## **Evo**Fix<sup>®</sup>

(Cefixime USP) Suspension & Capsules

**EvoFix-DS**<sup>®</sup>

(Cefixime USP) Suspension

## COMPOSITION

EvoFix Capsules 400 mg: Each capsule contains: Cefixime ..... 400 mg (as Cefixime trihydrate) (PharmEvo Specs.)

EvoFix Granules for Oral Suspension: Each 5ml of reconstituted suspension contains Cefixime ..... 100 mg (as Cefixime trihydrate) (USP Specs.)

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## DESCRIPTION

Cefixime is a semisynthetic, cephalosporin antibacterial for oral administration. Chemically, it is (68,7R)-7.[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3vinyl 5-thia-1-azabicyclo [4.2.0] oct-2<sup>--</sup> ene-2-carboxylic acid, 72 -(2)-[O-(carboxy methyl) oxime] trihydrate. Chemical Formula is C<sub>16</sub>H<sub>15</sub>N<sub>8</sub>O<sub>7</sub>S<sub>2</sub>·3H<sub>2</sub>O

## CLINICAL PHARMACOLOGY

## Mechanism of action

Mechanism of action This third-generation oral cephalosporin acts by binding to one or more penicillin-bind-ing proteins; it arrests bacterial cell-wall synthesis and inhibits bacterial growth. Cefixime is stable in the presence of certain beta-lactamase enzymes. As a result, certain organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases may be susceptible to cefixime.

## MICROBIOLOGY

Susceptible organisms In-vitro antimicrobial activity and clinical efficacy has been shown for: Streptococcus pneumonia, Streptococcus pyogenes, Neisseria gonorrhea, Proteus mirabilis, Moraxella catarrhalis, Enterobacter species, Escherichia coli, Haemophilus influenza

Favorable in-vitro susceptibility has been shown for: Klebsiella species, Haemophilus parainfluenzae, Proteus vulgaris, Shigella species, Salmonella species, Pasteurella multocida.

## Resistant organisms

Most strains of enterococci (Streptococcus faecalis, group D Streptococci) and Staphylococci (including coagulase positive and negative strains and meticillin-resistant strains) are resistant to cefixime. In addition, most strains of *Pseudomonas*, Bacteriodes fragailis, Listeria monocytogenes and *Clostridia* are resistant to Cefixime.

Mechanism of Resistance Resistance is most commonly attributed to alterations in penicillin binding proteins (PBPs)

## PHARMACOKINETICS

Absorption: Evofix capsules are also 40% - 50% absorbed after oral administration. Peak serum concentrations usually occur between 3 and 8 hours following oral administration of a single 400 mg capsule.

single 400 mg capsule. Evofix suspension, given orally, 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. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension.

*Distribution:* Serum protein binding is concentration independent with a bound fraction of approximately 65%. Adequate data on CSF levels of cefixime are not available.

Metabolism: There is no evidence of metabolism of cefixime in vivo

Elimination: 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.

## INDICATIONS

Cefixime is indicated in the treatment of adults and pediatric patients 6 months of age or older with the following infections when caused by susceptible micro-organisms:

## **Urinary Tract Infections**

Cefixime is used in the treatment of Urinary Tract Infections (cystitis, cysto-urethritis and un-complicated pyelonephritis) caused by *Escherichia coli* and *Proteus mirabilis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Klebsiella species*, *Haemophilus influenzae* (beta-lactamase positive and negative), Branhamella catarrhalis (beta-lact-amase positive and negative) and *Enterobacter species*.

## **Upper Respiratory Tract Infections:**

 Otitis Media: Cefixime is used in the treatment of Otitis media caused by Haemophilus influenzee, Moraxella catarrhalis, Streptococcus pyogenes and Streptococcus influenzae, pnemoniae.

Pharyngitis and Tonsillitis: Cefixime is indicated in Pharyngitis/Tonsillitis caused by Streptococcus pyogenes.

Acute Exacerbations of Chronic Bronchitis: Cefixime is indicated to treat acute exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Uncomplicated Gonorrhea (cervical/urethral): Cefixime is used to treat uncomplicat-ed cervical or urethral gonorrhea caused by *Neisseria gonorrhoeae*.

## DOSAGE AND ADMINISTRATION

The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

Adult Dosage The recommended dose of cefixime in adults is 400 mg daily for the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended. In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

## Pediatric Dosage

In pediatric population, the recommended formulation is EvoFix Suspension or EvoFix DS Suspension.

## Children and Adolescents over 10 years The recommended dosage is 200-400 mg daily according to the severity of infection, given either as a single dose or in two divided doses.

Children 6 months to 10 years of age: 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.

		EVOFIX Suspension 100mg/5ml	EVOFIX-DS Suspension 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
12.6 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 or greater	400	20	10

**Dosage in Renal Impairment:** Cefixime 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. Patients whose creatinine clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given 6.5ml of Evofix for Oral Suspension (200 mg/5 mL) daily or 13 ml of Evofix for Oral Suspension (100 mg/5 mL) daily.

Patients whose creatinine clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given 200 mg daily (i.e. half of the 400 mg tablet).

Neither hemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.





