SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFAKS 125 mg/5 ml Granules for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 5 ml of suspension contains cefuroxime axetil equivalent to 125 mg cefuroxime.

Excipient(s):
Each 5 ml contains
Sucrose.....3024.6 mg
Aspartame.....30 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for oral suspension.
Dry powder:
Aromatic scent (strawberry), almost white granules
Reconstituted product:
When reconstituted as directed in labeling; almost white colored suspension with homogenous appearance and aromatic flavor (strawberry).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFAKS is indicated in the treatment of infections caused by susceptible microorganisms. Indications consist of the following:

- *Upper respiratory tract infections*, such as ear-nose-throat infections, otitis media, sinusitis, tonsillitis, pharyngitis.
- *Lower respiratory tract infections*, such acute bronchitis, acute exacerbations of chronic bronchitis, and pneumonia.
- *Genitourinary system infections*, such as pyelonephritis, cystitis and urethritis.
- *Skin and soft tissue infections*, such as furuncle, pyoderma, impetigo.
- *Gonorrhea*, such as acute and uncomplicated gonococcal urethritis and cervicitis.

It can be used for early treatment of Lyme disease and prevention of late Lyme disease in adults and children above age of 12.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Usual treatment duration is 7 days (5-10 days).

In adults

For many infections	250 mg, twice daily
Urinary system infections	125 mg, twice daily
Mild to moderate lower respiratory tract infections, such as bronchitis	250 mg, twice daily
Severe lower respiratory tract infections or when pneumonia is suspected	500 mg, twice daily
Pyelonephritis	250 mg, twice daily
Uncomplicated gonorrhea	1 g, single dose
Lyme disease in adults and children above age of 12	500 mg twice daily for 20 days

Sequential therapy
Cefuroxime is also available for parenteral administration as cefuroxime sodium salt (CEFAKS Injection). In cases where changing over from parenteral to oral treatment is clinically indicated, it enables parenteral treatment with Cefuroxime to be continued with oral (CEFAKS) treatment.

Duration of parenteral and oral treatments is determined depending on severity of the infection and clinical status of the patient.

Pneumonia
Following the cefuroxime sodium administration of 1.5 g given via IV or IM routes 2-3 times a day for 48-72 hours, the treatment is continued with 500 mg twice daily cefuroxime axetil oral therapy for 7 to 10 days.

Acute exacerbations of chronic bronchitis: Following the cefuroxime sodium administration of 750 mg given via IV or IM routes 2-3 times a day for 48-72 hours, the treatment is continued with 500 mg twice daily cefuroxime axetil oral therapy for 5 to 10 days.

In children
When prescription of a fixed dose is prepared, the recommended dose for most infections is 125 mg twice daily. In children aged two years or older with otitis media or where appropriate in children, with more severe infections, the dose is 250 mg twice daily to a maximum of 500 mg daily.

In infants and children, it may be preferable to adjust dosage according to weight or age. The dose in infants and children 3 months to 12 years is 10 mg/kg twice daily for most infections, to a maximum of 250 mg daily. In otitis media or more severe infections the recommended dose is 15 mg/kg twice daily to a maximum of 500 mg daily.

The following dosage table, divided by age group and weight, serve as a guideline for simplified administration, from measuring spoons (5 ml of measuring spoon contains 125 mg cefuroxime).

10 mg/kg dosage for most infections

Age	Approximate weight (kg)	Dose (mg) twice daily	Measuring spoon (5 ml = 125 mg)
3 months - 6 months	4 - 6	40 - 60	½
6 months - 2 years	6-12	60 - 120	½ - 1
2 years - 12 years	12 - >20	125	1

15 mg/kg dosage for otitis media and more serious infections

Age	Approximate weight (kg)	Dose (mg) twice daily	Measuring spoon (5 ml = 125 mg)
3 months - 6 months	4 - 6	60 - 90	½
6 months - 2 years	6 - 12	90 - 180	1 - ½
2 years - 12 years	12 - >20	180 - 250	1½ - 2

Route of Administration:
CEFAKS Suspension is taken orally.
For optimal absorption, cefuroxime axetil should be taken with food.
Shake the bottle vigorously until the suspension can be heard moving in the bottle before each use.
If desired, the reconstituted suspension may be added to drinks such as cold fruit juice, milk.

Additional information on special populations

Renal impairment:
The safety and efficacy of cefuroxime axetil in patients with renal impairment has not been established.
Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Creatinine Clearance	$T_{1/2}$ (hours)	Recommended dosage
≥30 ml/minute	1.4 – 2.4	No dose adjustment necessary (standard dose of 125 mg – 500 mg given twice daily)
10-29 ml/minute	4.6	Standard individual dose given every 24 hours
<10 ml/minute	16.8	Standard individual dose given every 48 hours
During hemodialysis	2 - 4	A single additional standard dose should be given at the end of each dialysis

Hepatic impairment: No data available.

