SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rexocef® 40 mg/5 ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

5 ml oral suspension contains 40 mg cefpodoxime as cefpodoxime proxetil
1 ml oral suspension contains 8 mg cefpodoxime as cefpodoxime proxetil

Excipients:
Sucrose 2465 mg/ 5 ml
Aspartame (E951) 20 mg/ 5 ml
Sodium benzoate (E211) 10 mg/ 5 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

* Powder for oral suspension.

Almost white to pale yellow coloured powder. After it is mixed with water it turns into off-white to pale yellow suspension with a characteristic banana odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rexocef powder for oral suspension is indicated for the treatment of the following infections when caused by bacteria susceptible to cefpodoxime (see section 5.1) in children at the age of 4 weeks to 12 years who need oral therapy.

Ear, nose and throat infections:
- tonsillitis, pharyngitis;
- sinusitis;
- acute otitis media.

Lower respiratory tract infections:
- pneumonia and bronchopneumonia;
- acute exacerbation of chronic bronchitis (AECB).

Non-complicated urinary tract infections.

Skin and soft tissue infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults and Elderly
Not applicable for this product.

Paediatric population
The dose for children at the age of 4 weeks to 12 years of age is 5 to 12 mg/kg body weight a day to be taken as 2 separate doses on every 12 hours.
The usual dose is 2 x 4 mg/kg body weight a day to the maximum daily dose of 2 x 100 mg cefpodoxime (in children with body weight above 25 kg).
Note that:
5 ml of suspension contains the equivalent to 40 mg Cefpodoxime.
1 ml of suspension contains the equivalent to 8 mg Cefpodoxime.

The dosing syringe is graduated in kg (from 5 to 25 kg) making possible directly to measure the individual dose of the medicine (one dose of medicine administration) depending on the child's body weight. The individual dose is being read directly.
It is necessary to take two separate doses per day.
Eg.: label No. 12 corresponds to the individual dose to be administered to a child with 12 kg, and twice a day.

Safety and efficacy of cefpodoxime in infants at the age under 4 weeks have not been determined.

In children over 25 kg body weight, using 200 mg/day, the 100 mg tablet may be used.

Hepatic Impairment:
The dosage does not require modification in cases of hepatic impairment.

Renal Impairment:

Rexocef is contraindicated for infants with renal impairment at the age of 4 weeks to 3 months (see section 4.3).

For children with renal impairment with creatinine clearance under 40 ml/min the time interval between the doses must be prolonged and the total daily dose reduced in accordance with the following table (see sections 4.4 and 5.2.):

Creatinine clearance	Dosing	Time interval between doses
From 40 to 10 ml / min / 1.73 m^2	usual dose (single dose)	24 hours (corresponds to a half of the usual daily dose).
Below 10 ml / min / 1.73 m2	usual dose (single dose)	48 hours (corresponds to a half of the usual daily dose).
Patients on haemodialysis	usual dose (single dose)	after each haemodialysis (corresponds to a half of the usual daily dose).

Duration

The duration of therapy is usually 5-10 days.

When treating infections caused by Streptococcus pyogenes the duration of the therapy is at least 10 days in order to prevent further complications such as rheumatic fever or occurrence of severe renal disease, glomerulonephritis.

Method of administration

For oral administration.

This product should be taken during meals for optimal absorption.
For instructions on reconstitution of the product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance cefpodoxime proxetil, to other cephalosporins or to any of the excipients.

Previously known hypersensitivity type 1 or severe hypersensitive reactions, anaphylaxis to penicillin or to other β-lactam antibiotics.

Since Rexocef powder for oral suspension contains aspartame, this medicine must not be given to children with phenylketonuria.

For infants at the age under 28 days and infants from 4 weeks to 3 months with renal insufficiency, therapy with Rexocef powder for oral suspension is not recommended because there is not enough data on the use of this medicine so far.

4.4 Special warnings and precautions for use

Special caution should be exercised when giving Rexocef powder for oral suspension to patients hypersensitive to penicillin or other β-lactam antibiotics, because of possible allergic cross-reactivity (for contraindications with known hypersensitivity reactions see section 4.3).

When prescribing Rexocef , special attention should also be taken with patients with allergic diathesis or asthma, because in these cases the risk of occurrence of severe hypersensitivity reactions is increased.
During the administration of Rexocef powder for oral suspension, hypersensitivity reactions with different severity of clinical features up to the anaphylactic shock may occur (see section 4.8).
Upon the occurrence of severe hypersensitivity reaction, the therapy with Rexocef powder for oral suspension should be discontinued immediately and adequate therapy should be given.

