SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
FIXEF 100 mg/5 ml Dry Powder for Pediatric Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml prepared suspension (1 spoon) contains:
Active Substance(s):
Cefixime trihydrate.....111.9 mg (equal to 100 mg cefixime)
Excipient(s) with known effect:
Saccharose.....2510.2 mg
For the full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM
Powder for oral suspension.
White to off-white powder constitutes a white to off-white suspension with raspberry odor when reconstituted.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
FIXEF is effective against following infections:
- Acute otitis media: caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*;
- Acute sinusitis: caused by *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*;
- Acute tonsillitis or pharyngitis: antibacterial therapy is indicated only if caused by *Streptococcus pyogenes*;
- Acute bacterial exacerbations of chronic bronchitis: caused by *Streptococcus pneumoniae* and *Haemophilus influenzae*;
- Uncomplicated urinary tract infections;
- Uncomplicated gonococcal infections.

4.2 Posology and method of administration
Posology / duration and frequency of administration
Dosage for children aged 12 years and under;
The recommended dose is 8 mg/kg total daily. In clinical use, a single dose of 8 mg/kg per day or 8 mg/kg daily divided into two doses of 4 mg/kg is recommended.

Bodyweight (kg)	Daily dosage (mg)	Daily dosage (mL)
5 – 7.5	50	2.5
7.6 - 10	80	4
10.1- 12.5	100	5
12.6 – 20.5	150	7.5
20.6 - 28	200	10
28.1 – 33	250	12.5
33.1 – 40	300	15
40.1 – 45	350	17.5
45.1 and over	400	20

Dosage for adults and children over 12 years of age:
The recommended adult dosage is 400 mg daily, given either as a single dose or in two divided doses of 200 mg each. FIXEF can be taken on an empty or a full stomach.

400 mg single dose should be used in uncomplicated gonococcal infections.
The treatment of streptococcal tonsillopharyngitis must be 10 days.

Adults should use recommended doses and pharmaceutical dosage forms suitable for adults. Oral suspension and sachet forms can be used in patients who have difficulty swallowing solid foods.

Method of administration
Oral administration.

Preparation of FIXEF suspension:
FIXEF is in powder form, so it must be reconstituted first.

Follow the steps below for reconstitution of FIXEF.
Lightly tap on the bottle to loosen all powder.

1. Add water gradually until it fills up to 2/3 of the mark on the bottle and shake vigorously (Boiled and cooled water should be preferred for preparing a suspension).

2. Allow to stand for 5 minutes to ensure full dispersion.
3. Add water up to the mark on the bottle (remaining 1/3) and shake well again (Boiled and cooled water should be preferred for preparing a suspension).
4. The dose recommended by the doctor is given to the patient using a 5 ml measuring spoon that is supplied with the bottle.

Shake the bottle well before each dose.
After use, close the bottle tightly right away.
Each 5 ml of the prepared suspension (1 measuring spoon), contains 100 mg of cefixime.

Prepared suspension can be stored for 14 days at room temperature below 25°C without losing efficacy. After 14 days, the remaining suspension in the bottle cannot be used. It should not be put into the refrigerator.

Additional information on special populations
Pediatric population
The safety and efficacy of cefixime has not been established in children less than 6 months.

Renal impairment
Dosage should be reduced in patients with significant renal function impairment. If the creatinine clearance is <20 ml/min/1.73 m^2 or if adults or children over 12 years are maintained on chronic ambulatory peritoneal dialysis, daily dosage of cefixime should be 1×200 mg. Hemodialysis or peritoneal dialysis does not ensure elimination of the drug in significant amounts.

Hepatic impairment
Dose adjustment is not required.

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

4.3 Contraindications
It is contraindicated in patients with known hypersensitivity to cefixime, other 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 under Dosage in Renal Impairment).

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.

Otitis media should be treated with the suspension. Clinical trials of otitis media were conducted with suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose.

Each 5 ml FIXEF contains 2510.2 mg saccharose. This should be taken into consideration in diabetic patients. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Cephalosporin use may alter the results of some laboratory tests. Benedict, Fehling and Clinitest tests may give a false positive result.

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

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
Data on pediatric population are not available.

4.6 Fertility, pregnancy and lactation

General Recommendation
Pregnancy category is “B”.

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

Pregnancy
There are no adequate and well-controlled studies 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.

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, if 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 reactions 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	Dizziness, 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 via the national reporting system.

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 4x250 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: Third-generation cephalosporins
ATC code: J01DD08

Mechanism 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:
Cefixime is easily absorbed when taken orally. Presence of food does not affect is absorption.

Distribution:

At doses ranging from 200 mg to 2000 mg, the peak concentration in blood serum and the area under the curve (AUC) of serum concentrations show a linear increase.

Peak concentrations of 2-4 mcg/ml and 3-5 mcg/ml are obtained in the serum after 3-4 hours after oral administration of 200 mg and 400 mg doses, respectively. In repeated dosing, the drug does not accumulate in serum or urine. Serum protein binding was 65%; in healthy subjects, serum half-life is 3-4 hours.

Biotransformation:
Cefixime is not metabolized *in vivo.*

Elimination:
Approximately 50% of the absorbed dose is excreted in the urine unchanged in 24 hours. 10% of the given dose is excreted via bile. In patients with moderately impaired renal function (creatinine clearance 20-40 ml/min) serum half-life of cefixime is 6.4 hours, and in severe renal impairment (creatinine clearance 5-20 ml/min) half-life is prolonged to 11.5 hours.

Characteristics in patients
Elderly:
Age does not significantly affect the pharmacokinetic properties of the drug.

Renal impairment:
The drug is not significantly removed from the blood stream via hemodialysis or peritoneal dialysis.

5.3 Preclinical safety data
LD50 values between 3.5 g/kg and 10 g/kg were observed after parenteral administration, with maximum doses of 10 g/kg generally 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 three-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 has been determined at 100 mg/kg/day 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 cecum, 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.

Studies on three 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

Saccharose
Xanthan gum
Sodium benzoate
Raspberry flavor
Colloidal silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Dry powder should be stored at room temperature below 25°C. Reconstituted suspension should be stored at room temperature below 25°C and used within 14 days.

6.5 Nature and contents of container

Dry powder in a colored glass bottle with pilfer proof HDPE cap within a carton box + Polypropylene measuring spoon, (50 ml).

Dry powder in a colored glass bottle with P.E/P.P childproof plastic cap within a carton box + Polypropylene measuring spoon, (100 ml).

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER(S)

220/92

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization : 18.09.2009
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT