CEFPODOXIME 200 mg with CLAVULANIC ACID 125 mg

Clavpod 325 mg tablets

1. NAME OF THE MEDICINAL PRODUCT

Cefpodoxime 200 mg with clavulanic acid 125 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Cefpodoxime Proxetil
Equivalent to Cefpodoxime …… 200 mg
Clavulanate Potassium diluted IP
Equivalent to Clavulanic Acid ……125 mg

3. PHARMACEUTICAL FORM

Oral tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cefpodoxime and clavulanic acid tablets 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.
Note: Only penicillin by the intramuscular route of administration has been shown to be effective in the prophylaxis of rheumatic fever. 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 (Branhamella) catarrhalis. Data are

insufficient at this time to establish efficacy in patientswith acute bacterial exacerbations of chronic bronchitis caused by beta-lactamase-producingstrains of Haemophilus influenzae.
Acute, uncomplicated urethral and cervical gonorrhoea caused by Neisseria gonorrhoeae (including penicillinase-producing strains).
Acute, uncomplicated ano-rectal infections in women due to Neisseria gonorrhoeae (including penicillinase-producing strains).
Note: The efficacy of cefpodoxime in treating male patients with rectal infections caused by Neisseria gonorrhoeae has not been established. Data do not support the use of cefpodoxime proxetil in the treatment of pharyngeal infections due to Neisseria gonorrhoeae in men or women.
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.
Note: In clinical trials, successful treatment of uncomplicated skin and skin structure infections was dose-related. The effective therapeutic dose for skin infections was higher than those used in other recommended indications.
Acute maxillary sinusitis caused by Haemophilus influenzae (including beta-lactamase-producing strains), Streptococcus pneumoniae and Moraxella (Branhamella) catarrhalis.
Uncomplicated urinary tract infections (cystitis) caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Staphylococcus saprophyticus.
Note: In considering the use of cefpodoxime proxetil in the treatment of cystitis, the lower bacterial eradication rates of cefpodoxime proxetil should be weighed against the increased eradication rates and different safety profiles of some other classes of approved agents.

4.2 Posology and Method of Administration

Cefpodoxime and clavulanic acid tablets should be swallowed whole without chewing.
Adults and Adolescents
The recommended dosages, duration of treatment and applicable patient population are as described in the following table:

Patients with Normal Renal Function 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	400 mg	200 mg q12 hours	10 days

bronchitis			
Skin and skin structure	800 mg	400 mg q12 hours	7–14 days

Paediatric Use

General dosage recommendations for cefpodoxime in children are presented below: Type of infection	Total daily dose* of cefpodoxime	Dose frequency	Duration
Acute otitis media	10 mg/kg/day (Max 400 mg/day)	5 mg/kg q12 hours (Max 200 mg/dose)	5 days
Pharyngitis and tonsillitis	10 mg/kg/day (Max 200 mg/day)	5 mg/kg q12 hours (Max 100 mg/dose)	5–10 days
Acute maxillary sinusitis	10 mg/kg/day (Max 400 mg/day)	5 mg/kg q12 hours (Max 200 mg/dose	10 days
*Dose of Combination tablets is based on the cefpodoxime component.			

Patients with Impaired Renal Function

Adults

The dosage of Cefpodoxime and clavulanic acid combination does not require modification if creatinine clearance exceeds 40 mL/min-1/1.73 m2.

Below this value, pharmacokinetic studies indicate an increase in the plasma elimination half-life and the maximum plasma concentrations; hence, the dosage should be adjusted appropriately. Creatinine Clearance (mL/min)	
39–10	Unit dose1 administered as a single dose every 24 hours (i.e. half of the usual adult dose).
<10	Unit dose1 administered as a single dose every 48 hours (i.e. quarter of the usual adult dose).
Haemodialysis patients	Unit dose[1] administered after each dialysis session. The dose frequency should be three times/week after haemodialysis.

