Biocefixim

200 mg/5 ml

100 mg/5ml

Dry powder for oral suspension

Composition:

Each 5 ml of oral suspension comtaining:

Active ingredient:

Cefixime trihydrate 223.84 mg (equ.to cefixime base 200mg)

Cefixime trihydrate 111.92 mg (equ. To cefixime base 100 mg)

Inactive : Sucrose.Aerosil, sodium benzoate, carboxymethyl cellulose, xanthan gum, strawberry flavor. (+ Sucralose for 100 mg only)

1 INDICATIONS AND USAGE

1.1 Uncomplicated Urinary Tract Infections

Biocefixim for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated urinary tract infections caused by susceptible isolates of *Escherichia coli* and *Proteus mirabilis*.

1.2 Otitis Media

Biocefixim for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with otitis media caused by susceptible isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. (Efficacy for *Streptococcus pyogenes* in this organ system was studied in fewer than 10 infections.)

Note: For patients with otitis media caused by Streptococcus pneumoniae, overall response was approximately 10% lower for Biocefixim than for the comparator .

1.3 Pharyngitis and Tonsillitis

Biocefixim for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with pharyngitis and tonsillitis caused by susceptible isolates of Streptococcus pyogenes. (Note: Penicillin is the usual drug of choice in the treatment of Streptococcus pyogenes infections. Biocefixim for oral suspension is generally effective in the eradication of Streptococcus pyogenes from the nasopharynx; however, data establishing the efficacy of Biocefixim for oral suspension in the subsequent prevention of rheumatic fever is not available.)

1.4 Acute Exacerbations of Chronic Bronchitis

Biocefixim for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with acute exacerbations of chronic bronchitis caused by susceptible isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

1.5 Uncomplicated Gonorrhea (cervical/urethral)

Biocefixim for oral suspension is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated gonorrhea (cervical/urethral) caused by susceptible isolates of *Neisseria gonorrhoeae* (penicillinase-and non-penicillinase-producing isolates).

1.6 Usage

To reduce the development of drug resistant bacteria and maintain the effectiveness of Biocefixim and other antibacterial drugs, Biocefixim for oral suspension should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Adults

The recommended dose of Biocefixim is 400 mg daily. This may be given as a 400 mg capsule daily. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.
The capsule may be administered without regard to food.
In the treatment of infections due to Streptococcus pyogenes, a therapeutic dosage of Biocefixim should be administered for at least 10 days.

2.2 Pediatric Patients (6 months or older)

The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.
Note: A suggested dose has been determined for each pediatric weight range. Refer to Table 1. Ensure all orders that specify a dose in milliliters include a concentration, because Biocefixim for oral suspension is available in two different concentrations (100 mg/5 mL and 200 mg/5 mL).

PEDIATRIC DOSAGE CHART
Doses are suggested for each weight range and rounded for ease of administration

		100mg/5ml	**200mg/5ml**
Patient Weight (kg)	**Dose/Day (mg)**	**Dose/Day (ml)**	**Dose/Day (ml)**
5 to 7.5	50	2.5	--
7.6 to 10	80	4	2
10.1 to 12.5	100	5	2.5
12.5 to 20.5	150	7.5	4
20.6 to 28	200	10	5
28.1 to 33	250	12.5	6
33.1 to 40	300	15	7.5
40.1to 45	350	17.5	9
45.1 to greater	400	20	10

Children weighing more than 45 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical trials of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose.
Therefore, the tablet or capsule should not be substituted for the suspension in the treatment of otitis media *[see Clinical Pharmacology (12.3)]*.
In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of Biocefixim should be administered for at least 10 days.

2.3 Renal Impairment

Biocefixim may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Refer to Table 2 for dose adjustments for adults with renal impairment. Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

Table 2. Doses for Adults with Renal Impairment

al Dysfunction	**Biocefixim for Oral Suspension**	
Creatinine Clearance (mL/min)	**100 mg/5 mL**	**200 mg/5 mL**
	Dose/Day (mL)	Dose/Day (mL)
60 or greater	Normal dose	Normal dose
21 to 59*OR renal hemodialysis*	13	6.5
20 or less OR continuous peritoneal dialysis	8.6	4.4

* The preferred concentration of oral suspension to use is 200 mg/5 mL for patients with this renal dysfunction

2.4 Reconstitution Directions for Oral Suspension

Strength	**Bottle Size**	**Reconstitution Directions**
200 mg/5 mL	60 mL	To reconstitute, suspend with **Add to mark of water tomixture in the bottle** Method: Tap the bottle several times to loosen powder contents prio r to reconstitution. Add water for reconstitution and shake well. Add the remainder of water and shake well.
100 mg/5 mL and 200 mg/5 mL	60 mL	To reconstitute, suspend with **Add to mark of water tomixture in the bottle** . Method: Tap the bottle several times to loosen powder contents pri or to reconstitution. Add water for reconstitution and shake well. A dd the remainder of water and shake well.

After reconstitution, the suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days.

