SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
CEFAKS 250 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substance:
Cefuroxime (as axetil)..... 250 mg

Excipients:
Sodium lauryl sulfate.....4.500 mg
Croscarmellose sodium.....40.000 mg
Methyl paraben..... 0.066 mg
Propyl paraben..... 0.053 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film tablet
White film-coated, homogeneous oblong tablets, plain on one side and debossed with “250” on the other.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
CEFAKS is indicated in the treatment of infections caused by susceptible microorganisms. Indications include the following:

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

It can be used for treatment of early 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:
The usual course of therapy is 7 days (5 to 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
More severe lower respiratory tract infections or when pneumonia is suspected	500 mg, twice daily

Pyelonephritis	250 mg, twice daily
Uncomplicated gonorrhoea	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 Injectable). 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 cefuroxime sodium administration of 1.5 g given via i.v or i.m routes 2 or 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 cefuroxime sodium administration of 750 mg given via i.v or i.m routes 2 or 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;

For most infections	125 mg twice daily to a maximum of 250 mg a day (2×125 mg)
In children at or above age of 2 with otitis media or for more severe infections	250 mg twice daily to a maximum of 500 mg a day (2×250 mg or 4×125 mg)

CEFAKS tablets should not be crushed. Therefore it is unsuitable for treatment of patients who cannot swallow tablets such as little children. In children CEFAKS suspension may be used.

Route of administration:
CEFAKS tablets are taken orally.
CEFAKS tablets should be taken after food for optimum absorption.

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. 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/min	1.4 – 2.4	No dose adjustment necessary (standard dose of 125 mg – 500 mg, twice daily)
10-29 ml/min	4.6	Standard single dose given every 24 hours
<10 ml/min	16.8	Standard single dose given every 48 hours

Patients undergoing hemodialysis	2 - 4	A single additional standard dose should be given at the end of each dialysis.

Liver impairment:
No data available.

Pediatric population:
There is no experience of cefuroxime use 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 excipients 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 penicillin, monobactams, carbapenems).

4.4 Special warnings and precautions for use
Patients who have had allergic reactions to penicillin or other beta-lactam antibiotics should be carefully evaluated before starting treatment. Since cross-hypersensitivity reactions may develop against beta-lactam antibiotics, it has been reported that when given to patients with penicillin allergy, cross-hypersensitivity reactions may develop in up to 10% of these patients. If an allergic reaction at a clinically relevant level occurs, the drug should be discontinued and appropriate therapy instituted. In case of severe and acute hypersensitivity reactions, epinephrine treatment and other clinically necessary emergency procedures (oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, airway procedures) may be necessary.

Use of cefuroxime axetil may result in the excessive proliferation of *Candida* as with the other antibiotics. Prolonged use may also result in the excessive proliferation of other non-susceptible microorganisms (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 using of 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 immediately and the patient further examined.

The Jarisch-Herxheimer reaction has been seen following cefuroxime treatment of Lyme disease. It results from the bactericidal activity of cefuroxime on the causative bacteria of Lyme disease, the pathogen spirochaete *Borrelia burgdorferi.* Patients should be told 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).

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil.

In sequential therapy the timing of change from parenteral to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved in the disease. Unless any clinical improvement is observed within 72 hours, then the parenteral course of treatment must be continued. Please refer to the relevant prescribing information for cefuroxime sodium (CEFAKS injectable) before initiating sequential therapy.

CEFAKS contains methyl paraben and propyl paraben which may cause allergic reactions (possibly delayed) and bronchospasm, which is extraordinary.

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, i.e. it is essentially “sodium-free”.

4.5 Interactions with other medicinal products and other forms of interaction
Drugs which reduce gastric acidity may reduce the bioavailability of CEFAKS in the fasting state and may eliminate the increase in absorption of CEFAKS after meals.

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

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

Concomitant use with oral anticoagulants may give rise to increased International Normalized Ratio (INR).