Pediatric population: There is no experience of using CEFAKS in children under the age of 3 months. Its use is not recommended for this age group.

Geriatric population: No data available.

4.3 Contraindications
Hypersensitivity to cefuroxime or the other ingredients the drug contains.
It is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics.
It is contraindicated in individuals with a history of hypersensitivity to beta-lactam antibiotics (such as penicillins, monobactams, carbapenems).

4.4 Special warnings and precautions for use

Before therapy is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to CEFAKS, other cephalosporins, penicillins or other drugs. Due to the fact that cross-hypersensitivity reaction to beta-lactam antibiotics may occur, when it was administered to patients with penicillin allergy, it was reported that cross-

hypersensitivity reaction would occur in 10% of these patients. If a clinically significant allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted. When serious acute hypersensitivity reactions occur, epinephrine treatment and other emergency interventions (such as oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, operations for performed on airways) may be required.

As with other antibiotics, use of cefuroxime axetil may result in overgrowth of *Candida*. Prolonged use may also result in the overgrowth of other non-susceptible microorganism (e.g. *enterococci* and *Clostridium difficile*), which may require interruption of treatment.

Cases of pseudomembranous colitis, which may range in severity from mild to severe, have been reported with the use of antibiotics. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of any antibiotics. Following the diagnosis of pseudomembranous colitis appropriate therapy should be instituted. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. However, in moderate to severe cases consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibiotic effective against *Clostridium difficile*. If prolonged or severe diarrhea, or stomach cramps occur in the patient the treatment should be discontinued and the patient further examined.

The Jarisch-Herxheimer reaction (fever, chills, muscle pain, headache, tachycardia) has occurred following the treatment of Lyme disease with CEFAKS. It results directly from the bactericidal activity of CEFAKS on the causative bacteria of Lyme disease, *Borrelia burgdorferi.* Patients should be reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood (see section 4.8).

It is recommended that either the glucose oxidase or hexokinase methods be used to determine blood/plasma glucose levels in patients receiving cefuroxime as a false negative result may occur in the Ferricyanide test.

CEFAKS contains aspartame, which is a source of phenylalanine. May be harmful for people with phenylketonuria.

CEFAKS contains sucrose. Therefore, patients with rare heredity problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltese insufficiency should not take this medicine.

The sucrose content of cefuroxime axetil suspension and granules (see section 6.1) should be taken into account when treating diabetic patients and appropriate advice provided.

4.5 Interactions with other medicinal products and other forms of interaction

Drugs which reduce gastric acidity may result in a lower bioavailability of CEFAKS compared with that of the fasting state and tend to cancel the effect of enhanced postprandial absorption of CEFAKS.

In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant administration of probenecid is not recommended. The concomitant administration of probenecid significantly increases the peak concentration, area under the serum concentration-time curve, and elimination half-life of cefuroxime.

Concurrent oral anticoagulant administration may lead to elevated International Normalized Ratio (INR).

It is recommended that either the glucose oxidase or hexokinase methods be used to determine blood/plasma glucose levels in patients receiving cefuroxime as a false negative result may occur in the Ferricyanide test. This antibiotic does not interfere with the alkaline picrate assay for creatinine.

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely hemolytic anemia.

4.6 Fertility, pregnancy and lactation

General principles
Pregnancy category is B

Women of child-bearing potential/Contraception
In common with other antibiotics, cefuroxime may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

Pregnancy
There are not sufficient data on the use of cefuroxime axetil in pregnant women.
Studies in animals have shown no harmful effects on pregnancy, embryonal or fetal development, parturition or postnatal development. Care should be taken while administering to pregnant women.
Cefuroxime has been shown to cross the placenta and attain therapeutic levels in amniotic fluid and cord blood after intramuscular or intravenous dose to the mother.

Breast-feeding
Cefuroxime is excreted in human milk. A decision on whether to discontinue/continue cefuroxime axetil treatment or breast-feeding should be made.

Fertility
No data is available.

4.7 Effects on ability to drive and use machines
Patients should be warned to be cautious when driving or operating machinery as CEFAKS may cause dizziness.

4.8 Undesirable effects
Adverse effects of Cefuroxime axetil are generally mild and transient in nature.

The most prevalent adverse effects are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example obtained from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10.000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not available. Incidences have been calculated from clinical trial data, these were based on drug-related data.

Frequencies have been defined as follows: very common ≥1/10; common ≥1/100 to <1/10, uncommon ≥1/1.000 to <1/100; rare ≥1/10.000 to <1/1.000; very rare <1/10.000 and not known (cannot be estimated from the available data).

