CEFOPROX CV Tablets / Suspension (Cefpodoxime proxetil + Clavulanate potassium)

Composition

CEFOPROX CV Tablets

Each film-coated tablet contains:

Cefpodoxime Proxetil, IP,

equivalent to Cefpodoxime ..... 200 mg

Clavulanate Potassium diluted, IP

equivalent to Clavulanic Acid .....125 mg

Excipients.....q.s.

Colours:

Lake Sunset Yellow & Titanium Dioxide IP

CEFOPROX CV Suspension

Each 5 ml of the reconstituted Suspension contains:

Cefpodoxime Proxetil IP

Equivalent to Cefpodoxime ..... 50 mg

Potassium Clavulnate Diluted IP

Equivalent to Clavulanic Acid ..... 31.25 mg

Excipients ..... q.s.

Colour: Sunset Yellow Supra

CEFOPROX CV Suspension

Each 5 ml of the reconstituted Suspension contains:

Cefpodoxime Proxetil IP

Equivalent to Cefpodoxime ..... 100 mg

Potassium Clavulnate Diluted IP

Equivalent to Clavulanic Acid ..... 62.5 mg

Excipients ..... q.s.

Colour: Sunset Yellow FCF

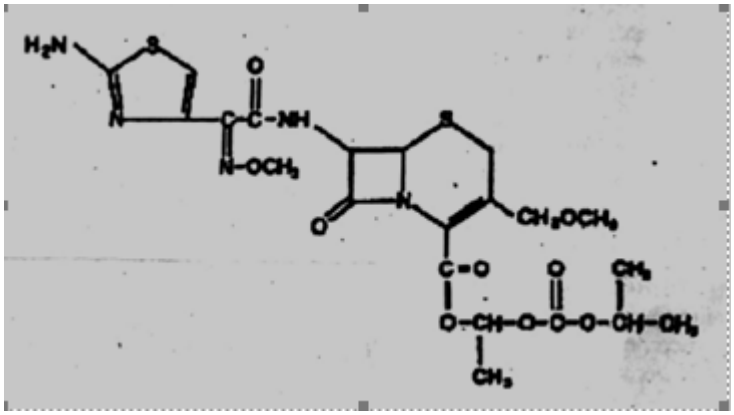
Dosage Form

Film-coated tablet, powder for oral suspension

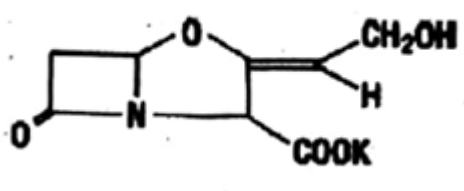
Pharmacology

Pharmacodynamics

CEFOPROX CV 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-[--(2-amino-4-thiazolyl)-2-{(Z)methoxyimino}acetamido]-3-methoxymethyl-8-oxo-5-thia-I-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Its empirical formula is $C_{21}H_{27}N_5O_9S_2$. The molecular weight of cefpodoxime proxetil is 557.6 and its structural formula is represented below:



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-ox--4-oxa-1-azabicyclo[3.2.1]-heptane-2-carboxylate, and may be represented structurally as:



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 $\leq$ 2.0 mcg/mL against most ($\geq$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

Pharmacokinetics

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 $T_{1/2}$ 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.

Indications

CEFOPROX CV 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-lactamas--producing strains), *Streptococcus pneumoniae* and *Moraxella catarrhalis*.
- **Uncomplicated urinary tract infections (cystitis)** caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Staphylococcus saprophyticus*.

Dosage and Administration

CEFOPROX CV Tablets

CEFOPROX CV Tablets should be swallowed whole without chewing.

The recommended dosages, duration of treatment and applicable patient population are as described in the following table:

Adults and Adolescents (aged 12 years and older)			
Type of infection	**Total daily dose**	**Dose frequency**	**Duration**

Pharyngitis and/or tonsillitis	200 mg	100 mg q12 hours	5–10 days
Acute community-acquired pneumonia	400 mg	200 mg q12 hours	14 days
Acute bacterial exacerbations of chronic bronchitis	400 mg	200 mg q12 hours	10 days
Uncomplicated gonorrhoea (men and women) and rectal gonococcal infections (women)	200 mg	Single dose	
Skin and skin structure	800 mg	400 mg q12 hours	7–14 days
Acute maxillary sinusitis	400 mg	200 mg q12 hours	10 days
Uncomplicated urinary tract infection	200 mg	100 mg q12 hours	7 days
*Dose of **CEFOPROX CV Tablets** is based on the cefpodoxime component.			

CEFOPROX CV Suspension

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)	

Contraindications

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

Warnings and Precautions

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*.

Drug interactions

Antacids

Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H_2-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 T_{max}), 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 **CEFOPROX CV Tablets** 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 (please refer to **DOSAGE AND ADMINISTRATION**).

Hepatic impairment

No dose adjustment is recommended for patients with hepatic insufficiency.

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, **CEFOPROX CV Tablets** 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 **CEFOPROX CV** 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.

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.