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime. Cefuroxime axetil does not interfere with the alkaline picrate assay for creatinine.

Cephalosporin group medicines tend to be absorbed onto the red cells membranes and react with antibodies directed against the drug, leading to a positive Coombs' test and very rarely hemolytic anemia.

4.6 Pregnancy and lactation
General recommendation
Pregnancy category: B

Women of child-bearing potential/Birth control (Contraception)
It may lead to reduced effectiveness of combined oral contraceptives.

Pregnancy
There are not sufficient data on the use of cefuroxime axetil in pregnant women. Caution when given to pregnant women.

There is no experimental evidence of embryopathic or teratogenic effects attributable to cefuroxime axetil but, as with all drugs, it should be used with caution during the early periods of pregnancy.

Breast-feeding
Cefuroxime is also excreted in human milk. It should be decided whether to stop breastfeeding or whether to stop cefuroxime axetil treatment.

Reproductive ability/Fertility
No data is available.

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

4.8 Undesirable effects
Side effects of cefuroxime axetil are generally mild and transient.
The most common undesirable effects are *Candida* proliferation, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the side effects are estimates, as for most reactions suitable data (for example data from placebo-controlled studies) as in placebo-controlled studies for calculating incidence were not available. In addition the incidence of side effects 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 (<1/10,000) were mainly determined using post-marketing data and refer to a reporting rate. Placebo-controlled trial data were not available. The incidences have been calculated from clinical trial data, and these were based on drug-related data.

Frequencies were defined as very common (≥ 1/10); common (≥ 1/100 and < 1/10), uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 and < 1/1,000); very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations

Common:	Candida proliferation
Not known:	*Clostridium difficile* proliferation

Blood and lymphatic system disorders

Common:	Eosinophilia
Uncommon:	Positive Coomb's test, thrombocytopenia, leukopenia (sometimes severe)
Not known:	Hemolytic anemia

Cephalosporin group antibiotics tend to be absorbed to the surface of the red blood cell membrane and interact with antibodies directed against the drug, resulting in a positive Coomb's test (which can affect blood cross-interaction) and, very rarely hemolytic anemia.

Immune system disorders
Not known: Drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction

Nervous system disorders
Common: Headache, dizziness

Gastrointestinal disorders
Common: Gastrointestinal discomfort such as diarrhea, nausea, abdominal pain
Uncommon: Vomiting
Not known: Pseudomembranous colitis (see Section 4.4)

Liver and gall bladder disorders
Common: Transient elevations in hepatic enzyme levels (LDH, ALT (SGPT), AST (SGOT))
Not known: Jaundice (predominantly cholestatic), hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Skin rashes
Not known: Urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis), angioneurotic edema (see Immune system disorders)

Cephalosporins tend to be absorbed to the surface of the red blood cell membrane and interact with antibodies produced against the drug, resulting in a positive Coomb's test (which can affect blood cross-interaction) and, very rarely hemolytic anemia.

Transient increases in serum liver enzymes have been observed and are usually 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 in accordance with local requirements.

4.9 Overdose and treatment
Overdosage of cephalosporins can cause cerebral irritation leading to encephalopathy, convulsion and coma. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Second-generation cephalosporins
ATC code: J01D C02

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 this is indicated with an (*) sign.
Commonly Susceptible Species
Gram-Positive Aerobes: *Staphylococcus aureus* (methicillin-susceptible)* Coagulase negative *Staphylococcus* (methicillin-susceptible) *Streptococcus pyogenes** Beta-hemolytic streptococcus
Gram-Negative Aerobes: *Haemophilus influenzae**; including ampicillin resistant strains *Haemophilus parainfluenzae** *Moraxella catarrhalis** *Neisseria gonorrhoea**; including penicillinase producing and non-penicillinase producing strains
Gram-Positive Anaerobes: *Peptostreptococcus* species *Propionibacterium* species
Spirochetes: *Borrelia burgdorferi**
Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes: *Streptococcus pneumoniae**
Gram-Negative Aerobes: *Citrobacter* species; excluding *C. freundii* *Enterobacter* species excluding *E. aerogenes* and *E. cloacae* *Escherichia coli** *Klebsiella* species; including *Klebsiella pneumoniae** *Proteus mirabilis* *Proteus* species; excluding *P. penneri* and *P. vulgaris* *Providencia* species
Gram-Positive Anaerobes: *Clostridium* species; excluding *C. difficile*
Gram-Negative Anaerobes: *Bacteroides* species; excluding *B. fragilis* *Fusobacterium* species
Inherently resistant organisms
Gram-Positive Aerobes: *Enterococcus* species; excluding *E. faecalis* and *E. faecium* *Listeria monocytogenes*
Gram-Negative Aerobes: *Acinetobacter* species *Burkholderia cepacia* *Campylobacter* species

Citrobacter freundii *Enterobacter aerogenes* *Enterobacter cloacae* *Morganella morganii* *Proteus penneri* *Proteus vulgaris* *Pseudomonas* species; including *P. aeruginosa* *Serratia* species *Stenotrophomonas maltophilia*
Gram-Positive Anaerobes: *Clostridium difficile*
Gram-Negative Anaerobes: *Bacteroides fragilis*
Others**:** *Chlamydia* species *Mycoplasma* species *Legionella* species

5.2 Pharmacokinetic properties

General properties

Absorption:

After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood to release cefuroxime into the circulation. Absorption of cefuroxime axetil suspension is increased with food.

Optimum absorption occurs when it is administered shortly after a meal.

When cefuroxime axetil tablets were taken after meals, peak plasma levels reached approximately 2 to 3 hours later were 2.1 mg/l for a 125 mg dose, 4.14 mg/l for a 250 mg dose, 7.0 mg/l for a 500 mg dose and 13.6 mg/l for a 1 g dose. The rate of absorption of cefuroxime from the suspension is reduced compared with the tablets, leading to later, lower peak serum levels and reduced systemic bioavailability (4 to 17% less).

Distribution:

Protein binding rate varies between 33-50% depending on the methodology used.

Biotransformation:

Cefuroxime is not metabolized.

Elimination:

The serum half-life is 1 - 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 in the pharmacokinetics of cefuroxime were observed between males and females.

Geriatric

No special precaution is necessary in the elderly patients with normal renal function at dosages up to the normal maximum of 1 g per day. Elderly patients are more likely to have decreased renal function; therefore, the dose should be adjusted in accordance with the renal function in the elderly (see Section 4.2).

Pediatric
In older infants (aged >3) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults.

There is no clinical trial data available on the use of cefuroxime axetil in children under the age of 3 months.

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

Hepatic impairment
There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

PK/PD relationship
For cephalosporins, the most important pharmacokinetic-pharmacodynamic index correlating with *in vivo* efficacy has been shown to be the percentage of the dosing interval (%T) that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefuroxime for each target species (i.e. %T>MIC).

Characteristic features in patients
No data available.

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
Microcrystalline cellulose
Sodium lauryl sulfate
Hydrogenated vegetable oil
Croscarmellose sodium
Colloidal silicon dioxide

Film coating materials
- Hydroxypropylmethyl cellulose
- Propylene glycol
- Methyl paraben

- Propyl paraben

Opaspray M-1-7120 white
- Titanium dioxide
- Sodium benzoate
- Hydroxypropylmethyl cellulose

6.2 Incompatibilities
No data available.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Should be stored at room temperature below 25°C in a dry place.

6.5 Nature and contents of container
Presented in 10, 14 or 20 tablets in Alu-Alu plate 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
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No:1 34303 Küçükçekmece/İSTANBUL/TÜRKİYE
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8. MARKETING AUTHORIZATION NUMBER
189/59

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 12.01.1999
Date of last renewal : 03.10.2011

10. DATE OF REVISION OF THE TEXT