SUMMARY OF PRODUCT CHARACTERISTICS

EVOFIX CAPSULE
(Cefixime)

1. NAME OF THE MEDICINAL PRODUCT

EVOFIX CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400 mg of Cefixime (as Cefixime trihydrate)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Off white to pale yellow color powder filled in Hard Gelatin Capsule size 0 with dark opaque purple cap & white opaque body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

EVOFIX capsules are indicated in the treatment of adults 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 uncomplicated pyelonephritis) caused by *Escherichia coli* and *Proteus mirabilis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative), *Branhamella catarrhalis* (beta-lactamase positive and negative) and *Enterobacter* species.

Upper Respiratory Tract Infections

- **Otitis Media**: Cefixime is used in the treatment of Otitis media caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes* and *Streptococcus 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 uncomplicated cervical or urethral gonorrhea caused by *Neisseria gonorrhoeae.*

4.2 Posology and method of administration

Posology

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.

Note: In the treatment of infections due to Streptococcus pyogenes, a therapeutic dosage of cefixime should be administered for at least 10 days.

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. The 200 mg daily dose or divided doses cannot be administered via 400 mg EVOFIX capsule.

Dose adjustment in special populations

Dosing in Adults & Adolescents 12 - < 18 years of age with 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 250 mg of Cefixime daily. This dose is not achievable via 400 mg EVOFIX capsules and EVOFIX suspension should be used to achieve the dose of 250 mg.

Patients whose creatinine clearance is 20 mL/min or less, or patients who are on continuous ambulatory peritoneal dialysis may be given 175 - 200 mg daily. EVOFIX suspension should be used to achieve the dose of 175-200 mg daily of cefixime.

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

Administration requirements

EVOFIX capsule should be administered as a single dose preferably at the same time each day.

4.3 Contraindications

- Known hypersensitivity to cephalosporin antibiotics

4.4 Special warnings and precautions for use

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 caution to patients with a history of hypersensitivity to penicillins 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 occurs with Cefixime, the drug should be discontinued and the patient treated with appropriate agents, if necessary.

Clostridium-difficile associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has 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.

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 cephalosporin's 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 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 with required dosage adjustment in patients with markedly impaired renal function. (See DOSAGE AND ADMINISTRATION)

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 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, if required.

Development of drug-resistant bacteria
To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefixime and other antibacterial drugs, Cefixime should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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.

Other forms of interaction:

A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets in patients taking Cefixime, but not with tests based on enzymatic glucose oxidase reactions.

A false positive direct Coombs test (used to detect auto-immune hemolytic anemia) has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the drug.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are 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, only if clearly needed.

Lactation

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

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
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

Fertility

In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

4.7 Effects on ability to drive and use machines

Cefixime does not affect the ability to drive or use machines

4.8 Undesirable effects

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

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antibacterial antibiotics, Beta-lactams; Third generation cephalosporins.

ATC code: J01DD08

Mechanism of action

This third-generation oral cephalosporin acts by binding to one or more penicillin-binding 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).

5.2 Pharmacokinetic properties

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.

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

Excretion

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.

5.3 Pre-clinical safety data

Carcinogenesis, Mutagenesis and Impairment of fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 25 times the adult therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Calcium carboxy methyl Cellulose
- Colloidal Silicon dioxide (Aerosil 200)
- Magnesium Stearate
- Polyoxyl 40 stearate
- Empty Hard Gelatin Shell
  Size: # 0
  BODY: White Opaque
  CAP: Dark Purple

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

N/A

6.5 Nature and contents of container

Alu -Alu blister is packed in a cardboard unit carton contain 10 capsules

6.6 Special precautions for disposal

N/A

7. MARKETING AUTHORISATION HOLDER

PharmEvo (Pvt) Ltd.
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FAX: +92-21-34720161

8. MARKETING AUTHORISATION NUMBER(S)

029151

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4th Dec 2002

10. DATE OF REVISION OF THE TEXT

05/08/2016

Patient Information leaflet (PIL)

PATIENT INFORMATION LEAFLET

EVOFIX CAPSULES

(Cefixime)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1) What EVOFIX is and what it is used for
2) What you need to know before you take EVOFIX
3) How to take EVOFIX
4) Possible side effects
5) How to store EVOFIX
6) Contents of the pack and other information

1) What EVOFIX is and what it is used for

EVOFIX capsule contains a substance from a group of medicines called Cephalosporins, which are a class of antibiotics used to treat infections caused by bacteria.

These include infections of the:

- Ear
- Throat (such as tonsillitis, pharyngitis)
- Chest and lungs (such as bronchitis, pneumonia)
- Urinary system (such as cystitis and kidney infections) etc.

2) What you need to know before you take EVOFIX

Do not take EVOFIX:

If you are allergic (hypersensitive) to cefixime, any other cephalosporin antibiotics including penicillin or to any of the other ingredients of this medicine listed in section 6 of this leaflet.

Signs of an allergic reaction include: a rash, swallowing or breathing problems, swelling of the lips, face, throat and tongue.

