SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SEFTECH 200 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Cefpodoxime proxetil 260.88 mg (equivalent to 200 mg cefpodoxime)

Excipient(s) with known effect:
Lactose monohydrate (from cow milk) 35.12 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet
White-off white, oblong film coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SEFTECH is used in the treatment of infections, especially the following, caused by susceptible microorganisms.

- Upper respiratory tract infections
  - Tonsillitis, pharyngitis
  - Acute sinusitis
  - Acute otitis media (in children only)
- Lower respiratory tract infections
  - Acute bronchitis
  - Pneumonia
- Superinfections of chronic obstructive pulmonary disease
- Uncomplicated upper and lower urinary tract infections
- Uncomplicated gonococcal urethritis
- Skin and soft tissue infections

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The recommended dosage for SEFTECH is given in the table below:

Indication	Daily dose	Dosing frequency
Upper respiratory tract infections		
Tonsillitis, pharyngitis	200 mg	100 mg every 12 hours
Acute sinusitis	400 mg	200 mg every 12 hours
Lower respiratory tract infections		
Acute bronchitis*	200 mg	100 mg every 12 hours
Bacterial pneumonia	400 mg	200 mg every 12 hours
Superinfections of chronic obstructive pulmonary	400 mg	200 mg every 12 hours

disease		
Urinary tract infections		
Uncomplicated lower urinary tract infections	200 mg	100 mg every 12 hours
Uncomplicated upper urinary tract infections	400 mg	200 mg every 12 hours
Uncomplicated gonococcal urethritis	200 mg	Single dose
Skin and soft tissue infections	400 mg	200 mg every 12 hours

*Depending on the severity of the infection, the dose can be increased up to 200 mg every 12 hours.

Method of administration:
Taken orally. The film tablet is swallowed whole with the help of a glass of water. It should be administered orally with food to increase absorption.

Additional information on special populations:
Renal impairment
There is no need for dose adjustment if creatinine clearance is over 40 ml/min. When it is lower, it is necessary to adjust the dose according to the following table.

Creatinine clearance	**Recommended dosage**
≥40 ml/min	100 or 200 mg every 12 hours
10-39 ml/min	100 or 200 mg every 24 hours
<10 ml/min	100 or 200 mg every 48 hours
Hemodialysis patients	100 or 200 mg after each dialysis

Pediatric patients with renal impairment
If the creatinine clearance is below 40 $ml.min^{-1}/1.73\ m^2$, the dose interval should be adjusted as follows:
- Creatinine clearance 10-39 $ml.min^{-1}/1.73\ m^2$ = unit dose every 24 hours
- Creatinine clearance < 10 $ml.min^{-1}/1.73\ m^2$ = unit dose every 48 hours
- In hemodialysis patients, a unit dose is administered after each dialysis application.

Liver impairment
No dose adjustment is required in hepatic impairment.

Pediatric population
SEFTECH has a dry powder form for the preparation of oral suspension, which is produced for use in children. The average recommended dose is 8 mg/kg/day in two divided doses. Tablets should be used at doses above 200 mg/day. Above this dose, 100 mg tablets can be used.

Geriatric population
No dosage adjustment is required in the elderly with normal renal function.

4.3 Contraindications

- Hypersensitivity to cefpodoxime or other cephalosporins or other excipients contained in the medicine.
- Previous history of immediate and/or severe hypersensitivity reaction (anaphylaxis) to penicillin or other beta-lactam antibiotics.

4.4 Special warnings and precautions for use

Cefpodoxime is not a preferred antibiotic for the treatment of staphylococcal pneumonia and should not be used in the treatment of atypical pneumonia caused by organisms such as *Legionella, Mycoplasma* and *Chlamydia.* Cefpodoxime is not recommended for the treatment of pneumonia caused by *S. pneumoniae* (see section 5.1).

As with all beta-lactam antibacterial agents, serious and rarely fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefpodoxime must be discontinued immediately and appropriate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefpodoxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefpodoxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

In cases of severe renal insufficiency, it may be necessary to reduce the dosage regimen dependent on the creatinine clearance (see section 4.2).

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including cefpodoxime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of cefpodoxime (see section 4.8). Discontinuation of therapy with cefpodoxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Cefpodoxime should always be prescribed with caution in patients with a history of gastrointestinal disease, particularly colitis.

As with all beta-lactam antibiotics, neutropenia and more rarely agranulocytosis may develop particularly during extended treatment. For cases of treatment lasting longer than 10 days, the blood count should be monitored and treatment discontinued if neutropenia is found.

Cephalosporins may be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug. This can produce a positive Coomb's test and very rarely, hemolytic anemia. Cross-reactivity may occur with penicillin for this reaction.