In severe gastrointestinal disorders, accompanied with vomiting and diarrhoea, treatment with Rexocef powder for oral suspension should be avoided, since the absorption into the gastrointestinal tract will not be sufficient.

During the therapy with Rexocef powder for oral suspension or afterwards, inflammation of the colon may occur (e.g. pseudomembranous colitis) characterised with severe and persistent diarrhoea that sometimes may be life-threatening. In that case, the therapy with Rexocef powder for oral suspension should be discontinued immediately and adequate therapy should be given.
Use of medicines that inhibit the peristaltic is contraindicated.

Use of Rexocef powder for oral suspension may induce vomiting and diarrhoea (see section 4.8). In this case, the efficiency of this and/or other medicines (e.g. oral contraceptives) can be reduced.

Long term or repeated use of Rexocef powder for oral suspension may cause superinfection and colonisation with resistant bacteria or fungi (e.g. oral candidiasis, vaginitis).

Erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome:
If these conditions occur, the use of the drug should be discontinued immediately.

Children with renal impairment:
In patients with creatinine clearance above 40 ml/min change of the dose is not required. In patients with creatinine clearance below 40 ml/min and in patients treated with haemodialysis, extension of the time interval between the doses is required (see section 4.2 Dosing, administration and time of use).

Effects on the clinical and chemical parameters
During the treatment with cephalosporins both the Coomb's test and the non-enzymatic methods for glucose determination in the urine can show false-positive results.

Rexocef powder for oral suspension contains aspartame (E951). Aspartame is hydrolysed in the gastrointestinal tract when orally ingested. One of the major hydrolysis products is phenylalanine. Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Rexocef powder for oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

Rexocef powder for oral suspension contains sodium benzoate (E211).
Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicaments and other forms of interaction

With parenteral administration of high cephalosporin doses and concurrent use of strong diuretics (e.g. furosemide) or potentially nephrotoxic drugs (eg. aminoglycoside antibiotics) possibility for impairment of the renal function cannot be excluded. However, pharmacological data and clinical experience show that it is not likely to occur with the use of the recommended doses of Rexocef powder for oral suspension.

Antacids and H2-blockers
Concurrent administration of preparations that increase the pH value in the stomach and cefpodoxime in volunteers on an empty stomach, decreased the bioavailability of cefpodoxime by about 30%.
Studies carried out so far have shown the following results:

Antacids
Aluminium hydroxide – 27%
Sodium bicarbonate – 32%

H2-blockers
Ranitidine – 29%

Therefore, these medicines should be taken 2 - 3 hours before or after the use of Rexocef powder for oral suspension.

Bacteriostatic antibiotics
Rexocef powder for oral suspension should not be used concomitantly with bacteriostatic antibiotics (such as chloramphenicol, erythromycin, sulfonamides, and tetracyclines), because the effect of Rexocef powder for oral suspension can be reduced.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no adequate data on the use of cefpodoxime proxetil in pregnancy. Studies carried out on animals have not shown evidence for teratogenic or fetotoxic effects of cefpodoxime. Because of the lack of clinical experience, in particular in the first three months of pregnancy, Rexocef powder for oral suspension should be prescribed only after careful assessment and taking into account the risk from its use.

Breast-feeding
The active ingredient cefpodoxime proxetil passes into breast milk in small amounts. In breastfed infants it can lead to change in the intestinal flora accompanied with diarrhoea and parasite colonisation of the bowels, so the breastfeeding will have to be discontinued. In addition, possibility of sensibilisation should also be considered. Therefore, Rexocef powder for oral suspension should be used only after careful assessment and taking into account the risk from their use.

4.7 Effects on ability to drive and use machines

Experience so far shows that Rexocef powder for oral suspension do not influence the ability to react and concentration. Still, in rare cases, side effects such as hypotension or dizziness can reduce the ability to perform the stated activities (see section 4.8 Possible side effects).

