1.3 Product Information

1.3.1 Summary of Product Characteristics (SMPC)

1 Name of the medicinal product: Podaxef 81.25 SACHETS

1.1 (Invented) name of the medicinal product:

Cefpodoxime 50mg and Clavulanic Acid 31.25 mg for Oral Suspension Powder in Sachet

2. Qualitative and quantitative composition

a) Qualitative declaration

Label Claim :

Each sachet Contains:

Cefpodoxime Proxetil USP

equivalent to Anhydrous Cefpodoxime 50 mg

Diluted Potassium Clavulanate BP

equivalent to Clavulanic Acid 31.25 mg

Excipients q.s.

b) Quantitative declaration

Batch size: 100,000 Sachets

S.No.	Raw materials	Specification	Qty./ Sachet (gm)	Overages (%)	Quantity / Batch (kg)	Functional Category
1.	Cefpodoxime Proxetil*	USP	0.0728	6%	7.280	Active
2	Diluted Potassium Clavulanate *	BP	0.0881	20%	8.810	Active
3.	Simeticone	BP	0.010	-	1.000	Antifoaming agent
4.	Neotame	USP	0.0042	-	0.420	sweetening agent
5.	Sodium Carboxy methyl cellulose	BP	0.025	-	2.500	Viscosity-increasing agent
6.	Sodium Citrate	BP	0.010	-	1.000	Acidifying agent
7.	Colloidal anhydrous silica	BP	0.010	-	1.000	Suspending agent
8.	Xanthan gum	BP	0.0025	-	0.250	Binding agent
9.	Anhydrous citric Acid	BP	0.0113	-	1.130	Acidifying agent
10.	Sodium Lauryl Suphate	BP	0.0025	-	0.250	Anionic surfactant
11	Orange flavour	IHS	0.025	-	2.500	Flavouring agent
12.	Sunset yellow supra	IHS	0.0013	-	0.130	Colouring agent
13.	Mannitol**	BP	0.7373	-	73.730	Sweetening agent

***** Actual Quantity of active drug will be vary based on assay and moisture Content.

**Actual quantity of Mannitol will vary based on assay value and moisture content of active drugs to adjust the fill weight.

3. Pharmaceutical form

Description: White colour granular powder, filled in sachet.

4. Clinical particulars

4.1 Therapeutic indications

PODAXEF are indicated for the treatment of patients with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Acute otitis media caused by *Streptococcus pneumoniae* (excluding penicillin-resistant strains), *Streptococcus pyogenes, Haemophilus influenzae* (including beta-lactamase-producing strains), or *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains).
- Pharyngitis and/or tonsillitis caused by *Streptococcus pyogenes.*

  Cefpodoxime proxetil is generally effective in the eradication of streptococci from the oropharynx. However, data establishing the efficacy of cefpodoxime proxetil for the prophylaxis of subsequent rheumatic fever are not available.

- Community-acquired pneumonia caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* (including beta-lactamase-producing strains).
- Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (non-beta-lactamase-producing strains only), or *Moraxella catarrhalis*.
- Acute, uncomplicated urethral and cervical gonorrhea caused by *Neisseria gonorrhoeae* (including penicillinase-producing strains).
- Acute, uncomplicated ano-rectal infections in women due to *Neisseria gonorrhoeae* (including penicillinase-producing strains).
- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) or *Streptococcus pyogenes.* Abscesses should be surgically drained as clinically indicated.
- Acute maxillary sinusitis caused by *Haemophilus influenzae* (including beta-lactamase-producing strains), *Streptococcus pneumoniae* and *Moraxella catarrhalis*.
- Uncomplicated urinary tract infections (cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Staphylococcus saprophyticus*.

4.2 Posology and method of administration

PODAXEF

Children (age below 12 years)

The liquid suspension form of this medication must be shaken well before using. General dosage recommendations for cefpodoxime in children are presented below:

Type of infection	Total daily dose	Dose frequency	Duration
Otitis media	8-10 mg/kg/day (Max 400 mg/day)	4-5 mg/kg q12 hours (Max 200 mg/dose)	5 days
Respiratory tract infections	8-10 mg/kg/day (Max 400 mg/day)	4-5 mg/kg q12 hours (Max 200 mg/dose)	5–10 days
Urinary tract infections	8-10 mg/kg/day (Max 400 mg/day)	4-5 mg/kg q12 hours (Max 200 mg/dose)	
Skin infections	8-10 mg/kg/day (Max 400 mg/day)	4-5 mg/kg q12 hours (Max 200 mg/dose)	

4.3 Contraindications

Is contraindicated in patients with a known allergy to cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

General

Before therapy with cefpodoxime proxetil is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefpodoxime, other cephalosporins, penicillins, or other drugs. If cefpodoxime is to be administered to penicillin-sensitive patients, caution should be exercised because cross-hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of

penicillin allergy. If an allergic reaction to cefpodoxime proxetil occurs, the drug should be discontinued. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine and airway management as clinically indicated.

