SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cefpodoxime Proxetil for oral suspension 40mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of suspension contains 52.18 mg cefpodoxime proxetil (equivalent to 40 mg cefpodoxime).

Excipients: Lactose monohydrate and sucrose.
Each 5 ml volume contains 162 mg lactose monohydrate and 2737.3 mg sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension

Dry powder: Off-white coloured granular powder.
After reconstitution with water: Off-white coloured suspension with Banana flavor.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefpodoxime is indicated for the treatment of the following infections caused by cefpodoxime susceptible pathogens (see sections 4.4 and 5.1) in children up to 11 years:

Upper respiratory tract infections

- Acute bacterial sinusitis
- Tonsillitis
- Acute otitis media

Lower respiratory tract infections

- Bacterial pneumonia

In case of bacterial pneumonia cefpodoxime might not be suitable option depending on the pathogen involved, please see section 4.4.

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

4.2 Posology and method of administration

Route of administration: oral.

Adults and Elderly:
Not applicable for this product.

Infants(> 28 days), toddlers, Children (up to 11 years):
The recommended mean dosage for children is 8mg/kg/day, administered in two divided doses at 12-hour intervals.

The dose to be taken is indicated on the measuring spoon. The graduations correspond to the child's weight in kg from 5 kg (2.5 ml) to 25 kg (12.5 ml) with intermittent graduations of 1 kg (0.5 ml) each. The dose to be taken is read directly from the spoon.

The following table provides dosage regimen for children as per the bodyweight graduations provided on the measuring spoon:

Body weight in kg	**Cefpodoxime dose in mg to be used twice daily**	**Cefpodoxime dose in ml to be used twice daily**
5	20	2.5
10	40	5
15	60	7.5
20	80	10
25	100	12.5

Children who weigh at least 25 kg take 12.5 ml of suspension twice daily or alternatively 100 mg film-coated tablet twice daily.

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

Renal Impairment:
The dosage of cefpodoxime does not require modification if creatinine clearance exceeds 40 ml.min-1/1.73m^2.

Below this value, pharmacokinetic studies indicate an increase in plasma elimination half-life and the maximum plasma concentrations, and hence the dosage should be adjusted appropriately.

CREATININE CLEARANCE (ml/min)	
39 – 10	Single dose administered every 24 hours instead of twice a day (i.e half of the usual dose).
< 10	Single dose administered every 48 hours (i.e quarter of the usual dose).
Haemodialysis Patients	Single dose administered after each dialysis session.

The suspension may be taken with or without food.
Instructions for Reconstitution
Before preparing the suspension the silica gel desiccant contained in the stopper inside the closure must be removed and disposed off. To prepare the suspension first shake the bottle to loosen granules. Add water upto about half of the 100 ml ring mark and shake vigorously. Further add water up to the

100 ml ring mark of the bottle and shake vigorously to obtain an evenly dispersed suspension.

4.3 Contraindications

Hypersensitivity to cefpodoxime or other cephalosporines or to any of the excipients.

Previous history of immediate and / or severe hypersensitivity reactions (anaphylaxis) to penicillin or other beta-lactam antibiotic

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 due to *S. pneumoniae* (see section 5.1).

As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefpodoxime must be discontinued immediately and adequate 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 (see section 4.3). 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 diarrhoea 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, haemolytic anaemia. 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, the 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.

Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency, glucose-galactose malabsorption or sucrase – isomaltase insufficiency should not take this medicine.

4.5 Interaction 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 oestrogens.

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 normalised 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 the 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 cefpodoxime administration.

4.6 Fertility, pregnancy and lactation

Not applicable.

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 below by system organ class and frequency. Frequencies are 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)

Blood and lymphatic system disorders

Rare: Haematological disorders such as reduction in haemoglobin, thrombocytosis, thrombocytopenia, leucopenia and eosinophilia

Very rare: Haemolytic anaemia.