Do not take this medicine if the above applies to you. If you are not sure, talk to your doctor or your pharmacist before taking EVOFIX

Warnings and precautions:

Talk to your doctor or pharmacist before taking EVOFIX.

- If you have ever had severe watery diarrhea called colitis with antibiotic use
- If you have kidney problems

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before initiating this medicine.

Other medicines and EVOFIX:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because EVOFIX can affect the way some other medicines work. Also some medicines can affect the way EVOFIX works.

In particular, tell your doctor if you are taking the following:

- Medicines for blood thinning such as warfarin
- Medicine known as carbamazepine used for epilepsy

Pregnancy and breast-feeding:

Talk to your doctor before taking this medicine if

• You are pregnant, might become pregnant or think you may be pregnant

• You are breast-feeding or planning to breast feed

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast feeding.

Lab tests:

If you require any tests such as blood or urine test while taking this medicine, please make sure your doctor knows that you are taking EVOFIX.

3) How to take EVOFIX

Always take this medicine as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

- Take this medicine by mouth
- Swallow capsules whole with water
- If you feel the effect of the medicine is too weak or too strong, do not change the dose yourself, but ask your doctor.
- The medicine should be taken for the prescribed number of days.

How much EVOFIX to take:

The usual dose of EVOFIX is

Adults, Children and Adolescents over 10 years

1 EVOFIX 400 mg capsule daily as a single dose

People with kidney problems

Your doctor may prescribe a lower dose

If you take more EVOFIX than you should:

Contact your doctor or nearest hospital for advice.

If you go into hospital or receive treatment for another condition, tell the medical staff that you're taking EVOFIX.

If you forget to take EVOFIX:

If you forget to take a dose, take it as soon as you remember it. However, if it is nearly time for the next dose, skip the missed dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking EVOFIX:

Do not stop taking this medicine without talking to your doctor. You should not stop taking EVOFIX just because you feel better. This is because the infection may come back or get worse again.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4) Possible Side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away or go to the nearest hospital casualty department if you notice any of the following serious side effects – you may need urgent medical treatment:

- You have an allergic reaction. The signs may include: a rash, joint pain, swallowing or breathing problems, swelling of your lips, face, throat or tongue.
- Blistering or bleeding of the skin around the lips, eyes, mouth, nose and genitals. Also flu-like symptoms and fever. This may be something called 'Stevens-Johnson syndrome.'
- Severe blistering rash where layers of the skin may peel off to leave large areas of raw exposed skin over the body. Also a feeling of being generally unwell, fever, chills and aching muscles. This may be something called 'Toxic epidermal necrolysis'
- You have a skin rash or skin lesions with a pink/red ring and a pale center which may be itchy, scaly or filled with fluid. The rash may appear especially on the palms or soles of your feet. These could be signs of a serious allergy to the medicine called 'erythema multiforme'
- You get infections more easily than usual. This could be because of a blood disorder. This normally gets better after stopping the medicine
- You bruise or bleed more easily than normal. This could be because of a blood disorder. This normally gets better after stopping the medicine.
- If you get nose bleeds, bleeding gums, chills, tiredness, pale skin (often with a yellow tinge), and shortness of breath. This may be due to hemolytic anemia.
- Changes in the way the kidneys are working or blood in your urine

Stop taking this medicine and contact your doctor without delay if you get:

- Severe watery diarrhea that will not stop and you are feeling weak and have a fever. This may be something called 'Pseudomembranous colitis'

Tell your doctor or pharmacist if any of the following side effects get serious or lasts longer than a few days:

- Feeling sick (nausea) or being sick (vomiting)
- Stomach pains, indigestion or gas
- Headaches
- Feeling dizzy
- Feeling itchy in the genital or vaginal area

Tell your doctor or pharmacist if you notice any side effects not listed in this leaflet.

Blood tests:

EVOFIX may cause blood clots or small changes to the way the liver and kidney work. This would be shown up in blood tests. This is not common and goes back to normal after stopping this medicine.

5) How to store EVOFIX

- Store below 30°C at room temperature
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the box/blisters/label after EXP. The expiry date refers to the last day of the month.

6) Contents of the pack and other information

What EVOFIX contains:

The active substance in EVOFIX is Cefixime. Each EVOFIX capsule contains Cefixime 400 mg (as Cefixime trihydrate)

The other ingredients are:

- Calcium carboxy methyl Cellulose
- Colloidal Silicon dioxide (Aerosil 200)
- Magnesium Stearate
- Polyoxyl 40 stearate
- Empty Hard Gelatin Shell
  Size: # 0
  BODY: White Opaque
  CAP: Dark Purple

What EVOFIX looks like and contents of the pack:

EVOFIX CAPSULE: Off white to pale yellow color powder filled in Hard Gelatin Capsule size 0 with dark opaque purple cap & white opaque body.
Pack size: 10's
Alu -Alu blister is packed in a cardboard unit carton

Marketing Authorization Holder:

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