Infections and infestations
Common: Candida overgrowth
Unknown: *Clostridium difficile* overgrowth

Blood and lymphatic system disorders
Common: Eosinophilia,
Uncommon: Positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)
Unknown: Hemolytic anemia

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely hemolytic anemia.

Immune system disorders
Unknown: Drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction

Nervous System disorders
Common: Headache, dizziness

Gastrointestinal disorders
Common: Gastrointestinal disturbances including diarrhea, nausea, abdominal pain
Uncommon: Vomiting
Unknown: Pseudomembranous colitis (see section 4.4)

Hepatobiliary disorders
Common: Transient increases in hepatic enzyme levels (LDH, ALT (SGPT), AST (SGOT))
Unknown: Jaundice (predominantly cholestatic), hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Skin rash
Unknown: Urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis), angioneurotic edema
(See also immune system disorders.)

Renal dysfunction, one of the urological disorders, has been reported among the side effects observed in the post-marketing experience.

Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely hemolytic anemia.

Transient increases in serum liver enzymes have been observed to occur, these are generally reversible.

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 Centre (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose
Overdosage of cephalosporins can cause cerebral irritation leading to convulsions, encephalopathy and coma. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.
In case of overdose, supportive treatment should be administered and the patient should be closely monitored. If seizures occur, the drug should be discontinued promptly and anticonvulsant therapy may be administered if clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Second-generation cephalosporins
ATC code: J01DC02

Mechanism of Action
Cefuroxime axetil is the oral prodrug of cefuroxime that is a bactericidal antibiotic. Cefuroxime exhibits great stability against bacterial beta-lactamases and consequently it is efficacious against most of ampicillin - or amoxicillin – resistant strains. Cefuroxime exerts its bactericidal activity by inhibiting bacterial cell wall synthesis by binding to essential target proteins.

Pharmacodynamic effects
The prevalence of acquired resistance is geographically and time dependent and for certain species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

In vitro susceptibility of microorganisms to Cefuroxime
Where clinical efficacy of cefuroxime axetil has been demonstrated in clinical trials is indicated with an asterisk (*).

Commonly Susceptible Species
Gram-Positive Aerobes:
Staphylococcus aereus (methicillin-susceptible)*

Coagulase negative staphylococcus (methicillin-susceptible)
*Streptococcus pyogenes**
Beta-hemolytic *streptococci*

Gram-Negative Aerobes:
*Hemophilus influenza** including ampicillin-resistant strains
*Hemophilus parainfluenzae**
*Moraxella catarrhalis**
*Neisseria gonorrheae** including penicillinase and non-penicillinase producing strains

Gram-Positive Anaerobes:
Peptostreptococcus spp.
Propionibacterium spp.

Spirochetes:
*Borrelia burgdorferi**

Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes:
*Streptococcus pneumoniae**

Gram-Negative Aerobes:
Citrobacter spp. excluding *C. freundii*
Enterobacter spp. excluding *E. aerogenes* and *E. cloacae*
*Escherichia coli**
Klebsiella spp. including *Klebsiella pneumoniae**
Proteus mirabilis
Proteus spp. excluding *P. penneri* and *P. vulgaris*
Providencia spp.

Gram-Positive Anaerobes:
Clostridium spp. excluding *C. difficile*

Gram-Negative Anaerobes:
Bacteroides spp. excluding *B. fragilis*
Fusobacterium spp.

Inherently resistant organisms
Gram-Positive Aerobes:
Enterococcus spp. including *E. faecalis* and *E. faecium*
Listeria monocytogenes

Gram-Negative Aerobes:
Acinetobacter spp.
Burkholderia cepacia
Campylobacter spp.
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae

Morganella morganii
Proteus penneri
Proteus vulgaris
Pseudomonas spp. including *Pseudomonas aeruginosa*
Serratia spp.
Stenotrophomonas maltophilia

Gram-Positive Anaerobes:
Clostridium difficile

Gram-Negative Anaerobes:
Bacteroides fragilis

Others:
Chlamydia spp.
Mycoplasma spp.
Legionella spp.

5.2 Pharmacokinetic properties

General properties
Absorption:
Cefuroxime axetil is absorbed from the gastrointestinal tract following oral administration and rapidly hydrolyzed in the intestinal mucosa and blood to release cefuroxime into the circulation. Food increases the absorption of Cefuroxime axetil suspension.
Optimum absorption occurs when it is administered shortly after a meal.
Following administration of cefuroxime axetil tablets after food, peak plasma levels achieved after approximately 2.4 hours are found to be 2.9 µg/ml for a 125 mg-dose, 4.4 µg/ml for a 250 mg-dose, 7.7 µg/ml for a 500 mg-dose and 13.6 µg/ml for a 1000 mg-dose. The rate of cefuroxime absorption from suspension and peak serum levels are lower compared to those occurring with tablets, and systemic bioavailability is reduced (4 to 17% less).

