AUC of the drug but did not affect protein binding, serum t 1/2 or renal clearance. This effect may not be clinically important since serum concentrations of cefixime remained higher than the MIC values reported for most susceptible organisms. However, some clinicians state that this effect may be clinically important in certain infections.</td>
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PREGNANCY AND LACTATION

Cefixime has been assigned to pregnancy category B by the FDA. Animal studies failed to reveal evidence of fetal harm. There are no controlled data in human pregnancy. Cefixime is only recommended for use during pregnancy when benefit outweighs risk. There are no data on the excretion of cefixime into human milk.

AVAILABILITY

100 mg/5 mL Granules for Suspension - in amber bottles X 30 mL X 60 mL (Box of 1's)

STORAGE

Granules for suspension: Store at temperatures not exceeding 30 °C. Protect from light.

Reconstituted suspension: Store for 7 days at temperatures not exceeding 30 °C or 14 days at 2-8°C. Keep container tightly closed. Protect from light. Shake well before use. Discard the unused portion after 7 or 14 days depending on how the reconstituted product is stored.

REFERENCES


http://www.drugs.com

http://www.drugbank.ca/drugs/DB00671

http://www.rxlist.com