Contraindications:

Hypersensitivity to the active substance, to other cephalosporins or to any of the excipients.
Previous immediate and/or severe hypersensitivity reaction to a penicillin or to any other beta-lactam medicinal products**.**

Warnings and precautions:

5.1 Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of Biocefixim.
Before therapy with Biocefixim is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to 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 antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Biocefixim occurs, discontinue the drug.
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with beta lactam antibiotics .

5.2 Clostridium difficile-Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Biocefixim, 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*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

5.3 Dose Adjustment in Renal Impairment

The dose of Biocefixim should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully [see Dosage and Administration (2)].

5.4 Coagulation Effects

Cephalosporins, including Biocefixim, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic 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.

5.5 Development of Drug-Resistant Bacteria

Prescribing Biocefixim in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the twice daily or the once daily regimen. Five percent (5%) of patients in the U.S. clinical trials discontinued therapy because of drug-related adverse reactions. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.

6.2 Post-marketing Experience

The following adverse reactions have been reported following the post-approval use of Biocefixim. Incidence rates were less than 1 in 50 (less than 2%).

Gastrointestinal

Several cases of documented pseudomembranous colitis were identified in clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Skin and subcutaneous tissue disorder

Frequency not known: Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS), Bullous exfoliative-dermatitis, Toxic epidermal necrolysis , Stevens-Johnson syndrome

Hepatic

Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal

Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System

Headaches, dizziness, seizures.

Hemic and Lymphatic System
Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.

Abnormal Laboratory Tests
Hyperbilirubinemia.
Other Adverse Reactions
Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

Adverse Reactions Reported for Cephalosporin-class Drugs
Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced [see Dosage And Administration (2) and Overdosage (10)]. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

7 DRUG INTERACTIONS

7.1 Carbamazepine

Elevated carbamazepine levels have been reported in postmarketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

7.2 Warfarin and Anticoagulants

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

7.3 Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.
The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest®**, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or TesTape®**) be used. A false-positive direct Coombs test has been reported during treatment with other cephalosporins; therefore, it should be recognized that a positive Coombs test may be due to the drug.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.
There are no adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

8.2 Labor and Delivery

cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

8.3 Nursing Mothers

It is not known whether cefiximeis excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

8.4 Pediatric Use

Safety and effectiveness of cefixime in children aged less than six months old have not been established. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

8.5 Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A pharmacokinetic study in the elderly detected differences in pharmacokinetic parameters [see Clinical Pharmacology (12.3)]. These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.

8.6 Renal Impairment

The dose of Biocefixim should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully [see Dosage and Administration (2.3)].

10 OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Biocefixim is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of Biocefixim did not differ from the profile seen in patients treated at the recommended doses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Biocefixim is a semisynthetic cephalosporin antibacterial drug .

12.3 Pharmacokinetics

cefixime, given orally, are 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 [see Dosage and Administration (2)]. Cross-over studies of tablet versus suspension have not been performed in children.

The 400 mg capsule is bioequivalent to the 400 mg tablet under fasting conditions. However, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on Cmax.

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg tablet, a single 400 mg tablet or 400 mg of cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension. Peak serum concentrations occur between 3 and 8 hours following oral administration of a single 400 mg capsule

Distribution

Serum protein binding 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. Adequate data on CSF levels of cefixime are not available.

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.

Special Populations

Geriatrics: Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults. Differences in the pharmacokinetic parameters between 12 young and 12 elderly subjects who received 400 mg of cefixime once daily for 5 days are summarized as follows:

*

Difference between age groups was significant. ($p<0.05$)

Pharmacokinetic Parameters (mean ± SD) for cefixime **in Both Young & Elderly Subjects**

Pharmacokinetic parameter	**Young**	**Elderly**
C_{max} (mg/L)	4.74 ± 1.43	5.68 ± 1.83
T_{max} (h) *	3.9 ± 0.3	4.3 ± 0.6
AUC (mg.h/L) *	34.9 ± 12.2	49.5 ± 19.1
$T_{½}$ (h) *	3.5 ± 0.6	4.2 ± 0.4
C_{ave} (mg/L)*	1.42 ±0.50	1.99 ± 0.75

However, these increases were not clinically significant *[see Dosage and Administration (2)]*.

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.

16-Packing

biocefixime powder for oral suspension, 100 mg/5 mL is an off-white to yellowish white crystalline powder. After reconstituted, each 5 mL of reconstituted suspension contains 100 mg of cefixime as the trihydrate and is supplied as 60 mL bottle + inner leaflet

Before reconstitution: Store at temperature not exceeding 30°C.
After reconstitution: Store at temperature (2-8) ºC to be used within 7days.

Biocefixim powder for oral suspension, 200 mg/5 mL is off-white to pale yellow colored powder. After reconstituted, each 5 mL of reconstituted suspension contains 200 mg of cefixime as the trihydrate and is supplied as 60ml bottle + inner LDPE foam liner+ inner leaflet.

Before reconstitution: Store at temperature not exceeding 30°C in a dry place used immediately after opening.
After reconstitution: Store at temperature (2-8) ºC to be used within 7days.