SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ENCEF 125 mg/5 ml Dry Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 5 mL of suspension contains 125 mg cefdinir.
Excipients:
Each 5 mL contains:

Sodium citrate anhydrous	0.92 mg
Sodium benzoate	8.00 mg
Powdered Sugar	2846.27 mg

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension
Whitish to light yellow-colored granular powder with characteristic aroma odor.
When reconstituted, it forms a creamy, light yellow viscous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENCEF is indicated for the treatment of the following infections.

Acute bacterial otitis media: Infections caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including beta-lactamase-producing strains).

Acute maxillary sinusitis: Infections caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including beta-lactamase-producing strains).

Acute bacterial rhinosinusitis: Infections caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae* (penicillin-susceptible strains only), and *Moraxella catarrhalis* (including beta-lactamase-producing strains).

Pharyngitis/tonsillitis: Infections caused by *Streptococcus pyogenes*.

Uncomplicated skin infections: Infections caused by *Staphylococcus aureus* (including beta-lactamase-producing strains) and *Streptococcus pyogenes*.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The total daily dose for all infections is 14 mg/kg.

Maximum recommended daily dose is 600 mg.
Once a day administration for 10 days is equally effective as BID administration.
Because a single dose administration was not proved useful in skin infections, ENCEF should be used twice a day for the treatment of such infections.
Recommended doses and treatment durations for pediatric patients aged 6 months to 12 years are listed in the table below:

Type of infection	Dose	Duration of treatment
Acute bacterial otitis media	7 mg/kg every 12 hours or 14 mg/kg once daily	5-10 days 10 days
Acute maxillary sinusitis	7 mg/kg every 12 hours or 14 mg/kg once daily	10 days 10 days
Pharyngitis/tonsillitis	7 mg/kg every 12 hours or 14 mg/kg once daily	5-10 days 10 days
Uncomplicated skin infections	7 mg/kg every 12 hours	10 days

The recommended dosing schedule for ENCEF suspension containing 125 mg cefdinir per 5 mL is presented in the table below:

Body weight	Recommended Dosing Schedule (For 125 mg/5 ml)
9kg	2.5 ml every 12 hours or 5 ml once daily
18 kg	5 ml every 12 hours or 10 ml once daily
27 kg	7.5 ml every 12 hours or 15 ml once daily
36 kg	10 ml every 12 hours or 20 ml once daily
≥ 43 kg	12 ml every 12 hours or 24 ml once daily

Children weighing 43 kg and above can take the maximum daily dose of 600 mg.
The measuring spoon supplied with the bottle should be used to take the dose accurately.

Method of administration:
For oral use only.
ENCEF can be taken before or after meals.

Preparation of suspension:
Fill with boiled and cooled drinking water up to half of the graduation mark on the bottle that contains the powder for oral suspension and shake well. Wait for 5 minutes for a homogeneous distribution. Add water up to the graduation mark on the bottle and shake again. The diluted suspension can be

stored for 10 days at controlled room temperature. The bottle should be thoroughly shaken before each use.

Additional information on special populations:
Renal impairment: Dose adjustment is required in patients with impaired renal function or patients undergoing hemodialysis.
In adult patients with creatinine clearance <30 mL/min, the dose of cefdinir should be 300 mg/day. Hemodialysis removes cefdinir from the body. In patients on chronic hemodialysis, the recommended initial dose is 7 mg/kg or 300 mg every other day. At the conclusion of each hemodialysis session, 300 mg (or 7 mg/kg) should be given. Subsequent doses of 300 mg (or 7 mg/kg) are then administered every other day (see section 5.2. Pharmacokinetic properties/Patient characteristics).

Hepatic impairment: Cefdinir is predominantly eliminated from kidneys without being metabolized. No dose adjustment is required in hepatic impairment.

Pediatric patients: The efficacy and safety of cefdinir in children younger than 6 months have not been demonstrated. In children aged 6 months through 12 years, cefdinir should be used as specified in the posology section.

Geriatric patients: Since cefdinir clearance has been shown to be primarily related to changes in renal function rather than age, old individuals do not require dosage adjustment unless they have compromised renal function. The capsule form of cefdinir is recommended for adults.

4.3 Contraindications

Cefdinir is contraindicated in patients with hypersensitivity to cephalosporin group medications.

