SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CEFAKS 500 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Cefuroxime (as axetil)……500 mg

Excipient(s) with known effect:
Methylparaben…….0.132 mg
Propylparaben……..0.106 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.
White, oblong, homogenous film coated tablets, plain on one side and debossed with '500' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEFAKS is indicated for the treatment of infections caused by susceptible microorganisms.
Indications include:

- *Upper respiratory tract infections*, for example ear, nose and throat infections such as otitis media, sinusitis, tonsillitis, pharyngitis.
- *Lower respiratory tract infections*, for example pneumonia, acute bronchitis, acute exacerbations of chronic bronchitis, and pneumonia.
- *Genito-urinary system infections*, for example pyelonephritis, cystitis and urethritis.
- *Skin and soft tissue infections*, for example furunculosis, pyoderma, impetigo.
- *Gonorrhea*, 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 over 12 years of age.

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).

Adults	
Most infections	250 mg, twice daily
Urinary tract infections	125 mg, twice daily
Mild to moderate lower respiratory tract infections, e.g. bronchitis	250 mg, twice daily
More severe lower respiratory tract infections, or if pneumonia is suspected	500 mg, twice daily

Pyelonephritis	250 mg, twice daily
Uncomplicated gonorrhea	1 g, single dose
Lyme disease in adults and children over the age of 12 years	500 mg twice daily for 20 days

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

Children	
Most infections	125 mg twice daily with a maximum daily dose of 250 mg (2×125 mg)
Children aged 2 years or older with otitis media or with more severe infections	250 mg twice daily with a maximum daily dose of 500 mg (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, such as young children. In children, cefuroxime oral suspension may be used.

Method of administration
CEFAKS tablets are for oral use.
CEFAKS tablets should be taken after food for optimum absorption.

Additional information on special populations
Renal failure:
The safety and efficacy of cefuroxime axetil in patients with renal failure 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/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
Patients undergoing	2 - 4	A single additional standard dose should be given at the end

hemodialysis		of each dialysis

Hepatic failure
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 to any of the excipients the drug contains.

It is contraindicated in patients with known hypersensitivity to cephalosporin antibiotics.
It is contraindicated in patients with a history of hypersensitivity to beta-lactam antibiotics (such as penicillins, monobactams, and carbapenems).

4.4 Special warnings and precautions for use
Before initiating therapy, careful enquiry is indicated in patients who have experienced an allergic reaction to penicillins, or other beta-lactams. A cross-hypersensitivity reaction may develop against beta-lactam antibiotics and it has been reported that up to 10% of these patients may develop a cross-hypersensitivity reaction when administered to patients with penicillin allergy. If a clinically significant allergic reaction occurs, the drug should be discontinued and an appropriate therapy instituted. When severe and acute hypersensitivity reactions develop, epinephrine treatment and other clinically necessary emergency measures (such as oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, procedures to be applied to the airways) may be necessary.

As with the other antibiotics, use of cefuroxime axetil may result in the overgrowth of *Candida*. 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 its diagnosis in patients who develop diarrhea during or after antibiotic use. 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 significant diarrhea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

The Jarisch-Herxheimer reaction has been seen following cefuroxime treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime on the causative bacteria of Lyme disease, the spirochete *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.

With a sequential therapy regime the timing of change to oral therapy is determined by severity of the infection, clinical status of the patient and susceptibility of the pathogens involved.

If there is no clinical improvement within 72 hours, then the parenteral course of treatment must be continued. Please refer to the relevant prescribing information for injectable cefuroxime sodium before initiating sequential therapy.

CEFAKS contains methyl paraben and propyl paraben, and those may cause allergic reactions (possibly delayed).

4.5 Interactions with other medicinal products and other forms of interaction
Drugs that 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 of CEFAKS after food.

In common with other antibiotics, cefuroxime 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 probenecid 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 and very rarely hemolytic anemia.

4.6 Fertility, pregnancy and lactation
General Recommendation
Pregnancy category is B.

Women of childbearing potential/Contraception
Cefuroxime may lead to reduced efficacy of combined oral contraceptives.

Pregnancy
Adequate data are not available on the use of cefuroxime axetil in pregnant women. Caution should be exercised when administered to pregnant women.

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

Breast-feeding
Cefuroxime is also excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue cefuroxime axetil therapy.

Reproduction 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
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 data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The classification of frequency is defined as: 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); not known (cannot be estimated from the available data).

Infections and infestations
Common: Candida overgrowth
Not known: *Clostridium difficile* overgrowth

Blood and lymphatic system disorders
Common: Eosinophilia
Uncommon: Positive Coombs' test, thrombocytopenia, leukopenia (sometimes profound)
Not known: 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
Not known: 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
Not known: Pseudomembranous colitis (see section 4.4)

Hepatobiliary disorders
Common: Transient increases of 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 also 'Immune system disorders'.

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 via the national reporting system.

4.9 Overdose
Overdosage of cephalosporins can cause cerebral irritation leading to encephalopathy, convulsions, 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, which is a bactericidal antibiotic. Cefuroxime exhibits great stability against bacterial beta-lactamases and consequently is effective against most strains resistant to ampicillin or amoxicillin. 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 dependent on geography and time, and may be very high for certain species. Local information on resistance is desirable, particularly when treating severe infections.

***In vitro* susceptibility of micro-organisms to Cefuroxime** Where clinical efficacy of cefuroxime axetil has been demonstrated in clinical trials, this is indicated with an asterisk (*).
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 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. 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.
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 hydrolyzed in the intestinal mucosa and blood to release cefuroxime into the circulation. The absorption of cefuroxime axetil suspension increases with food.

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

When cefuroxime axetil tablets are taken after meals, peak plasma levels are reached after approximately 2 - 3 hours, as 2.1 mg/l for the 125 mg dose, 4.14 mg/l for the 250 mg dose, 7 mg/l for the 500 mg dose, and 13.6 mg/l for 1 g dose. Cefuroxime suspension has a slower absorption rate than tablets, with lower peak serum levels and decreased systemic bioavailability (4-17% less).

Distribution

The protein binding rate varies between 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 population
No special precaution is needed in the elderly 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.

No clinical trial data is 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. 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 kidneys, 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 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 agents:
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 25°C and in a dry place.

6.5 Nature and contents of container
Presented in ALU/ALU blisters containing 10, 14 or 20 tablets.

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/TURKEY

8. MARKETING AUTHORIZATION NUMBER

189/60

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 30.12.1998
Date of last renewal : 03.10.2011

10. DATE OF REVISION OF THE TEXT

27.10.2021