4.8 Undesirable effects

The side effects are grouped as follows:

Common **≥ 1/100 to < 1/10**	**Uncommon** **≥ 1/1.000 to < 1/100**	**Rare** **≥ 1/10.000 to < 1/1.000**
Infections and infestations		
Superinfections with unsusceptible microorganisms, e.g. fungi - Candida (see section 4.4)		
Blood and lymphatic system disorders		
	Thrombocytosis In most cases this change is reversible after the discontinuation of the therapy.	Agranulocytosis, hemolytic anemia, eosinophilia, lymphocytosis, anemia, leukopenia, neutropenia, leukocytosis, thrombocytopenia
Immune system disorders		
		Hypersensitive reactions of different levels of severity like angioedema, bronchospasm to the life threatening shock (see section 4.4).

Metabolism and nutrition disorders		
Anorexia		
Nervous system disorders		
	Headache, paraesthesia, and dizziness.	
Ear and labyrinth disorders		
	Tinnitus	
Gastrointestinal disorders		
Stomach pains, nausea, vomiting, flatulence, or diarrhoea.		Pseudomembranous enterocolitis (see section 4.4) Acute pancreatitis
Hepatobiliary disorders		
	Increase of the hepatic enzymes concentration (transaminases, alkaline phosphatases) and/or bilirubin as a result of hepatic disorder (eg. cholestatic)	Acute hepatitis
Skin and subcutaneous tissue disorders		
	Skin lesions with or without itching (erythema, exanthema, urticaria, purpura) Pruritus	Erythema multiforme, Stevens-Johnson syndrome, Lyell syndrome
Renal and urinary system disorders		
		Increased serum urea and creatinine concentrations Acute renal insufficiency
General disorders and administration site conditions		

	Asthenia, fatigue, and malaise	

4.9 Overdose

There have been no cases of significant overdose in people. Overdosing in adults with the daily dose up to 1000 mg cefpodoxime has been reported in few cases. Side effects were the same as those that can occur with the use of usually recommended doses. Cefpodoxime is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Third-generation cephalosporins.
ATC code: J01DD13.

Cefpodoxime proxetil, i.e. the ester of cefpodoxime, is a beta-lactam antibiotic from the group of cephalosporins for peroral administration.

Mechanism of action
Cefpodoxime acts by inhibiting the synthesis of the bacterial cell wall (in the growth phase) through blocking the penicillin-binding proteins (PBP), such as trans peptidases. This results in bactericidal activity.

Relation between the pharmacokinetics and the pharmacodynamics of the drug
The efficacy mainly depends on the period in which the level of concentration of cefpodoxime in the serum is above the minimum inhibitory concentration (MIC) of the pathogen.

Mechanisms of Resistance
The resistance to cefpodoxime can be caused by some of the following mechanisms:
- Inactivation with beta-lactamase: Cefpodoxime may be hydrolysed with certain beta-lactamases, especially with the so called wide spectrum beta-lactamases (ESBLs) that were discovered in Escherichia coli and Klebsiella pneumoniae, or through chromosome-encoded beta-lactamases of the AmpC type, for example, found in Enterobacter cloacae. In infections caused by bacteria with inducible AmpC-type of beta-lactamase and *in-vitro* susceptability to cefpodoxime, there is a possibility for bacterial mutation and expression of the AmpC-type of beta-lactamase.
- Decrease of the affinity of the penicillin-binding proteins (PBP) to cefpodoxime: Acquired resistance of pneumococcus and other streptococcus types is based on the modification of PBP after mutation. However, the resistance to methicillin (oxacillin) resistant staphylococcus is attributed to the formation of additional PBP with decreased affinity for cefpodoxime.
- Decreased penetration of cefpodoxime through the cell wall of gram-negative bacteria, which results in the insufficient access of cefpodoxime to the penicillin-binding proteins.
- Presence of efflux pump that actively transports cefpodoxime out of the bacteria.

There is a partial or complete cross-resistance between cefpodoxime and other cephalosporins and penicillins.

Breakpoints:
The cefpodoxime test was performed using the standard dilution series. The following minimum inhibitory concentrations for sensitive and resistant bacteria have been identified:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Pathogenic microorganism	Susceptible	Resistant
Enterobacteriaceae [1)]	≤ 1 mg/l[1)]	> 1 mg/l[1)]
Staphylococcus spp. [2)]	- [2)]	- [2)]
Streptococcus spp. (Group A,B,C, and G) [3)]	- [3)]	- [3)]
Streptococcus pneumoniae	≤ 0.25 mg/l	> 0.5 mg/l
Haemophilus influenzae	≤ 0.25 mg/l	> 0.5 mg/l

1) Only for uncomplicated urinary tract infections
2) For Staphylococcus spp. the result from the test for oxacillin or cefoxitin is taken. Methicillin (oxacillin) resistant staphylococci are considered resistant, regardless of the test results.
3) For Streptococcus spp. (Groups A, B, C, G) the result from the test for the penicillin G is taken.