4.4 Special warnings and precautions for use

Before starting treatment with cefdinir, the patient should be investigated for hypersensitivity to cefdinir, other cephalosporins, penicillins, or other medicines. If cefdinir is to be administered to penicillin-sensitive patients, caution should be exercised, as 10% of patients with penicillin allergy may have cross-hypersensitivity. If an allergic reaction to cefdinir occurs, drug therapy should be discontinued. Serious acute hypersensitivity reactions may require treatment with epinephrine, intravenous fluids, intravenous antihistamines, corticosteroids, and pressor amines; the administration of oxygen, and the maintenance of airway patency.

Pseudomembranous colitis has been reported with almost all antibacterial drugs, including cefdinir. Therefore, caution should be exercised in cases of diarrhea after antibacterial treatment. Treatment with antibacterial drugs changes the normal flora of the intestine. Studies show that *Clostridium difficile* toxin is the primary cause of antibiotic-associated colitis. Appropriate treatment should be initiated following the diagnosis of pseudomembranous colitis. Patients with moderately severe pseudomembranous colitis usually respond adequately to the discontinuation of the drug. Patients with severe colitis require treatment with fluid and electrolyte replacement, protein supplementation, and antibacterials that are clinically effective against *Clostridium difficile*.

As with other broad-spectrum antibiotics, prolonged treatment may result in the growth of resistant organisms. Careful observation of the patient is essential. If superinfection develops during treatment, appropriate alternative therapy should be administered.

As with other broad-spectrum antibiotics, caution should be exercised when cefdinir is administered to people with a history of colitis.

Dose adjustment is required in patients with compromised renal function (creatinine clearance < 30 mL/min) (see section 4.2. Posology and method of administration/additional information on special populations)

This medicinal product contains sodium less than 1 mmol (23 mg) per each dose. At this dose, no sodium-associated adverse effects are expected.

Because ENCEF contains powdered sugar as an excipient, patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Antacids (containing aluminum or magnesium):
Concomitant administration of antacids with 300-mg cefdinir capsules reduces the rate (C_{max}) and extent (AUC) of absorption by approximately 40%. Time to reach C_{max} is also prolonged by 1 hour. If the antacid is administered 2 hours before or after cefdinir, no significant effects occur on cefdinir pharmacokinetics. If antacids are to be taken during cefdinir treatment, cefdinir should be taken not less than 2 hours before or after the intake of antacids.

Probenecid:
As with other beta-lactam antibiotics, probenecid inhibits the renal excretion of cefdinir, resulting in an approximate doubling in AUC, a 54% increase in peak cefdinir plasma concentrations, and a 50% prolongation in the elimination $t_{1/2}$.

Iron-containing products and foods:
Therapeutic products containing 60 mg of elemental iron (such as $FeSO_4$) or vitamins supplemented with 10 mg of elemental iron reduce the extent of absorption of cefdinir by 80% and 31%, respectively. If iron-containing products are to be taken during cefdinir treatment, cefdinir should be taken not less than 2 hours before or after taking these preparations.

There have been reports of reddish stools in patients receiving cefdinir. In many cases, patients were also receiving iron-containing products. The reddish color is due to the formation of a nonabsorbable complex between cefdinir or its breakdown products (clinically insignificant) and iron in the gastrointestinal tract.

Laboratory test interactions:
A false-positive reaction for ketones in the urine may occur with tests using nitroprusside, but not with those using nitroferricyanide.

During cefdinir therapy, measurement of glucose in the urine using Benedict's solution or Fehling's solution may cause false positive reactions. The use of tests based on the enzymatic glucose oxidase enzyme is recommended.
Cephalosporins usually induce a positive direct Coombs test.

Additional information on special populations
No interaction study has been conducted in special populations.

Pediatric patients:
No interaction study has been conducted in pediatric populations.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: B

Women of child-bearing potential/Birth control (Contraception)
There are no studies suggesting that ENCEF has an effect on contraception or the women of childbearing potential.

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/ embryonic/fetal development/parturition or postnatal development.
However, since no adequate and well-controlled studies on pregnant women have been available, its use is not recommended during pregnancy unless necessary.

Breast-feeding
Cefdinir was not detected in breast milk following the maximum daily dose of 600 mg.