Distribution:
Protein binding ranges between 33 and 50%, depending on the methodology used.

Biotransformation
Cefuroxime is not metabolized.

Elimination:
The serum half-life is between 1 and 1.5 hours.
Cefuroxime is excreted by glomerular filtration and tubular secretion. Concurrent administration of probenecid increases the area under the mean serum concentrations time curve by 50%.

Characteristics in patients
Gender
No differences have been observed between men and women as to pharmacokinetics of cefuroxime.

Geriatric
At doses up to the normal maximum daily dose of 1 g, no dose adjustment is required for elderly

patients with normal renal function. Renal dysfunction is more likely to occur in elderly patients; therefore, dosage should be adjusted to the degree of renal dysfunction in the elderly (see section 4.2).

Pediatric
In older infants (>3 months) and children pharmacokinetics of cefuroxime are similar to those observed in adults.
There is no clinical study as to the use of cefuroxime axetil in children below 3 months of age.

Renal impairment
The efficacy and safety of cefuroxime axetil have not been established in patients with renal impairment. Cefuroxime is primarily excreted by the kidneys. Therefore, as with all such antibiotics, in patients with markedly impaired renal function (creatinine clearance < 30 ml/min) it is recommended that the dosage of cefuroxime be reduced to compensate for its slower excretion (see section 4.2). Cefuroxime can effectively be removed by dialysis.

Hepatic impairment
No data are available for patients with hepatic impairment. As cefuroxime is primarily eliminated by the kidneys, no effect due to the presence of hepatic dysfunction is expected on pharmacokinetics of cefuroxime.

PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with the *in vivo* efficacy has been shown to be duration that the unbound drug concentration remains above the minimum inhibitory concentration (MIC) (meaning, %T > MIC) as a percentage of the dosing interval (%T).

5.3 Preclinical safety data
Animal toxicity studies have revealed that Cefuroxime axetil has a low order of toxicity without any significant finding.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Stearic acid
Sucrose
Strawberry flavor
Polyvinylpyrrolidone K-25
Acesulfame potassium
Aspartame

6.2 Incompatibilities
No data are available.

6.3 Shelf Life
48 months
Reconstituted suspension can be stored in refrigerator at 2-8°C in refrigerator for 10 days.

6.4 Special precautions for storage

Store granules at room temperature below 25°C, when reconstituted store in refrigerator at 2°-8°C.

6.5 Nature and contents of packaging

CEFAKS is presented in glass bottles containing dry granules to form 50 ml and 100 ml of a suspension with a child-resistant cap. Each cardboard box contains measuring spoon of 5 ml marked at 1.25 ml and 2.5 ml and measuring device marked at 22 ml (for 50 ml of suspension), measuring device marked at 43 ml of suspension (100 ml of suspension).

6.6 Special precautions for disposal and other handling

Instructions for use

As with all other medicines, it is important to take CEFAKS exactly as recommended by your doctor.

Always shake the bottle of CEFAKS suspension well before each use. The reconstituted suspension when refrigerated between 2°-8°C can be kept for up to 10 days.

RECONSTITUTION OF SUSPENSION:

CEFAKS suspension is supplied as dry granules and should be reconstituted before use. If desire, CEFAKS suspension can be diluted in cold fruit juices, or milk drinks and should be taken immediately.

Reconstituted suspension can be stored in refrigerator at 2-8°C in refrigerator for 10 days.

1. Shake the bottle containing granules a few times before uncapping.

2. Add boiled and then cooled water up to the mark (22 ml for 50 ml of suspension, 43 ml for 100 ml of suspension) on the measuring device into the content of bottle and replace the cap.

3. Invert the bottle and shake the bottle from side to side (for at least 15 seconds, until homogenous suspension may occur) as shown in figure.

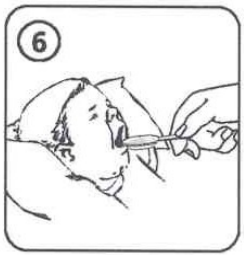
4. Allow the reconstituted suspension to stand for a certain period of time before taking the first dose.

5. Store immediately the CEFAKS suspension in refrigerator at between 2°- 8°C.

6. Prepared suspension should be rest at least one hour before taking the first dose.

7. Shake the bottle well before use. Your medicine is now ready to use.

8. The suspension can be administered with a measuring spoon.



Don't forget to shake the bottle well before each use.

7. MARKETING AUTHORIZATION HOLDER

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

8. MARKETING AUTHORIZATION NUMBER
199/96

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization: 18.04.2002
Renewal of the authorization:

10. DATE OF REVISION OF THE TEXT
02.05.2024