SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FIXEF 400 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Active Substance:
Cefixime trihydrate 447.669 mg (equal to 400 mg cefixime)

Excipient(s):
For full list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet for oral use.
White film coated, homogenous, oblong tablet, scored on one side (to help to divide the tablet into two equal parts).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FIXEF is indicated against following infections:

- Acute Otitis Media; caused by sensitive strains of *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
- Acute sinusitis; caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*
- Acute tonsillopharyngitis or pharyngitis, required only if caused by *Streptococcus pyogenes*
- Acute Exacerbations of Chronic Bronchitis caused by susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae,*
- Uncomplicated Urinary Tract Infections
- Uncomplicated gonorrhea

4.2 Posology and method of administration

Posology/duration and frequency of administration
Adults: FIXEF is taken 1 tablet daily (400 mg). If desired, the total daily dose can be taken in 2 equal parts. FIXEF can be taken on empty or full stomach.

a. FIXEF should be taken as single 400 mg dosage in uncomplicated gonorrhea.
b. Treatment for streptococcal tonsillopharyngitis is 10 days.

For children between 6 months – 12 years the proper dosage and pharmaceutical form should be used.

Method of administration
FIXEF is taken directly orally.

The presence of food has no negative effect on the absorption of Cefixime. The drug can be taken with or before meals.

Additional information on special populations

Renal impairment
The dose should be reduced in patients with severe renal impairment.
Daily dosage should be 1×200 mg cefixime for adults and children older than 12 years with a creatinine clearance <20 ml/min/1.73 m² or are undergoing continuous ambulatory peritoneal dialysis. Hemodialysis or peritoneal dialysis does not provide a significant removal of the drug from the body.

Hepatic impairment
Dose adjustment is not required.

Pediatric population
The efficacy and safety of cefixime in children under 6 months has not been established.

Geriatric population
There is no specific warning. Elderly patients may be given the same dose as recommended for adults.

4.3 Contraindications
It is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics or any of the other components of the product.

4.4 Special warnings and precautions for use
FIXEF should be given with caution to patients who have shown hypersensitivity to other drugs. As with other cephalosporins, cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins. Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with FIXEF, the drug should be discontinued and the patient treated with appropriate agents if necessary.

FIXEF should be administered with caution in patients with markedly impaired renal function (creatinine clearance <10 ml/min/1.73 m^2) (see section 4.2).

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome 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.

Prolonged use of FIXEF may result in overgrowth of non-susceptible organisms. Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of *Clostridium*. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhea. If severe diarrhea is observed during use, the intake of the drug should be stopped.

Management of pseudomembranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

Due to the possible decrease in bioavailability of the tablet formulation and because absorption is higher in oral suspension forms, suspension should be used in the treatment of acute otitis media instead of tablets.

4.5 Interaction with other medicinal products and other forms of interaction

In urine glucose tests with Benedict or Fehling Solutions or copper sulfate tablets, a false positive reaction may occur. Tests based on enzymatic glucose oxidase reactions show no such interaction.

The administering physician should be advised in case of concurrent drug use. Probenecide increases cefixime concentration. Cefixime increases carbamazepine levels. Food may delay the absorption of cefixime.

Positive direct Coombs tests have been reported during treatment with cephalosporin antibiotics.
If the Coombs test is positive, it should be considered that it may be due to drug interaction.

In common with other cephalosporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.

Additional information about special populations
Data on specific populations are not available.

Pediatric population
There is no data regarding pediatric population.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is B

Women of child-bearing potential/Contraception
Caution is advised when used in women with child-bearing potential. There is no information regarding the interaction with oral contraceptives.

Pregnancy
There are no adequate and well-controlled studies regarding exposure in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3).
Caution is advised when giving to pregnant women. Cefixime passes the placental barrier; the blood concentration in the umbilical cord is 1/6-1/2 of the maternal serum concentration.
Caution is advised when used in pregnant women.

Breast-feeding

No cefixime is determined in breast milk. However, until sufficient clinical data is complied, cefixime should not be administered to breast-feeding mothers.

Fertility
No embryotoxic effects were found in experimental studies.

