SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFAKS 250 mg Film Coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Cefuroxime (as axetil) 250 mg

Excipients:
Methylparaben 0.066 mg
Propylparaben 0.053 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet
White, oblong, homogenous film coated tablets, plain on one side and engraved with '250' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFAKS is indicated in the treatment of infections caused by susceptible strains of certain microorganisms listed below:

- ***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.
- ***Genitourinary 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 (may range from 5 to 10 days).

Table 1 - Adults and children (≥40 kg);

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 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 IV or IM 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 IV or IM 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.

Table 2 - Children (<40 kg);

For most infections	125 mg/kg 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/kg twice daily to a maximum of 500 mg a day (2×250 mg or 4×125 mg)

CEFAKS tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children CEFAKS oral suspension may be used.

Route of Administration:
Oral use.
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 given twice daily)
10-29 ml/min	4.6	Standard individual dose given every 24 hours
<10 ml/min	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

Liver impairment
No data available.

Pediatric population
There is no experience of CEFAKS 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 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 with is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised 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, the drug should be discontinued and appropriate therapy instituted.
Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Use of cefuroxime may result in the overgrowth of *Candida* as with the other antibiotics. Prolonged use may also result in the overgrowth 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 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 has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete *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).

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 parahydroxybenzoate and propyl parahydroxybenzoate which may cause allergic reactions (possibly delayed).

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 absorption after food.

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. Concurrent administration 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 axetil. 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 Recommendation
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. Caution when given to pregnant women.

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

Breast-feeding
Cefuroxime is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from cefuroxime therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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
Adverse effects of Cefuroxime axetil are generally mild and transient in nature.
The most common adverse reactions 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 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. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: 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).

System organ class	Common	Uncommon	Not known
Infections and infestations	*Candida* overgrowth		*Clostridium difficile* overgrowth
Blood and lymphatic system disorders	eosinophilia	positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound)	hemolytic anemia*
Immune system disorders			drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction

Nervous system disorders	headache, dizziness		
Gastrointestinal disorders	diarrhoea, nausea, abdominal pain	vomiting	pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders	transient increases of hepatic enzyme levels		jaundice (predominantly cholestatic), hepatitis
Skin and subcutaneous tissue disorders		skin rashes	urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (*see Immune system disorders*), angioneurotic oedema
Description of selected adverse reactions * 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 rises in serum liver enzymes have been observed which 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 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

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

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 ß-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 micro-organisms to Cefuroxime** Where clinical efficacy of cefuroxime has been demonstrated in clinical trials this is indicated with an asterisk (*).
Commonly Susceptible Species
Gram-Positive Aerobes: *Staphylococcus aureus (methicillin-suscpetible)** Coagulase negative *Staphylococcus (methicillin-suscpetible)* *Streptococcus pyogenes** Beta-hemolytic streptococcus
Gram-Negative Aerobes: *Haemophilus influenzae* including ampicillin resistant strains* *Haemophilus parainfluenzae** *Moraxella catarrhalis** *Neisseria gonorrhoea* including penicillinase and non-penicillinase producing strains* *Neisseria meningitidis* *Shigella spp.*
Gram-Positive Anaerobes: *Peptostreptococcus* spp. *Propionibacterium* spp.
Spirochetes: *Borrelia burgdorferi**
Organisms for which acquired resistance may be a problem
Gram-Positive Aerobes: *Streptococcus pneumoniae** Viridans group streptococcus
Gram-Negative Aerobes: *Bordetella pertussis* *Citrobacter* spp. not including *C. freundii* *Enterobacter* spp. not including *E. aerogenes* and *E. cloacae* *Escherichia coli** *Klebsiella* spp. including *K. pneumoniae** *Proteus mirabilis* *Proteus* spp. not including *P. penneri* and *P. vulgaris* *Providencia* spp. *Salmonella* spp.
Gram-Positive Anaerobes: Clostridium spp. not including *C. difficile*
Gram-Negative Anaerobes: Bacteroides spp. not including *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 *P. aeruginosa* *Serratia* spp. *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. Optimum absorption occurs when it is administered shortly after a meal.

Following administration of cefuroxime axetil tablets peak serum levels (2.1 µg/ml for a 125 mg dose, 4.1 µg/ml for a 250 mg dose, 7.0 µg/ml for a 500 mg dose and 13.6 µg/ml for a 1000 mg dose) occur approximately 2 to 3 hours after dosing when taken with food. 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 has been stated as 33-50% 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 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 population

In older infants (aged >3 months) 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 markedly impaired renal function (i.e. C1cr <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.

Pharmacokinetic/pharmacodynamic 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 individual target species (i.e. %T>MIC).

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
Hydroxypropylmethyl cellulose
Propylene glycol
Methylparaben
Propylparaben

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
Store at room temperature below 30°C in a dry place.

6.5 Nature and contents of container
Presented in 10, 14 and 20 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/TURKEY

8. MARKETING AUTHORIZATION NUMBER

07921/07439/REN/2020

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization :
Date of last renewal : Oct 9, 2022

10. DATE OF REVISION OF THE TEXT

07.07.2017