Note: 1The unit dose is either 100 mg or 200 mg, depending on the type of infection.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to estimate creatinine clearance (mL/min). For this estimate to be valid, the serum creatinine level should represent a steady state of renal function.

Males (mL/min) : Weight (kg) x (140 – age)

72 x serum creatinine (mg/100 mL)

Females (mL/min) : 0.85 × above value

Paediatric Use

There is no data available in the case of paediatric patients with impaired renal function.

4.3 Contraindications

Cefpodoxime and clavulanic acid Tablets are contraindicated in patients with a known allergy to penicillin, any other type of beta-lactam drug, the cephalosporin class of antibiotics, beta-lactamase inhibitors, or any other ingredients in this product formulation.

4.4 Special Warnings and Special Precautions for Use

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 diarrhoea (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.

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur even 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against Clostridium difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of Clostridium difficile, and surgical evaluation should be instituted as clinically indicated.

A concerted effort to monitor for Clostridium difficile in cefpodoxime-treated patients with diarrhoea was undertaken because of an increased incidence of CDAD in early trials in normal subjects. Clostridium difficile organisms or toxins were reported in 10% of the cefpodoxime-treated adult patients with diarrhoea; however, no specific diagnosis of pseudomembranous colitis was made in these patients.

Precautions

In patients with transient or persistent reduction in urinary output due to renal impairment, the total daily dose of cefpodoxime proxetil should be reduced because high and prolonged serum antibiotic concentrations can occur in such individuals following usual doses. Cefpodoxime, like other

cephalosporins, should be administered with caution to patients receiving concurrent treatment with potent diuretics.

As with other antibiotics, prolonged use of cefpodoxime proxetil may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. Prescribing cefpodoxime in the absence of a proven or strongly suspected bacterial infection, or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

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

Cephalosporins may be absorbed into 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. In such cases, cross-reactivity may occur with penicillin.

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

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminium 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 Cefpodoxime and clavulanic acid 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 sulphate test tablets, but not with tests based on enzymatic glucose oxidase reactions.

Renal Impairment

For patients with severe renal impairment (<30 mL/min creatinine clearance), the dosing intervals should be increased to q 24 hours. In patients maintained on haemodialysis, the dose frequency should be three times/week after haemodialysis. No data are available in case of paediatric patients with impaired renal function (please refer to 4.2).

Hepatic Impairment

Cefpodoxime pharmacokinetics in cirrhotic patients (with or without ascites) is similar to those in healthy subjects. Dose adjustment is not necessary in this population.

4.6 Fertility, Pregnancy and Lactation

Pregnancy Cefpodoxime and clavulanic acid tablets should be used during pregnancy only if clearly needed.

Lactation

Cefpodoxime proxetil: Cefpodoxime is excreted in human milk. 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.

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.

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

Cefpodoxime Proxetil

● Incidence greater than 1% Adverse events	Incidence
Diarrhoea	7.0%
Nausea	3.3%
Vaginal fungal infections	1.0%
Vulvovaginal infections	1.3%
Abdominal pain	1.2%
Headaches	1.0%

Diarrhoea 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 diarrhoea, 10% had *Clostridium difficile* organisms or toxins in the stool

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 as a whole: Fungal infections, abdominal distention, malaise, fatigue, asthenia, fever, chest pain, back pain, chills, generalized pain, abnormal microbiological tests, moniliasis, abscess, allergic reaction, facial oedema, bacterial infections, parasitic infections, localized oedema, localized pain.

Cardiovascular: Congestive heart failure, migraine, palpitations, vasodilation, haematoma, 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.

Blood and lymphatic: Anaemia

Metabolic and nutritional: Dehydration, gout, peripheral oedema, weight increase.

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, dyspnoea, 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.

Special senses: Taste alterations, eye irritation, taste loss, tinnitus.

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

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%

Diarrhoea: 1.2%

● Incidence less than 1%

Central nervous system: Dizziness, headache, syncope.

Dermatologic: Rash.