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including cefpodoxime proxetil, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to the overgrowth of Clostridium difficile.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H2-blockers reduces peak plasma levels by 24–42% and the extent of absorption by 27–32%, respectively. The rate of absorption is not altered by these concomitant medications. Oral anti-cholinergics (e.g., propantheline) delay peak plasma levels (47% increase in the Tmax), but do not affect the extent of absorption (AUC).

Probenecid

As with other beta-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in the AUC and a 20% increase in peak cefpodoxime plasma levels.

Nephrotoxic Drugs

Although nephrotoxicity has not been noted when cefpodoxime proxetil was given alone, close monitoring of renal function is advised when cefpodoxime proxetil is administered concomitantly with compounds of known nephrotoxic potential.

Food

The bioavailability increases if PRODAXEF are administered during meals.

Drug/Laboratory Test Interactions

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

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

Sunset yellow (E110) may cause allergic reactions.

Renal impairment

For patients with severe renal impairment (<30 mL/min creatinine clearance), the dosing intervals should be increased to q24 hours. In patients maintained on hemodialysis, the dose frequency should be three times/week after hemodialysis. No data are available in case of pediatric patients with impaired renal function.

Hepatic impairment

No dose adjustment is recommended for patients with hepatic insufficiency.

4.6 Pregnancy and lactation

Pregnancy

Pregnancy category B. There are no adequate and well-controlled studies of cefpodoxime proxetil use in pregnant women. Because animal reproduction studies are not always predictive of human response, PODAXEF should be used during pregnancy only if clearly needed.

Lactation

Cefpodoxime Proxetil: Cefpodoxime is excreted in human milk.

Clavulanate Potassium: In studies, excretion of clavulanate potassium in milk occurs to a limited extent, the concentrations being lower than those detected in the serum. Because of the potential for serious reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy of Podaxef in infants less than 2 months of age have not been established.

Geriatric Use

Dose adjustment in elderly patients with normal renal function is not necessary.

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 events thought possibly or probably related, or of unknown relationship to cefpodoxime proxetil for oral suspension in multiple-dose clinical trials (N=2128 patients treated with cefpodoxime) were:

Incidence Greater Than 1%

Diarrhoea: 6.0%

The incidence of diarrhea in infants and toddlers (age 1 month to 2 years) was 12.8%.

Diaper rash/Fungal skin rash: 2.0% (includes moniliasis)

The incidence of diaper rash in infants and toddlers was 8.5%.

Other skin rashes: 1.8%

Vomiting: 2.3%

Incidence Less Than 1%

Body: Localized abdominal pain, abdominal cramp, headache, monilia, generalized abdominal pain, asthenia, fever, fungal infection.

Digestive: Nausea, monilia, anorexia, dry mouth, stomatitis, pseudomembranous colitis.

Hemic & Lymphatic: Thrombocythemia, positive direct Coombs' test, eosinophilia, leukocytosis, leukopenia, prolonged partial thromboplastin time, thrombocytopenic purpura.

Metabolic & Nutritional: Increased SGPT.

Musculo-Skeletal: Myalgia.

Nervous: Hallucination, hyperkinesia, nervousness, somnolence.

Respiratory: Epistaxis, rhinitis.

Skin: Skin moniliasis, urticaria, fungal dermatitis, acne, exfoliative dermatitis, maculopapular rash.

Special Senses: Taste perversion.

4.9 Overdose

In the event of a serious toxic reaction from overdosage, hemodialysis or peritoneal dialysis may aid in the removal of cefpodoxime from the body, particularly if renal function is compromised.

The toxic symptoms following an overdose of beta-lactam antibiotics may include nausea, vomiting, epigastric distress, and diarrhea.