4.7 Effects on ability to drive and use machines
There is no information to suggest that cefixime has a direct adverse effect on the ability to drive and use machines. However, the underlying disease or some undesirable effects of cefixime (e.g. gastrointestinal disorders) may affect the ability to drive and use machines.

4.8 Undesirable effects
Adverse effects may be seen as in all medications. With cephalosporins, these effects are usually limited to gastrointestinal disorders and rarely hypersensitivity reactions can occur. The likelihood of such an effect is higher in people who have previously had hypersensitivity reactions or allergies, allergic fever, urticaria and allergic asthma.

Adverse events, reported more as with placebo in double-blind clinical trials and as being least likely to be associated with cefixime therapy as a result of the assessment of the available data for causality, are listed below using the following classifications:
Very common ≥1/10, Common ≥1/100 to <1/10, Uncommon ≥1.000 to <1/100, Rare ≥1/10.000 to <1/1.000, Very rare <1/10.000, Not known (cannot be estimated from the available data)

Infections and infestations	
Not known	Pseudomembranous colitis
Blood and lymphatic system disorders	
Rare	Changes in hemogram (Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, eosinophilia)
Very rare	Blood coagulation disorders
Immunity system disorders	
Rare	Urticaria or angioedema. After treatment is discontinued, these reaction usually disappear. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have also been seen rarely. Hypersensitivity reactions ranging from allergic cutaneous reactions to anaphylactic shock (e.g. Facial edema, glossoncus, internal laryngeal edema with restriction of respiratory tract, tachycardia, dyspnea, decrease of blood pressure, leading even to shock)
Very rare	Drug Fever, Serum sickness-like reaction, hemolytic anemia, interstitial nephritis
Nervous system disorders	
Rare	Vertigo, headache
Very rare	Transient hyperactivity, trend to convulsion
Respiratory, thoracic and mediastinal disorders:	
Not known	Dyspnea
Gastrointestinal disorders	
Very common	Fullness of stomach, nausea, vomiting, loss of appetite and flatulence.
Common	Soft stool or diarrhea
Very rare	Antibiotic-associated colitis (e.g. pseudomembranous colitis), superinfections due to resistant bacteria or *Blastomyces*
Hepatobiliary disorders	
Rare	Increase in serum liver enzymes (transaminases, alkaline phosphatase).

Very rare	Hepatitis, cholestatic hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Skin rash (exanthema, erythema, erythema excitativum multiforme and Lyell's syndrome in isolated cases), pruritus, mucosal inflammation.
Renal and urinary disorders	
Rare	Increase in serum creatinine and urea concentrations
General disorders and administration site conditions	
Not known	Genital pruritus and vaginitis

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00 08; fax: +90 312 218 35 99)

4.9 Overdose
No definitive intoxication cases are known.
In case of persistent severe diarrhea cases during or after treatment, pseudomembranous colitis should be considered. Discontinue treatment and start appropriate therapy (e.g. vancomycin orally 4×250 mg). Medicines to inhibit peristaltic of intestines are contraindicated.

In case of anaphylactic shock, emergency measures should be taken as soon as the first symptoms of shock are seen.
Treatment for anaphylactic shock: In addition to general emergency measures, the airways should be kept open.

For emergency treatment, epinephrine is accompanied with antihistamines and glucocorticoids (prednisolone). Artificial respiration, oxygen inhalation, calcium administration should also be considered. Patients should be monitored very closely.

Cefixime is not removed from the circulation in significant quantities by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Oral cephalosporines
ATC code: J01DD08

Mode of Action
Cefixime, an oral used cephalosporin, is similar regarding structure, spectrum and beta-lactamase resistance, to a parenteral used cephalosporin: cefotaxime. Cefixime has bactericidal effect like all members of this molecule group. Cefixime acts by inhibiting bacteria cell wall synthesis. It is very resistant to beta-lactamase enzymes. Therefore, it is effective against microorganisms which are resistant to penicillins due to beta-lactamase presence and some microorganisms which are resistant some cephalosporins.

Cefixime is effective against these pathogens:
Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Klebsiella oxytoca.

Resistant microorganisms
Pseudomonas spp., enterococci, Listeria monocytogenes, most *Staphylococci* (coagulase positive and negative strains as well as methicillin resistant strains), most *Enterobacter* strains, *Bacteroides fragilis* strains and *Clostridium spp.* are resistant to cefixime.

5.2 Pharmacokinetic properties

General properties

Absorption:
After oral administration of 400 mg Cefixime, mean maximum serum concentrations between 2.5 and 4.9 µg/ml were reported 3-4 hours after application.

Distribution:
The serum protein binding of cefixime is approximately 65%.
Blister fluid showed somewhat higher cefixime concentrations than those measured in serum (on average 133% of the equivalent serum concentration). At 6.7 hours, maximum concentration was achieved later than in serum.
A once-only oral dose of 400 mg cefixime results in urine concentrations that exceed the MIC for relevant bacteria over 24 hours.
High concentrations are achieved in the bile. Patients undergoing cholecystectomy received 2x200 mg/day cefixime for two days before surgery, 13-17 h after the last dose, the mean biliary level was 199.3 µg/ml.
Concentrations were determined for the following tissue and body fluids as follows: tonsils 5 hours after administration of 4 mg/kg (right on average 0.74 µg/g, left on average 0.53 µg/g); lung tissue 7.8 hours after administration of 200 mg on average 0.99 µg/g, 8 hours after administration of 400 mg 1.76 µg/g: Otorrhea 2 to 3 hours after administration of twice daily 100 mg over several days >1 µg/ml; nasal sinus mucous membranes 2 to 3 hours after administration of 200 mg 1.2- 1.4 µg/g; sputum after 100 mg 0.02 to 0.05 µg/ml.

Biotransformation:
There is no evidence of metabolization of cefixime.

Elimination:
The elimination half-life is 3-4 hours and is not dependent on either the dose or the galenic formulation. Following an oral dose of 200 to 400 mg, 10-20% of the substance is excreted unchanged with urine within 24 hours; this is equivalent to 50-55% of the absorbed amount of substance.
10% of the given cefixime is excreted via bile

5.3 Preclinical safety data

LD50 values of between 3.5 g/kg and 10 g/kg were observed after parenteral administration. Maximal doses of 10 g/kg generally were tolerated after oral administration. The investigations on

toxicity after repeated application showed substance-related effects in the gastrointestinal system and in the kidneys. Cefixime is, as other cephalosporins, to be classified as potentially nephrotoxic.

In 3-week old dogs the daily oral administration of 400 mg/kg/day cefixime over 5 weeks led to occasional necrosis of the tubule epithelia of the kidneys. The non-toxic dose was determined at 100 mg/kg/day d in this study, which is equivalent to approximately fifteen times the therapeutic dose. In adult dogs histological signs of nephrotoxicity were observed after a 14-day IV. administration of 1 g//kg/day cefixime (regeneration of renal tubuli after previous necrosis).

In rats, the administration of 1 g/kg/day over one year led to chronic nephropathy with increased renal weight and proteinuria. The only further finding described was enlargement of the caecum which is typical for antibiotics.

In rabbits cefixime exerted toxic action even at low doses. This was primarily related to damage to the species-specific gram-positive intestinal flora.

For rats and rabbits, a threshold dose was determined of approximately 500 mg/kg/day for toxic action on the proximal renal tubuli after one or only a few parenteral applications. With an effective dose of 12 mg/kg/day the therapeutic spectrum is wide.

Studies on 3 animal species (rat, mouse, rabbit) have shown no evidence of teratogenic properties. An influence on perinatal or postnatal development and fertility in rats has not been observed.

Cefixime passes through the placenta. The concentrations in umbilical cord blood were 1/6 – 1/2 of the maternal serum concentrations. No cefixime concentrations could be proved in breast milk.
Only limited experience is available on use in humans during pregnancy and lactation.

Several *in vitro* and *in vivo* mutagenicity tests have proved negative. Mutagenic action of cefixime in humans can therefore be safely excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose
Prejelatinized starch
Calcium phosphate dibasic dihydrate
Magnesium stearate
Opadry white OY-D-7233 (hypromellose, titanium dioxide, talc, polyethylene glycol/macrogol, sodium lauryl sulfate)

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 30°C.

6.5 Nature and contents of container

Each carton contains 10 film coated tablets in one side transparent PVC/PVDC, other side printed aluminum foil coated blisters.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

08164/09251/NMR/2021

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : Dec 2, 2022
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT

15.04.2019