Reproductive ability/Fertility
Reproductive ability and fertility in rats: The use of 1,000 mg/kg/day (70 times the human therapeutic dose) did not affect reproductive ability and fertility.

4.7 Effects on ability to drive and use machines

There are no reports of effect on ability to drive and use machines.

4.8 Undesirable effects

Based on data obtained from clinical trials, where the oral suspension was used (in pediatric patients), the following undesirable effects are presented below according to system-organ classification and frequency. The relationship between the observed undesirable effects and cefdinir was evaluated by the researchers as “possibly”,“probably”, or “definitely associated”.

The frequencies can be listed 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); unknown (cannot be estimated from available data)

Infections and infestations
Uncommon:
Vaginal moniliasis, vaginitis

Blood and lymphatic system disorders
Uncommon:
Leukopenia

Gastrointestinal disorders
Common:

Diarrhea, vomiting, nausea
Uncommon:
Abdominal pain, altered defecation, dyspepsia

Hepatobiliary disorders
Uncommon:
Increased aspartate aminotransferase (AST)

Skin and subcutaneous tissue disorders
Common:
Rash
Uncommon:
Cutaneous moniliasis, maculopapular rash

Musculoskeletal, connective tissue, and bone disorders
Uncommon:
Hyperkinesia

Laboratory tests
Laboratory value changes of potential clinical significance (irrespective of relationship to therapy with cefdinir) in clinical trials, where oral suspension was used (in pediatric patients), are as follows:
Common:
Increased or decreased lymphocyte count, increased alkaline phosphatase, decreased bicarbonate, increased eosinophil count, increased lactate dehydrogenase, increased platelet count, increased or decreased polymorphonuclear leukocytes, increased urine protein.
Uncommon:
Increased or decreased phosphorus, increased urine pH, increased or decreased leukocyte count, decreased calcium, decreased hemoglobin, increased urine leukocyte count, increased monocytes, increased AST, increased potassium, increased or decreased urine density, decreased hematocrit.

Post-marketing undesirable effects
Undesirable effects and laboratory value changes encountered during cefdinir therapy, irrespective of relationship to cefdinir use, are as follows:

Blood and lymphatic system disorders
Unknown:
Idiopathic thrombocytopenic purpura, hemolytic anemia

Immune system disorders
Unknown:
Shock, sometimes fatal anaphylaxis, facial and laryngeal edema, feeling of suffocation, serum sickness-like reactions

Nervous system disorders
Unknown:
Loss of consciousness

Eye disorders
Unknown:

Conjunctivitis

Cardiac disorders
Unknown:
Heart failure, chest pain, myocardial infarction

Vascular disorders
Unknown:
Hypertension, allergic vasculitis

Respiratory, thoracic and mediastinal disorders
Unknown:
Acute respiratory failure, asthma attack, drug-induced pneumonia, eosinophilic pneumonia, idiopathic interstitial pneumonia

Gastrointestinal disorders
Unknown:
Stomatitis, acute enterocolitis, bloody diarrhea, hemorrhagic colitis, melena, pseudomembranous colitis, upper gastrointestinal tract bleeding, peptic ulcer, ileus

Hepatobiliary disorders
Unknown:
Acute hepatitis, cholestasis, fulminant hepatitis, liver failure, jaundice

Skin and subcutaneous tissue disorders
Unknown:
Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, erythema nodosum

Musculoskeletal, connective tissue, and bone disorders
Unknown:
Involuntary movements, rhabdomyolysis

Renal and urinary disorders
Unknown:
Acute renal failure, nephropathy

General disorders and administration site conditions
Unknown: Fever

Laboratory tests
Unknown:
Pancytopenia, granulocytopenia, leukopenia, thrombocytopenia, increased amylase

Other
Unknown:
Possible cefdinir-diclofenac interaction

Cephalosporin class undesirable effects
Below are the undesirable effects and laboratory value changes reported for cephalosporin antibiotics in general:

Allergic reactions, anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, renal dysfunction, toxic nephropathy, liver dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, false-positive urine glucose test, neutropenia, pancytopenia, and agranulocytosis. Symptoms of pseudomembraneous colitis may occur during or after antibiotic therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is essential. It allows continued monitoring of the benefit/risk ratio of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose and treatment