Genital: Vaginitis.

Gastrointestinal: Abdominal pain.

Psychiatric: Anxiety

Laboratory Changes

Significant laboratory changes that have been reported in adult and paediatric patients in clinical trials of cefpodoxime proxetil, without regard to drug relationship were as below:

Hepatic: Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin and LDH.

Haematologic: Eosinophils, leucocytosis, lymphocytosis, granulocytosis, basophilia monocytosis, thrombocytosis, decreased haemoglobin, decreased haematocrit, leucopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocythaemia, positive Coomb's test, and prolonged PT and PTT.

Serum chemistry: Hyperglycaemia, hypoglycaemia, hypoalbuminaemia, hypoproteinaemia, hyperkalaemia and hyponatraemia.

Renal: Increases in BUN and creatinine.

Most of these abnormalities were transient and not clinically significant.

Postmarketing 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 diarrhoea 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 Labelling

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 anaemia, haemolytic anaemia, serum sickness-like reactions, haemorrhage, 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.

Clavulanate Potassium

Hepatic Adverse Events

The amoxicillin/clavulanate potassium combination has been reported to cause hepatic injury, especially cholestatic hepatitis. The amoxicillin/clavulanate potassium combination-induced hepatotoxicity usually manifests 2–4 weeks after starting treatment and, in many cases, the first symptoms of liver injury may appear long after completion of the course of antibiotics. Immunoallergic mechanisms have been implicated in the amoxicillin/clavulanate potassium combination-induced hepatotoxicity. There is indirect evidence to support the central role of clavulanate potassium in these cases. Several patients who had experienced hepatitis induced by the amoxicillin/clavulanate potassium combination tolerated the subsequent administration of amoxicillin alone. Moreover, amoxicillin alone has not been associated with an excess risk of acute liver injury.

In addition, similar cases of cholestasis have been reported after administration of a ticarcillin/clavulanate potassium combination, while no such cases have been reported with the use of ticarcillin alone.

Gastrointestinal Adverse Events

Gastrointestinal side effects, such as nausea, vomiting and diarrhoea, are seen more commonly with the amoxicillin/clavulanate potassium combination than with amoxicillin alone. The incidence of such gastrointestinal side effects has been found to be related to the dose of clavulanate potassium in the

combination. In a clinical study evaluating the efficacy of the amoxicillin/clavulanate potassium combination for the treatment of urinary tract infections, patients were treated with either a 2:1 or a 4:1 combination of amoxicillin/clavulanate potassium. Upper digestive intolerance (nausea, vomiting and gastric pain) were found to be more common (5/10 patients) in the high-dose (500 mg amoxicillin/250 mg clavulanate potassium) group as compared to the low-dose (500 mg amoxicillin/125 mg clavulanate potassium) group (2/14 patients).

4.9 Overdose

Cefpodoxime Proxetil

In the event of a serious toxic reaction from overdosage, haemodialysis 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 diarrhoea.

Clavulanate Potassium

The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanate potassium, together with information from a single patient with renal impairment, all suggest that this compound may also be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

clavpod 325 Tablets are a fixed-dose combination of cefpodoxime proxetil and clavulanate potassium.

Cefpodoxime proxetil is an orally administered, extended-spectrum, semi-synthetic antibiotic of the cephalosporin class and clavulanate potassium is a beta-lactamase inhibitor.

Clavulanate potassium is a beta-lactam structurally related to the penicillins and possesses the ability to inactivate a wide variety of beta-lactams structurally related to the penicillins and also inactivate a wide variety of beta-lactamases by blocking the active sites of these enzymes.

The presence of clavulanate potassium in clavpod 325 Tablets effectively extends the antibiotic spectrum of cefpodoxime to include many bacteria normally resistant to it and to other beta-lactam antibiotics. Thus, clavpod 325 Tablets possess the properties of a broad-spectrum antibiotic and a beta-lactamase inhibitor.