Susceptibility and resistance
Prevalence of acquired resistance can vary geographically and temporally for certain species. Thus, it is desirable to have the local information on resistance available, especially when severe infections should be treated. When required, advice from an expert should be sought, if due to the local prevalence of the resistance the efficacy of cefpodoxime proxetil is compromised. In particular, in cases of serious infections or failure of the treatment, it is desirable to make microbiological diagnosis and determine which pathogen caused the infection and its susceptibility to cefpodoxime.

Usually susceptible species:

Aerobic gram-positive microorganisms
Staphylococcus aureus (Methicillin susceptible)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram -negative microorganisms
Haemophilus influenzae
Neisseria gonorrhoeae°
Proteus mirabilis%

Species with which acquired resistance may be a problem:

Aerobic gram-positive microorganisms
Staphylococcus aureus $ ʒ
Staphylococcus epidermidis $ +
Staphylococcus haemolyticus $ +
Staphylococcus hominis $ +
Staphylococcus saprophyticus $
Streptococcus pneumoniae (Penicillin-intermediary)

Aerobic Gram -negative microorganisms
Citrobacter freundii $
Enterobacter cloacae $
Escherichia coli % & ʒ
Klebsiella pneumoniae %
Moraxella catarrhalis $
Serratia marcescens $

Naturally resistant species:

Aerobic gram-positive microorganisms
Enterococcus spp.
Staphylococcus aureus (Meticillin-resistant)
Streptococcus pneumoniae (Penicillin-resistant)

Aerobic Gram -negative microorganisms
Morganella morganii
Pseudomonas aeruginosa

Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.

° Current data was not available at the time of publishing of the table. The conclusion on the susceptibility of the species is derived from the recommendations in literature and usual recommendations for the therapy.
$ Natural susceptibility of the most of isolates is within the intermediate range.
+ In at least one region, the resistance rate is above 50%.
% Strains that produce wide spectrum β-lactamases (ESBLs) are always resistant.
& In isolates from patients with uncomplicated cystitis, the rate of resistance is <10 %, otherwise it is ≥10%.
Ʒ In hospital conditions, the rate of resistance is <10%.

5.2 Pharmacokinetic properties

Cefpodoxim proxetil is a prodrug of cefpodoxim.

Resorption

Upon oral administration, cefpodoxim is absorbed in the gastrointestinal tract and is quickly hydrolysed in the intestinal mycosis into cefpodoxim.

Distribution

Children
After oral administration of a dose of 5 mg cefpodoxim * / kg body weight (maximum 200 mg *) in children between 4 and 12 years the average (Tmax) was 2 - 4 hours. Maximum plasma levels (Cmax) is 2.6 mg / l. The average plasma concentrations, 8 and 12 hours after administration, were 0.39 and 0.08 mg / l, respectively.

Single-dose in adults
After a single oral dose of 100 mg of cefpodoxim* maximum plasma concentration (Cmax) is from 1 to 1,2 mg/l, and following the single dose of 200 mg of cefpodoxim* Cmax is 2.2 to 2.5 mg/l. In both cases (100 mg/200 mg) Cmax is reached in 2 to 3 hours (Tmax).

Repeated doses in adults
With repeated doses of 100 or 200 mg cefpodoxim* within the time intervals of 12 hours during 14.5 days, the pharmacokinetic parameters have not shown any changes and occurrence of accumulation.

Elderly patients

In patients at the age of 70 and older, after repeated dosing of cefpodoxim* of 200 mg within 12-hour time intervals during 6 to 10 days, a steady state is reached. In the steady state Cmax is 3.05 mg/l and Tmax is 2.7 hours on average.

Patients with liver cirrhosis
After a single dose of 200 mg cefpodoxim* in patients with cirrhosis with or without ascites, Cmax is about 1.67 mg/l, what corresponds to the Cmax 12 hours after the administration of the drug to healthy volunteers.

Patients with chronic renal insufficiency
Plasma concentration of the drug in patients with chronic renal insufficiency, depends on the severity of the renal insufficiency. With persons with the creatinine clearance below 40 ml / min (10-40 ml / min), Cmax after the administered dose of 200 mg cefpodoxime* is twice as high as in healthy volunteers on average, while the Tmax is around 4 hours.