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

Pharmacodynamics

Podaxef are a fixed-dose combination of cefpodoxime proxetil and potassium clavulanate. Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class. The chemical name is (RS)-I(isopropoxycarbonyloxy) ethyl (+)-(6R,7R)-7--3-methoxymethyl-8-oxo-5-thia-I-azabicyclooct-2-ene-2-carboxylate.

Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a beta-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of beta-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated beta-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo-heptane-2-carboxylate

Microbiology

The bactericidal action of cefpodoxime results from inhibition of cell wall synthesis. Cefpodoxime is active against a wide-spectrum of Gram-positive and Gram-negative bacteria. Cefpodoxime has shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections.

Antibacterial Spectrum

Commonly Susceptible Species

Aerobic Gram-positive microorganisms

Staphylococcus aureus (including penicillinase-producing strains)

Staphylococcus saprophyticus

Streptococcus pneumoniae (excluding penicillin-resistant strains)

Streptococcus pyogenes

Aerobic Gram-negative microorganisms

Haemophilus influenza (including beta-lactamase producing strains)

Moraxella (Branhamella) catarrhalis

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Neisseria gonorrhoeae (including penicillinase-producing strains)

The following in vitro data are available, but their clinical significance is unknown. Cefpodoxime exhibits in vitro inhibitory concentrations (MICs) of < 2.0 mcg/mL against most (>90%) of isolates of the following microorganisms.

Aerobic Gram-positive microorganisms

Streptococcus agalactiae

Streptococcus spp. (Groups C, G, F)

Aerobic Gram-negative microorganisms

Citrobacter divercus

Klebsiella oxytoca

Proteus vulgaris

Providencia rettgeri

Haemophilus parainfluenzae

Anaerobic Gram-positive microorganisms

Peptostreptococcus magnus

5.2 Pharmacokinetic properties

Cefpodoxime proxetil

Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime.

Absorption: Bioavailability of cefpodoxime is 50% in fasting subjects and it increases in presence of food.

Distribution: Well distributed after oral administration. Cefpodoxime reaches therapeutic concentrations in respiratory tract and genito-urinary tracts and bile. Protein binding of cefpodoxime ranges from 20 to 30%. The plasma half-life of cefpodoxime is about 2 to 3 hours and is prolonged in patients with impaired renal function.

Excretion: Cefpodoxime is excreted unchanged in urine.

Clavulanate Potassium

Absorption: Well absorbed after oral administration

Distribution: Well distributed after oral administration. Protein binding of clavulanic acid is about 30%. The plasma half-life of clavulanic acid is one hour.

Excretion: About 60% of clavulanic acid is excreted unchanged in urine. The clavulanic acid component protects cefpodoxime from degradation by beta-lactamase enzymes and effectively extends the antibiotic spectrum of cefpodoxime to include many bacteria normally resistant to cefpodoxime and other beta-lactam antibiotics. Thus, possesses the distinctive properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

Special Population

Renal Impairment: Elimination of cefpodoxime is reduced in patients with moderate to severe renal impairment (<50 mL/min creatinine clearance). In subjects with mild impairment of renal function (50 to 80 mL/min creatinine clearance), the average plasma half-life of cefpodoxime was 3.5 hours. In subjects with moderate (30 to 49 mL/min creatinine clearance) or severe renal impairment (5 to 29 mL/min creatinine clearance), the half-life increased to 5.9 and 9.8 hours, respectively. Approximately 23% of the administered dose was cleared from the body during a standard 3-hour hemodialysis procedure.

Hepatic Impairment: Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean cefpodoxime T1/2 and renal clearance in cirrhotic patients were similar to those derived in studies of healthy subjects. Ascites did not appear to affect values in cirrhotic subjects. No dosage adjustment is recommended in this patient population.

Geriatrics: Elderly subjects do not require dosage adjustments unless they have diminished renal function.

5.3 Preclinical safety data

NOT APPLICABLE

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Simethicone BP

Sodium Caboxymethyl Cellulose BP

Neotame USP

Sodium citrate BP

Colloidal Anhydrous Silica BP

Xanthan Gum BP

Anhydrous Citric Acid BP

Sodium lauryl Sulphate BP

Orange Flavour IHS

SunsetYellowColour IHS

Mannitol BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at a temperature not exceeding 25º C. Protect from light and moisture.

6.5 Nature and contents of container

1 x 10's Sachets are Packed in Carton along with Package Insert

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. APPLICANT/MANUFACTURER

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