Microbiology

While in vitro studies of cefpodoxime have demonstrated the susceptibility of most strains of the organisms listed below, clinical efficacy for infections other than those included in the INDICATIONS section has not been documented.

Both cefpodoxime and clavulanate potassium are usually effective against the following microorganisms:

Aerobic Gram-positive microorganisms

Staphylococcus aureus (including penicillinase-producing strains)

Note: Cefpodoxime is inactive against methicillin-resistant staphylococci.

Staphylococcus saprophyticus

Streptococcus pneumoniae (excluding penicillin-resistant strains)

Streptococcus pyogenes

Aerobic Gram-negative microorganisms

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Haemophilus influenzae (including beta-lactamase-producing strains)

Moraxella (Branhamella) catarrhalis

Neisseria gonorrhoeae (including penicillinase-producing strains)

The following in vitro data are available, but their clinical significance is unknown. Cefpodoxime exhibits in vitro minimum inhibitory concentrations (MICs) of <2.0 µg/mL against most (>90%) of isolates of the microorganisms listed below. However, the safety and efficacy of cefpodoxime in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials:

Aerobic Gram-positive microorganisms

Streptococcus agalactiae

Streptococcus agalactiae

Streptococcus spp. (Groups C, F, G)

Note: Cefpodoxime is inactive against enterococci.

Aerobic Gram-negative microorganisms

Citrobacter diversus

Klebsiella oxytoca

Proteus vulgaris

Providencia rettgeri

Haemophilus parainfluenzae

Note: Cefpodoxime is inactive against most strains of Pseudomonas and Enterobacter.

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. Following oral administration of 100 mg of cefpodoxime proxetil to fasting subjects, approximately 50% of the administered cefpodoxime dose was absorbed systemically. Over the recommended dosing range (100 to 400 mg), approximately 29–33% of the administered cefpodoxime dose was excreted unchanged in the urine in 12 hours. There is minimal metabolism of cefpodoxime *in vivo*.

The extent of absorption (mean AUC) and the mean peak plasma concentration increased when the film-coated tablets were administered with food. Following a 200 mg tablet dose taken with food, the AUC was 21–33% higher than under fasting conditions, and the peak plasma concentration averaged 3.1 µg/mL in fed subjects versus 2.6 µg/mL in fasted subjects. Time to peak concentration was not significantly different between fed and fasted subjects.

Over the recommended dosing range (100 to 400 mg), the rate and extent of cefpodoxime absorption exhibited dose-dependency; the dose-normalized Cmax and AUC decreased by up to 32% with

increasing dose. Over the recommended dosing range, the Tmax was approximately 2–3 hours and the T1/2 ranged from 2.09 hours to 2.84 hours. Mean Cmax was 1.4 µg/mL for the 100 mg dose, 2.3 µg/mL for the 200 mg dose, and 3.9 µg/mL for the 400 mg dose. In patients with normal renal function, neither accumulation nor significant changes in other pharmacokinetic parameters were noted following multiple oral doses of up to 400 mg q12 hours.

Cefpodoxime plasma levels (µg/mL) in fasted subjects after film-coated tablet administration (single dose)

Dose (Cefpodoxime equivalents)	**Time after oral ingestion**					
1 hour	2 hours	3 hours	4 hours	6 hours	8 hours	12 hours
100 mg	0.98	1.4	1.3	1.0	0.59	0.29	0.08
200 mg	1.5	2.2	2.2	1.8	1.2	0.62	0.18
400 mg	2.2	3.7	3.8	3.3	2.3	1.3	0.38