Changes in renal function have been observed with cephalosporin antibiotics, particularly when given concurrently with potentially nephrotoxic drugs such as aminoglycosides and/or potential diuretics. In such cases, renal function should be monitored.

As with other antibiotics, prolonged use of cefpodoxime may result in the overgrowth of non-susceptible organisms (Candida and Clostridium difficile), which may require interruption of treatment.

Interaction with laboratory tests:
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

This medicine contains lactose. Therefore, patients with rare hereditary problems of galactose

intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

No clinically significant drug interactions have been reported during the course of clinical studies.

Histamine H_2-antagonists and antacids reduce the bioavailability of cefpodoxime. Probenecid reduces the excretion of cephalosporins. Cephalosporins potentially enhance the anticoagulant effect of coumarins and reduce the contraceptive effect of estrogens.

Oral anticoagulants:
Simultaneous administration of cefpodoxime with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including cephalosporins. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the cephalosporins to the increase in INR (international normalized ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of cefpodoxime with an oral anti-coagulant agent.

Studies have shown that bioavailability is decreased by approximately 30% when cefpodoxime is administered with drugs, which neutralize gastric pH or inhibit acid secretions. Therefore, such drugs as antacids of the mineral type and H_2 blockers such as ranitidine, which can cause an increase in gastric pH, should be taken 2 to 3 hours after SEFTECH administration.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is B

Women of childbearing potential/Contraception
There is no data on women of childbearing potential or contraception.

Pregnancy
There are no or limited amount of data from the use of cefpodoxime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Due to the benefit of antibiotic treatment, the use of cefpodoxime may be considered during pregnancy if necessary.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development/parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Breast-feeding
Cefpodoxime is excreted in breast milk in small amounts. Cefpodoxime may be used during breast-feeding. Continuation of breast-feeding should be questioned in case of diarrhea or mucosal fungus infection in the breastfed infant. The possibility of sensitization should be borne in mind.

Reproduction ability / Fertility
In embryotoxicity studies in rats and rabbits, no evidence of teratogenic potential has emerged. Cefpodoxime did not cause an undesirable effect in fertility studies and peri- and postnatal studies in rats. It has been determined that it passes through the placenta in rats and the active substance or metabolites are seen in the milk. There is no experience regarding the use in human pregnancy.

4.7 Effects on ability to drive and use machines

Dizziness has been reported during treatment with cefpodoxime and may affect the ability to drive and use machines.

4.8 Undesirable effects

Adverse drug reactions are listed according to the following frequencies:
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
Excessive growth of non-sensitive organisms (see section 4.4)

Blood and lymphatic system disorders
Rare: Hematological disorders such as reduction in hemoglobin levels, thrombocytosis, thrombocytopenia, leucopenia and eosinophilia
Very rare: Hemolytic anemia

Immune system disorders
Hypersensitivity reactions of all degrees of severity have been observed (see section 4.4).
Very rare: Anaphylactic reactions, bronchospasm, purpura, angioedema

Metabolism and nutrition disorders
Common: Loss of appetite

Nervous system disorders
Uncommon: Headache, paresthesia, dizziness

Ear and labyrinth disorders
Uncommon: Tinnitus

Gastrointestinal disorders
Common: Gastric pressure, nausea, vomiting, abdominal pain, flatulence, diarrhea.

Bloody diarrhea can occur as a symptom of enterocolitis.
The possibility of pseudomembranous enterocolitis should be considered if severe or persistent diarrhea occurs during or after treatment (see section 4.4).

Hepato-biliary disorders
Rare: Transient moderate elevations of AST, ALT and alkaline phosphatase and/or bilirubin. These laboratory abnormalities, which may be explained by the infection, may rarely exceed twice the upper limit of the named range and elicit a pattern of

liver injury, usually cholestatic and most often asymptomatic.
Very rare: Liver damage

Skin and subcutaneous tissue disorders
Uncommon: Hypersensitivity mucocutaneous reactions, rash, urticaria, pruritus
Very rare: Stevens- Johnson syndrome, toxic epidermal necrolysis and erythema multiforme

Renal and urinary disorders
Very rare: Slight increases in blood urea and creatinine

General disorders and administration site conditions
Uncommon: Asthenia or malaise

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 reaction via the national reporting system.

4.9 Overdose

In the event of overdosage with cefpodoxime, supportive and symptomatic therapy is indicated.

In cases of overdosage, particularly in patients with renal insufficiency, encephalopathy has been reported. The encephalopathy is usually reversible once cefpodoxime plasma levels have fallen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Third-generation cephalosporins
ATC code: J01DD13

Mechanism of action:
Cefpodoxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

Mechanism of resistance:
Resistance to cephalosporins results from a variety of mechanisms:
1) Alteration of the cell-wall permeability of gram-negative bacteria.
2) Alteration of the penicillin binding proteins (PBPs)
3) β-lactamase production
4) Bacterial efflux pumps

Break points:
EUCAST (European Committee on Antimicrobial Susceptibility Testing) clinical breakpoints for the minimum inhibitory concentration (MIC) testing are presented below.