Undesirable Effects

Cefpodoxime is well tolerated.

Most common gastrointestinal adverse effects seen is diarrhoea, vomiting and abdominal pain.

- **Incidence Greater Than 1%**

Adverse events	**Incidence**

Diarrhea Diarrhea or loose stools were dose-related, decreasing from 10.4% for patients receiving 800 mg per day to 5.7% for those receiving 200 mg per day. Of the patients with diarrhea, 10% had *Clostridium difficile* organisms or toxins in the stool	7.0%
Nausea	3.3%
Vaginal fungal infections	1.0%
Vulvovaginal infections	1.3%
Abdominal pain	1.2%
Headache	1.0%

Incidence Less Than 1%

Adverse events, by body system in decreasing order, considered possibly or probably related to cefpodoxime proxetil and which occurred in less than 1% of patients, were as follows:

Body: fungal infections, abdominal distention, malaise, fatigue, asthenia, fever, chest pain, back pain, chills, generalized pain, abnormal microbiological tests, moniliasis, abscess, allergic reaction, facial edema, bacterial infections, parasitic infections, localized edema, localized pain.

Cardiovascular: congestive heart failure, migraine, palpitations, vasodilation, hematoma, hypertension, hypotension.

Digestive: vomiting, dyspepsia, dry mouth, flatulence, decreased appetite, constipation, oral moniliasis, anorexia, eructation, gastritis, mouth ulcers, gastrointestinal disorders, rectal disorders, tongue disorders, increased thirst, oral lesions, tenesmus, dry throat, toothache, gastric pressure.

Blood and Lymphatic: anemia.

Metabolic and Nutritional: dehydration, gout, peripheral edema, weight increase. Increased SGPT, ASAT, ALAT and alkaline phosphatase and/or bilirubin, liver damage.

Musculoskeletal: myalgia.

Nervous: dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paraesthesia, vertigo

Respiratory: asthma, cough, epistaxis, rhinitis, wheezing bronchitis, dyspnea, pleural effusion, pneumonia, sinusitis.

Skin: urticaria, rash, pruritus non-application site, diaphoresis, maculopapular rash, fungal dermatitis, desquamation, dry skin non-application site, hair loss, vesiculobullous rash, sunburn, hypersensitivity mucocutaneous reactions.

Special Senses: taste alterations, eye irritation, taste loss, tinnitus.

Urogenital: Hematuria, urinary tract infections, metrorrhagia, dysuria, urinary frequency, nocturia, penile infection, proteinuria, vaginal pain.

Immune system disorders: anaphylactic reactions, bronchospasm, purpura and angioedema.

Granules for Oral Suspension (Multiple dose)

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.

Film-coated Tablets (Single Dose)

In reported clinical trials using a single dose of cefpodoxime proxetil film-coated tablets, patients were treated with the recommended dosage of cefpodoxime (200 mg). There were no deaths or permanent disabilities considered to be related to drug toxicity in these studies. Adverse events considered as possibly or probably related to cefpodoxime in single-dose clinical trials conducted by the innovator were as follows:

- ***Incidence Greater Than 1%***

Nausea: 1.4%

Diarrhea: 1.2%

- ***Incidence Less Than 1%***

Central Nervous System: Dizziness, headache, syncope.

Dermatologic: Rash.

Genital: Vaginitis.

Gastrointestinal: Abdominal pain.

Psychiatric: Anxiety

Most of these abnormalities were transient and not clinically significant.

The additional adverse events as per the EMC data were as follows:

Gastrointestinal disorders

Common: Gastric pressure bloody diarrhea can occur as a symptom of enterocolitis. Bloody diarrhea can occur as a symptom of enterocolitis.

Metabolism and nutrition disorders:

Common: Loss of appetite

Immune system disorders: Hypersensitivity reactions of all degrees of severity have been observed. Very rare immune system disorders include; anaphylactic reactions, bronchospasm, purpura and angioedema

Hepato-biliary disorders

Rare: Transient moderate elevations of ASAT, ALAT 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:

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme

Post marketing Experience

The following serious adverse experiences have been reported:

allergic reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and serum sickness-like reactions, pseudomembranous colitis, bloody diarrhea with abdominal pain, ulcerative colitis, rectorrhagia with hypotension, anaphylactic shock, acute liver injury, *in utero* exposure with miscarriage, purpuric nephritis, pulmonary infiltrate with eosinophilia,

and eyelid dermatitis. One death was attributed to pseudomembranous colitis and disseminated intravascular coagulation.

Cephalosporin-Class Labeling

In addition to the adverse reactions listed above, which have been observed in patients treated with cefpodoxime proxetil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions and Abnormal Laboratory Tests

Renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reactions, hemorrhage, agranulocytosis, and pancytopenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Overdosage

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.

Storage and Handling Instructions

Store in a cool, dry place. Protect from light.

Keep out of the reach of children.

Packaging Information

CEFOPROX CV Tablets .....Strip pack of 10 tablets

CEFOPROX CV Suspension .....Bottle of 30 ml

Last updated: Oct 2018

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