## ADMINISTRATION REQUIREMENTS

## Re-constitution directions for EvoFix Suspension and EvoFix DS Suspension

Brand Name	Strength	Bottle Volume	Instructions
EvoFix granules for oral suspension	100mg/5ml	30 ml	To reconstitute, add 20 ml of (previously boiled and cooled) water to the bottle containing granules. Mix well and make up the volume with water, up to the 30 ml mark. Shake well to prepare suspension. The prepared suspension can be used within 7 days, if stored at room temperature not exceeding 30°C and 14 days under refrigerated conditions (2-8°C).
		60 ml	To reconstitute, add 40 ml of (previously boiled and cooled) water to the bottle containing granules. Mix well and make up the volume with water, up to the 30 ml mark. Shake well to prepare suspension. The prepared suspension can be used within 7 days, if stored at room temperature not exceeding 30°C and 14 days under refrigerated conditions (2-8°C).
EvoFix DS granules for oral suspension	200mg/5 ml	30 ml	To reconstitute, add 20 ml of (previously boiled and cooled) water to the bottle containing granules. Mix well and make up the volume with water, up to the 30 ml mark. Shake well to prepare suspension. The prepared suspension can be used within 7 days, if stored at room temperature not exceeding 30°C and 14 days under refrierated conditions (2.8°C).

## CONTRAINDICATIONS

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tients with known hypersensitivity to cephalosporin antibiotics

## WARNINGS AND PRECAUTIONS

Severe cutaneous adverse reactions Toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on cefixime. When severe cutaneous adverse reactions occur, cefixime should be discontinued and appropriate therapy and/or measures should be taken. *Hypersensitivity reactions (history of penicillin allergy)* Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime. Cefixime should be given with catalities) have been reported with the use of cefixime. Cefixime should be given with catalities have been 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 occurs with Cefixime, the drug should be discontinued and the patient treated with appropriate agents, if necessary.

the drug should be discontinued and the patient treated with appropriate agents, if necessary. Clostridium-difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ceftxime, 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. Hemolytic anemia Drug-induced hemolytic anemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of hemolytic anemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated hemolytic anemia has also been reported. Acute Renal Failure As with other cephalosporins, cefixime may cause acute renal failure including

Acute Renal Failure As with other cephalosporins, cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, cefixime should be discontinued and appropriate therapy and/or measures should be taken. **Renal impairment** Cefixime should be administered with caution in patients with markedly impaired renal function. (See DOSAGE AND ADMINISTRATION) Coaculation Effects

Coagulation Effects

Coagulation Effects Cephalosporins, including Cefixime, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutrition-al 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, if required.

## ADVERSE REACTIONS

Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

Nervous system disorders	Dizziness, Headache
Respiratory, thoracic and mediastinal disorders	Dyspnea
Renal and urinary disorders	Renal failure acute including tubulointerstitial nephritis
Immune System disorders, administrative site conditions, skin and subcutaneous tissue	Anaphylactic reaction, Serum sickness-like reaction, Drug rash with eosinophilia and systemic symptoms (DRESS), Pruritus, Rash Drug Fever, Arthralgia, Erythema multiforme Stevens-Johnson syndrome, Toxic epidermal necrolysis, Angio-oedema, Urticaria, Pyrexia Face, Edema, Genital pruritus, Vaginitis

Blood and lymphatic system disorders	Eosinophilia, Agranulocytosis, Leucopenia, Neutropenia Granulocytopenia, Hemolytic anemia Thrombocytopenia
Gastrointestinal disorders	Abdominal pain, Diarrhea, Dyspepsia Nausea, Vomiting, Flatulence
Hepatobiliary disorders	Jaundice
Infections and infestations	Pseudomembranous colitis
Investigations	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased

## DRUG INTERACTIONS

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.

detecting alterations in carbamazepine plasma concentrations. Anticoagulants: As with other cephalosporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy. Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin Since cefixime may enhance effects of the anticoagulants, prolonged prothrombin time with or without bleeding may occur.

## USE IN SPECIAL POPULATIONS

**Pregnancy** US FDA Pregnancy Category: B. There is no adequate and well-controlled studies regarding use of cefixime in pregnant women. Animal studies have revealed no harm to the fetus. Nevertheless, cefixime should only be used in pregnant women, if clearly

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

Comparable to the incidence seen in adult patients receiving tablets. **Renal Impairment** Cefixime 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. The dose of cefixime 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 ADMINIS-TOTATION TRATION)

## OVER DOSAGE

OVER DOSAGE There is no experience with overdoses of Cefixime. Adverse reactions seen at dose levels up to 2 g Cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Cefixime is not removed from the circulation in significant quantities by dialysis. No specific antidote exists. General supportive measures are recommended.

## PRESENTATION

PRESENTATION EvoFix capsules 200mg: Pack of 10 capsules EvoFix capsules 400mg: Pack of 10 capsules EvoFix granules for oral suspension 100mg/5ml: Bottle of 30 ml (after reconstitution) EvoFix DS granules for oral suspension 200mg/5ml: Bottle of 30 ml (after reconstitution)

INSTRUCTIONS: INSTRUCTIONS: Use as advised by the physician. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical

Protect from light, heat and moisture. Store below 30°C. For suspected adverse drug reaction, email us at reports@pharmevo.biz

For more information on our products call PharmAssist helpline 0800-82222 Monday to Friday 9:00 am to 6:00 pm or email us at : pharmassist@pharmevo.biz



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مسینٹن نیار کرنے کے لئے پہلے سے اُبال کر شعند اکیا ہوا پانی بوتل پردیجے کئے نشان تک ڈالیس اوراچھی طرح ہلائیں تا کہ تمام پاؤڈ ریکساں طور پرحل ہوجائے۔ تیارشد و سینشن کوسات دن کے اندراستعال کریں۔ م**دایات:** ڈاکٹر کی ہدایات کے مطابق استعال کریں۔

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