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Enterobacteriaceae (uncomplicated UTI only)	≤ 1	>1

Staphylococcus spp.	Note[1]	Note[1]
Streptococcus groups A, B, C and G	Note[2]	Note[2]
Streptococcus pneumoniae	≤ 0.25	>0.5
Haemophilus influenzae	≤ 0.25 Note[3]	>0.5
Moraxella catarrhalis	≤ 0.25 Note[3]	>0.5
Neisseria gonorrhoeae	Insufficient data	Insufficient data
Non-species related breakpoint	Insufficient fata	Insufficient data

[1] Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility.
[2] The beta-lactam susceptibility of beta-hemolytic streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.
[3] Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory.

Susceptibility:
The prevalence of acquired resistance may vary geographically and with time for *selected* species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Antibacterial spectrum
Commonly susceptible species
Aerobic Gram positive organisms:
Staphylococcus aureus (Methicillin-susceptible)
Streptococcus pyogenes
Aerobic Gram negative organisms:
Haemophilus influenzae
Moraxella catarrhalis
Proteus mirabilis[%]
Species for which acquired resistance may be a problem
Aerobic Gram positive organisms
Streptococcus pneumoniae
Aerobic Gram negative organisms
Citrobacter freundi[$]
Enterobacter cloacae[$]
Escherichia coli[%]
Klebsiella pneumoniae[%]
Serratia marcescens[$]
Inherently resistant organisms
Aerobic Gram positive organisms
Enterococcus spp.
Staphylococcus aureus (methicillin resistant)
Aerobic Gram negative organisms
Morganella morganii
Pseudomonas aeruginosa

Others
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.

[$] Natural intermediate susceptibility
[%] ESBL producing species are always resistant

5.2 Pharmacokinetic properties

Absorption:
Cefpodoxime is taken up in the intestine and is hydrolyzed to the active metabolite cefpodoxime. When cefpodoxime proxetil is administered orally to fasting subjects as a tablet corresponding to 100 mg of cefpodoxime, 51.5% is absorbed and absorption is increased by food intake.

Distribution:
The volume of distribution is 32.3 L and peak levels of cefpodoxime occur 2 to 3 hours after dosing. The maximum plasma concentration is 1.2 mg/L and 2.5 mg/L after doses of 100 mg and 200 mg respectively. Following administration of 100 mg and 200 mg twice daily over 14.5 days, the plasma pharmacokinetic parameters of cefpodoxime remain unchanged.

Serum protein binding of cefpodoxime, 40% principally to albumin. This binding is non-saturable in type.

Concentrations of cefpodoxime in excess of the minimum inhibitory levels (MIC) for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.

Elimination:
As the majority of cefpodoxime is eliminated in the urine, the concentration is high (Concentrations in 0-4, 4-8, 8-12 hour fractions after a single dose exceed MIC_{90} of common urinary pathogens). Good diffusion of cefpodoxime is also seen into renal tissue, with concentrations above MIC_{90} of the common urinary pathogens, 3-12 hours after an administration of a single 200 mg dose (1.6 - 3.1 µg/g). Concentrations of cefpodoxime in the medullary and cortical tissues is similar.

Studies in healthy volunteers show median concentrations of cefpodoxime in the total ejaculate 6-12 hours following administration of a single 200 mg dose to be above the MIC_{90} of *N. gonorrhoeae*.

The main route of excretion is renal, 80% is excreted unchanged in the urine, with an elimination half-life of approximately 2.4 hours.

Pharmacokinetic/pharmacodynamic relationship
For cephalosporins, the most important pharmacokinetic-pharmacokinetic indicator of *in vivo* efficacy is the percent of dosage range (%T>MIC) that the non-bound concentration for each target species remains above the minimum inhibitor concentration of cefpodoxime (MIC).

5.3 Preclinical safety data

Preclinical data reveal no additional hazard for humans other than those indicated, based on

conventional studies of acute toxicity, repeated dose toxicity, reproductive toxicity and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carboxymethylcellulose calcium
Croscarmellose sodium
Sodium lauryl sulfate
Hydroxypropylcellulose
Lactose monohydrate (from cow milk)
Magnezyum stearate
Opadry white Y-1-7000 (hypromellose, titanium dioxide, polyethylene glycol)

6.2 Incompatibilities

There is no known incompatibility.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C in a dry place and in its package.

6.5 Nature and contents of container

SEFTECH is packaged in aluminum - aluminum blister as 15 and 20 film 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

241/79

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 20.04.2012
Date of last renewal :

10. DATE OF REVISION OF THE TEXT

11.12.2018