Nervous system disorders

Uncommon: Headache, paraesthesia, dizziness

Ear and labyrinth disorders

Uncommon: Tinnitus

Gastrointestinal disorders

Common: Gastric pressure, nausea, vomiting, abdominal pain, flatulence, diarrhoea. Bloody diarrhoea can be seen as signs of enterocollitis.

The possibility of a pseudomembranous enterocolitis should be considered if severe or persistent diarrhea occurs during or after treatment (see Section 4.4).

Metabolic and nutritional disorders

Common: Loss of appetite

Immune system disorders:

Hypersensitivity reactions of all degrees of severity have been observed (see section 4.4).

Very rare: anaphylactic reactions, bronchospasm, purpura and angioedema.

Renal and urinary disorders

Very rare: Slight increases in blood urea and creatinine

Hepatobiliary disorders
Rare: Transient moderate elevations of ASAT, ALAT and alkaline phosphatases and/or bilirubin
These laboratory abnormalities, which may also 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

Infections and infestations
There can be multiplication of non-sensitive micro-organisms (see section 4.4)

General disorders and administration site conditions
Uncommon: Asthenia or malaise

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 may occur. The encephalopathy is usually reversible once cefpodoxime plasma levels have fallen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other beta-lactam antibacterials, 3rd generation cephalosporins.
ATC Code: J01DD13

Mode 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.

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 that the unbound concentration remains above the minimum inhibitory concentration (MIC) of cefpodoxime for individual target species (i.e. %T>MIC).

Mechanism(s) 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

Breakpoints:

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below. EUCAST clinical MIC breakpoints for cefpodoxime (2011-01-05, v 1.3)

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	IE	IE
Non-species related breakpoint	IE	IE

1 Susceptibility of staphylococci to cephalosporins is inferred from the cefoxitin susceptibility.
2 The beta-lactam susceptibility of beta-haemolytic 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.
*Insufficient evidence

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
[+]Resistance rates >50% in at least 1 region
[%] ESBL producing species are always resistant

5.2 Pharmacokinetic properties

Cefpodoxime proxetil is taken up in the intestine and is hydrolysed 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. The volume of distribution is 32.3 L and peak levels of cefpodoxime occur 2 to 3 hrs 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.

As the majority of cefpodoxime is eliminated in the urine, the concentration is high. (Concentrations in 0-4, 4-8, 8-12 hr 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 hrs after an administration of a single 200 mg dose (1.6-3.1µg/g). Concentrations of cefpodoxime in the medullary and cortical tissues is similar.

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

CHILDREN

In children, studies have shown the maximum plasma concentration occurs approximately 2-4 hours after dosing. A single 5mg/kg dose in 4-12 year olds produced a maximum concentration similar to that in adults given a 200mg dose.

In patients below 2 years receiving repeated doses of 5mg/kg 12 hourly, the average plasma concentrations, 2hrs post dose, are between 2.7mg/l (1-6 months) and 2.0mg/l (7 months-2 years).

In patients between 1 month and 12 years receiving repeated doses of 5mg/kg 12 hourly, the residual plasma concentrations at steady state are between 0.2-0.3mg/l (1 month-2 years) and 0.1mg/l (2-12 years).

5.3 Preclinical safety data

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans.

Furthermore, in vivo and in vitro studies did not yield any indication of a potential to cause reproductive toxicity or mutagenicity. Studies on carcinogenicity have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Croscarmellose sodium
Ferric oxide yellow
Hydroxypropyl cellulose
Dispersible cellulose
Silica colloidal anhydrous
Citric acid anhydrous
Sodium citrate
Sodium benzoate
Durarome flavour banana
Sucrose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Dry powder: 24 months

Reconstituted suspension: Once reconstituted, store in a refrigerator at 2 - 8°C and to be used within 10 days.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Off-white colored granular powder filled in a bottle, packed in a printed carton along with a package insert..

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Ltd.,

Plot No: 2, Maitrivihar,

Ameerpet, Hyderabad-500 038,

Telangaga State, India

8 DATE OF REVISION OF THE TEXT

October, 2020