Protein binding of cefpodoxime ranges from 22% to 33% in serum and from 21% to 29% in plasma
Concentrations of cefpodoxime in excess of the MICs for common pathogens can be achieved in lung parenchyma, bronchial mucosa, pleural fluid, tonsils, interstitial fluid and prostate tissue.
Skin blister: Following multiple-dose administration, every 12 hours for 5 days, of 200 mg or 400 mg cefpodoxime proxetil, the mean maximum cefpodoxime concentration in skin blister fluid averaged 1.6 and 2.6 µg/ml, respectively. Skin blister fluid cefpodoxime levels at 12 hours after dosing averaged 0.2 and 0.4 µg/mL for the 200 mg and 400 mg multiple-dose regimens, respectively.
Tonsil tissue: Following a single oral dose of 100 mg cefpodoxime proxetil, the mean maximum cefpodoxime concentration in tonsil tissue averaged 0.24 µg/g at 4 hours post-dosing and 0.09 µg/g at 7 hours post-dosing. Equilibrium was achieved between plasma and tonsil tissue within 4 hours of dosing. No detection of cefpodoxime in tonsillar tissue was reported 12 hours after dosing. These results demonstrated that the concentrations of cefpodoxime exceeded the MIC90 of Streptococcus pyogenes for at least 7 hours after dosing of 100 mg of cefpodoxime proxetil.
Lung tissue: Following a single oral dose of 200 mg cefpodoxime proxetil, the mean maximum cefpodoxime concentration in lung tissue averaged 0.63 µg/g at 3 hours post-dosing, 0.52 µg/g at 6 hours post-dosing, and 0.19 µg/g at 12 hours post-dosing. The results of this study indicated that cefpodoxime penetrated into lung tissue and produced sustained drug concentrations for at least 12 hours after dosing at levels that exceeded the MIC90 for Streptococcus pneumoniae and Haemophilus influenzae.
Cerebrospinal fluid (CSF): Adequate data on CSF levels of cefpodoxime are not available.
Clavulanate Potassium

Clavulanate potassium is well-absorbed from the gastrointestinal tract after oral administration of co-amoxiclav. Absorption of clavulanate potassium when taken with food is greater relative to the fasted state.
The half-life of clavulanate potassium after the oral administration of co-amoxiclav is 1.0 hour.

Concurrent administration of probenecid does not delay the renal excretion of clavulanate potassium.

Mean* clavulanate potassium pharmacokinetic parameters		
****Dose and regimen Co-amoxiclav**	**AUC (µg.hr/mL) (+ S.D.)**	**Cmax (µg.hr/mL) (+ S.D.)**
250/125 mg q8 hours	12.6 + 3.25	1.5 + 0.70
500/125 mg q12 hours	8.6 + 1.95	1.8 + 0.61
500/125 mg q12 hours	15.7 + 3.66	2.4 + 0.83
875/125 mg q12 hours	10.2 + 3.04	2.2 + 0.00

* Mean values of 14 normal volunteers (n = 15 for clavulanate potassium in the low-dose regimens). Peak concentrations occurred approximately 1.5 hours after the dose.
**Administered at the start of a light meal.
Clavulanate potassium has been found to be approximately 25% bound to human serum. The results of experiments involving the administration of
clavulanate potassium to animals suggest that this compound is well-distributed in body tissues.
The disposition of clavulanate potassium is also characterized by an initial rapid phase, indicating easy distribution to the peripheral compartment. The short t½β (0.8–1.5 hours in adults and children) is the consequence of the rapid elimination from the body produced by metabolism and renal excretion, the latter occurring primarily by glomerular filtration. The metabolites are excreted via the faeces, the urine and through the lungs, with 20–60% of the dose being excreted in the urine in the form of the parent drug.
Plasma and renal clearance values of 14.9 and 6.3 L/h/1.73 m2, respectively, have been reported for clavulanate potassium after intravenous administration to healthy subjects.

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

6.3 Shelf-life

18 months

6.4 Special Precautions for Storage

Store in cool Dry Place protected from light

6.5 Nature and Contents of Container

10 Blister Strip of 10 Tablets

7. MARKETED BY

Alkem Laboratories Ltd.
ALKEM HOUSE,
S. B. Road, Lower Parel (West),
Mumbai - 400 013. INDIA.

8. Date of Preparation/Revision of Text

17/04/2016