* Administered as cefpodoxime proxetil

Hemodialysis patients
Plasma concentration of the drug in patients with creatinine clearance below 10 ml/min (10 ml / min) is 1.5 times higher than in healthy volunteers on average while Tmax is around 6 hours.
Cefpodoxime is dialyzable; therefore a single dose of the drug has to be administered immediately after the haemodialysis.

Distribution volume
The distribution volume is 32.3 l in young subjects (+0.43 l/kg).

Plasma protein binding
The plasma protein binding is essentially based on albumins and is about 40%. This binding is not saturable.

Tissue distribution
Cefpodoxim diffuses well in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, kidney, prostate and interstitial fluids. The observed concentrations are above the MIC values of the sensitive microorganisms.

Metabolism and elimination

After the absorption, cefpodoxime proxetil is hydrolysed to the main metabolite cefpodoxime.
Cefpodoxime is difficult to metabolise and 80% of cefpodoximeproxetil is excreted through the kidneys unchanged.
Total clearance of cefpodoxime is 9.98 l/h, while the renal clearance is 7 l/h on average.
The half-life of elimination (T 1/2) of cefpodoxime is 2.4 hours.

In elderly patients, the half-life of elimination (T 1/2) is extended to 3.6 hours on average.
In patients with chronic renal insufficiency and the creatinine clearance below 40 ml/min, T 1/2 is more than 6 hours (7.7 hours on average in creatinine clearance between 10 and 40 ml/min).

Absolute bioavailability
Absolute bioavailability of cefpodoxime is about 40 - 50% after the oral administration of one tablet of cefpodoxim proxetil (containing to 100 mg cefpodoxime) on an empty stomach.

The absorption is increased by concomitant intake of a meal, therefore the powder for oral suspension should be administered with a meal.

5.3 Preclinical safety data

There are no findings on the chronic toxicity that would lead to suspicion that unknown effects with human use could occur.
Moreover, teratogenic or mutagenic potential has not been determined in *in vivo* or in *in vitro* studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose and Carboxymethyl cellulose sodium
Silica, Colloidal Anhydrous
Maize Starch
Hydroxypropyl cellulose
Sodium Benzoate (E211)
Anhydrous Citric acid
Aspartame (E951)
Artificial Banana Flavour Spray dry
Iron Oxide, yellow (E172)
Sucrose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unreconstituted product: 2 years.
Reconstituted suspension: 10 days stored in a refrigerator (2-8°C).

6.4 Special precautions for storage

Unreconstituted product should be stored below 25°C.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The powder for oral suspension is immediate packed in a 150 ml round, translucent HDPE bottle with child resistant closure and induction heat seal.
Cardboard box contains one (1) bottle, dosing syringe, graduated in kg, graduated measuring cup for preparation of suspension and an instruction leaflet. Each bottle contains 64.8 g powder for preparation of 100 ml oral suspension.

6.6 Special precautions for disposal and other handling

The suspension is for oral administration only.

Warning:
• A plastic graduated measuring cup is provided, which serves only to measure the amount of water needed to prepare the suspension
• After preparing the suspension, plastic measuring cup should be discarded.
• The graduated plastic measuring cup should never be used to give medicine to the child.

Preparation of suspension is done in the pharmacy, as follows:
1. Vigorously shake the bottle to separate the powder from the bottom of the bottle.
2. Unscrew the bottle by exerting pressure on the cap and turning at the same time (safety valve).
3. Remove the protective foil.
4. Fill the graduated plastic measuring cup with water to the mark 27 ml.
5. Pour completely the water of the measuring cup into the bottle and shake vigorously so that no remaining powder adhering to the walls of the bottle.

6. Fill it again graduated plastic measuring cup with water to the mark 27 ml.
7. Pour the water of the measuring cup into the bottle and shake vigorously to get almost white to light yellow homogenous suspension with a distinctive fruity taste.
8. Discard the graduated plastic measuring cup.

Shake well before each use!
Close the bottle carefully after each use!
The prepared suspension should be kept in a refrigerator (2-8° C), up to 10 days!

The reconstituted suspension is administered by dosing syringe, graduated in kg (from 5 to 25 kg)

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST MARKETING AUTHORIZATION/RENEWAL OF AUTHORIZATION

10. DATE OF REVISION OF THE TEXT