Information on cefdinir overdosage in humans is not available. In acute toxicity studies on rodents, a single oral dose of 5600 mg/kg did not cause adverse effects.
Toxic signs and symptoms that occur following overdose with other beta-lactam antibiotics include nausea, vomiting, epigastric pain, diarrhea, and convulsions.
Cefdinir is removed from the body by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial agents for systemic use/Third-generation cephalosporins
ATC code: J01DD15

ENCEF contains cefdinir, a broad-spectrum semisynthetic cephalosporin, as the active ingredient. Cefdinir is a third-generation cephalosporin with a bactericidal effect through the inhibition of the bacterial cell wall synthesis. Micro-organisms resistant to penicillins and certain cephalosporins are susceptible to cefdinir. Cefdinir has more affinity to penicillin binding protein (PBP) 3,2,1 of *S.aureus* and penicillin binding protein (PBP) 2 and 3 of *E.faecalis* than the other cephalosporins. Cefdinir inhibits myeloperoxidase release from neutrophils into the extracellular environment while neutrophils are being stimulated by soluble mediators.

Microbiology
Cefdinir has been shown to be effective on the following microorganisms:

- Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (including beta-lactamase-producing strains, excluding methicillin-resistant strains)
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes
Staphylococcus epidermidis (methicillin-susceptible strains only)
Streptococcus agalactiae
The viridans group streptococci

- Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including beta-lactamase producing strains)
Haemophilus parainfluenzae (including beta-lactamase producing strains)
Moraxella catarrhalis (including beta-lactamase producing strains)

Citrobacter diversus
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

5.2 Pharmacokinetic properties

General properties
Cefdinir maintains its peak concentration in blood for 1.8 hours. Despite decreasing levels of the medicine in blood over time, the activity on bacteria can last for 18-26 hours because of high rate of plasma protein binding of cefdinir (70%). Cefdinir belongs to the group of antibiotics that exert activity depending on the dose not the time. Therefore, the achievement of high blood levels once a day is sufficient for its lasting activity for 24 hours.

Absorption:
Maximal plasma cefdinir concentrations occur 2 to 4 hours after oral administration. The estimated absolute bioavailability of cefdinir suspension is 25%. Cefdinir can be taken before or after meals.
The mean cefdinir plasma concentrations and pharmacokinetic values obtained after a single dose administration of cefdinir suspension to children aged 6 months to 12 years are given in the table below:

Dose	C_{max} (mcg/mL)	t_{max} (h)	AUC (mcg.h/mL)
7 mg/kg	2.30 (±0.65)	2.2 (±0.6)	8.31 (±2.50)
14 mg/kg	3.86 (±0.62)	1.8 (±0.4)	13.4 (±2.64)

Multiple dosing: Cefdinir does not accumulate in plasma following once- or twice-daily administration to subjects with normal renal function.

Distribution:
The mean volume of distribution for cefdinir was 0.35 L/kg (± 0.29) in adults and 0.67 L/kg (± 0.38) in children (6 months to 12 years of age). Cefdinir is 60% to 70% bound to plasma proteins in both adults and children. Binding rates are independent of concentration.

- *Skin blister:* In adult subjects, maximal skin blister cefdinir concentrations of 0.65 (0.33-1.1) and 1.1 (0.49-1.9) mcg/ mL, were observed 4 to 5 hours following administration of 300- and 600-mg doses, respectively. Mean blister C_{max} and AUC values were 48% (±13) and 91% (±18) of the corresponding plasma values.
- *Tonsil tissue:* In adult patients undergoing elective tonsillectomy, mean cefdinir concentrations were found to be 0.25 (0.22-0.46) and 0.36 (0.22-0.80) mcg/g 4 hours after a single dose of 300 mg and 600 mg cefdinir administration. Mean tonsil tissue concentrations were 24% (± 8) of corresponding plasma concentrations.
- *Sinus tissue:* In adult patients undergoing elective maxillary and ethmoid sinus surgery, mean cefdinir concentrations were <0.12 (<0.12-0.46) and 0.21 (<0.12-2.0) mcg/g 4 hours after single doses of 300 mg and 600 mg cefdinir. Mean sinus tissue concentrations were 16% (± 20) of corresponding plasma concentrations.
- *Lung tissue:* In adult patients undergoing diagnostic bronchoscopy, mean cefdinir concentrations were 0.78 (<0.06-1.33) and 1.14 (<0.06-1.92) mcg/mL 4 hours after a single dose of 300 mg and 600 mg cefdinir administration and were 31% (± 18) of corresponding plasma concentrations. Mean epithelial fluid concentrations were 0.29 (<0.3-4.73) and 0.49 (<0.3-0.59) mcg/mL and were 35% (± 83) of corresponding plasma concentrations.

- *Middle ear fluid:* In pediatric patients with acute bacterial otitis media, mean concentrations in the middle ear fluid 3 hours after administration of single 7- and 14-mg/kg doses were 0.21 (<0.09-0.94) and 0.72 (0.14-1.42) mcg/mL, respectively. Mean middle ear fluid concentrations were 15% (± 15) of corresponding plasma concentrations.
- *Cerebrospinal fluid:* There are no data on cefdinir penetration to the cerebrospinal fluid.

Biotransformation:
Cefdinir is not appreciably metabolized. Activity is primarily due to parent drug. Cefdinir is excreted mainly via the kidneys with a mean plasma elimination half-life ($t_{1/2}$) of 1.7 (± 0.6) hours.

Elimination:
In healthy adults with normal renal function, renal clearance is 2.0 (±1.0) mL/min/kg, and oral clearance is 11.6 (±6.0) and 15.5 (±5.4) mL/min/kg following doses of 300 and 600 mg, respectively. The amounts excreted unchanged in the urine after 300 and 600 mg doses were 18.4% (± 6.4) and 11.6% (± 4.6%), respectively.

Linearity / non-linearity:
Plasma cefdinir concentrations increase with dose. However, the increases are lower in the dose range of 300 mg (7 mg/kg) - 600 mg (14 mg/kg) compared to linearity.

Patient characteristics
Patients with renal insufficiency:
Cefdinir clearance is decreased in patients with compromised renal function. Plasma cefdinir concentrations were higher and persisted longer in such patients. Because cefdinir is predominantly renally eliminated, dose adjustment is required in patients with impaired renal function or patients undergoing hemodialysis. In patients with creatinine clearance between 30 and 60 mL/min, C_{max} and t½ increased by 2-fold and AUC by 3-fold. In patients with creatinine clearance < 30 mL/min, C_{max} increased by approximately 2-fold, t½ by 5-fold, and AUC by 6-fold.

Patients undergoing hemodialysis:
Dialysis (4 hours duration) removed 63% of cefdinir from the body and reduced elimination t½ from 16 (±3.5) to 3.2 (±1.2) hours.

Geriatric patients:
It has been shown that cefdinir clearance is more related to renal function than to age.

Gender and race:
The results of a meta-analysis of clinical pharmacokinetics indicated no significant impact of either gender or race on cefdinir pharmacokinetics.

5.3 Preclinical safety data

Cefdinir was not teratogenic in rats at oral doses up to 1000 mg/kg/day (70 times the human dose based on mg/kg/day, 11 times based on mg/m^2/day) or in rabbits at oral doses up to 10 mg/kg/ day (0.7 times the human dose based on mg/kg/day, 23 times based on mg/m^2/day). Maternal toxicity (decreased body weight gain) was observed in rabbits at the maximum tolerated dose of 10 mg/kg/day without adverse effects on offspring. Decreased weight gain was observed in rat fetuses at doses ≥ 100 mg/kg/day and in offspring at doses > 32 mg/kg/day. No effects were observed on maternal reproductive parameters or offspring survival, development, behavior, or reproductive function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium citrate anhydrous
Sodium benzoate
Powdered sugar
Xanthan gum
Guar gum
Citric acid anhydrous
Strawberry flavor
Vanilla flavor

6.2. Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4. Special precautions for storage
Store the product in unopened packaging at room temperature below 25 °C.
Reconstituted product: It can be preserved for 10 days when stored at room temperature.

6.5. Nature and contents of the container
125 mL amber type III glass bottle with a graduation mark of 100 mL and a 31/18 mm white polypropylene cap.
75 mL amber type III glass bottle with a graduation mark of 60 mL and a 31/18 mm white polypropylene cap.

6.6. Special precautions for disposal and other handling
Any unused medicinal products or waste materials should be disposed of in accordance with local regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece/İSTANBUL/TURKEY

8. MARKETING AUTHORISATION NUMBER(S)
237/59

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Date of first authorization: 01.12.2011
Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT
12/2016