For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

U.V.A. CEF - CV 50 DRY SYRUP

1. Generic Name

Cefpodoxime Proxetil 50 mg and Potassium Clavulanate 31.25 mg Oral Suspension

2. Qualitative and quantitative composition

Each 5 ml of the reconstituted suspension contains:
Cefpodoxime Proxetil I.P. equivalent to Cefpodoxime…....50 mg
Potassium Clavulanate Diluted I.P. equivalent to Clavulanic acid….31.25 mg
Excipients…..q.s.
Colours: Sunset Yellow Supra

3. Dosage form and strength

Dosage Form: Dry Syrup

Strength: Cefpodoxime Proxetil I.P. equivalent to Cefpodoxime…....50 mg
Potassium Clavulanate Diluted I.P. equivalent to Clavulanic acid….31.25 mg

4. Clinical particulars

4.1 Therapeutic indication

Cefpodoxime + Clavulanic acid dry syrup (FDC Cefpodoxime + Clavulanic Acid) are indicated for the treatment of lower and upper respiratory tract infection and urinary tract infection.

4.2 Posology and method of administration

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FDC of cefpodoxime and clavulanic acid dry syrup and other antibacterial drugs, FDC of cefpodoxime and clavulanic acid dry syrup should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria susceptible to the combination.

Cefpodoxime +Clavulanic Acid Dry syrup (FDC Cefpodoxime + Clavulanic Acid) should be taken with food to enhance absorption. Cefpodoxime + clavulanic acid dry syrup (FDC Cefpodoxime + Clavulanic Acid) contain 1) cefpodoxime proxetil which is a prodrug and its active metabolite is cefpodoxime; and 2) clavulanic acid. Based on the cefpodoxime component, cefpodoxime + clavulanic acid dry syrup (FDC Cefpodoxime + Clavulanic Acid) should be dosed as follows:

The liquid suspension form of this medication must be shaken well before using and as directed by the physician. Direction for reconstitution:

1. Shake the bottle to loosen the powder.
2. Twist to open the ampoule of sterile water given with the pack.
3. Add 2/3rd of sterile water into bottle which contains powder.
4. Put the cap and shake the bottle vigorously.

5. Adjust the volume up to the ring mark on the bottle by adding more sterile water if required and shake well. Allow the suspension to stand for 5 mins.
6. Store the reconstituted suspension in a refrigerator. Content to be consumed within 7 days. Any extra portion left to be thrown away.

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)	

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 hemodialysis, the dose frequency should be 3 times/week after hemodialysis.
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.

$$\text{Males (ml/min):} \quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 ml)}}$$

Females (ml/min): 0.85 x above value

Hepatic Disease
Cefpodoxime pharmacokinetics in cirrhotic patients (with or without ascites) are similar to those in healthy subjects. Dose adjustment is not necessary in this population.The use of clavulanic acid with penicillins has been associated with an increased incidence of cholestatic jaundice and acute hepatitis during therapy or shortly after, particularly in men and those aged over 65 years. Cefpodoxime + Clavulanic acid tablets (FDC Cefpodoxime + Clavulanic Acid) are not recommended in patients with hepatic impairment (see **Undesirable Effects).**

4.3 Contraindications

Cefpodoxime + Clavulanic Acid Dry syrup (FDC Cefpodoxime + Clavulanic Acid) are contraindicated in patients with a known allergy to penicillin, any other type of beta-lactam

drug, cephalosporin class of antibiotics, beta-lactamase inhibitors or any other ingredients of this formulation.

4.4 Special warnings and 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 β-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, DISCONTINUE THE DRUG. 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 use of nearly all antibacterial agents, including cefpodoxime proxetil, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

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

In post-marketing experience outside the United States, reports of pseudomembranous colitis associated with the use of cefpodoxime proxetil have been received. Cefpodoxime + Clavulanic Acid Dry syrup contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions

General

In patients with transient or persistent reduction in urinary output due to renal insufficiency, 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 overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If super infection 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.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 β-lactam antibiotics, neutropenia, and more rarely agranulocytosis may develop, particularly during extended treatment. For cases of treatment lasting longer than 10 days, blood count should therefore 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 Coombs' test and very rarely, haemolytic anemia. Cross-reactivity may occur with penicillin for this reaction. 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 Drugs interactions

Antacids: Concomitant administration of high doses of antacids (sodium bicarbonate and aluminum hydroxide) or H2 blockers reduces peak plasma levels by 24% to 42% and the extent of absorption by 27% to 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 Tmax), but do not affect the extent of absorption (AUC).

Probenecid : As with other β-lactam antibiotics, renal excretion of cefpodoxime was inhibited by probenecid and resulted in an approximately 31% increase in AUC and 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 the product is 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.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Paediatrics

Cefpodoxime proxetil: Safety and efficacy of cefpodoxime in infants less than 2 months of age Have not been established.

Clavulanic acid: Safety and efficacy of FDC of clavulanic acid + ticarcillin have been established in the age groups 3 months to 16 years of age. Use of FDC of clavulanic acid +ticarcillin has been supported by evidence from adequately reported well controlled studies.

Pregnancy

Cefpodoxime proxetil: Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m2) or to rabbits at doses up to 30 mg/kg/day (1-2 times the human dose based on mg/m2).There are, however, no adequate and well-controlled studies of cefpodoxime proxetil use in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Cefpodoxime proxetil has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Clavulanic acid: The reproductive and developmental toxicity studies on clavulanic acid are available following oral administration; one generation in rat; teratogenic effects in rat: teratogenic effects in mouse (2 studies) and peri- and pos-natal development in the rat. The studies were adequately designed. Overall, a moderate reduction of female fertility and/or growth and survival of the fetuses were seen at dose levels eliciting slight systemic or maternal toxicity. Although a statistically non-significant, but dose-related, reduction in the mean number of copora lutea per dam was detected in both the rat F0-generation and the mouse Fl-generation at the lowest dose level in the testing programme, 10 mg/kg body weight/day, this dose level could be retained as a NOEL.

Lactation

Cefpodoxime proxetil: Cefpodoxime is excreted in human milk. At 4 hours following a 200 mg oral dose, levels of cefpodoxime in human milk were 0%, 2% and 6% of concomitant serum levels in 3 lactating women. At 6 hours post-dosing, levels were 0%, 9% and 16% of concomitant serum levels. 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.

Clavulanic acid: In animal studies, excretion of clavulanic acid in milk occurs to a limited extent, the concentrations being lower than those detected in the serum.

Geriatrics

Cefpodoxime proxetil: Of the 3338 patients in reported multiple-dose clinical studies of cefpodoxime proxetil film-coated tablets, 521 (16%) were 65 and over, while 214 (6%) were 75 and over. No overall differences in effectiveness or safety were observed between the elderly and younger patients. In healthy geriatric subjects with normal renal function, cefpodoxime half-life in plasma averaged 4.2 hours and urinary recovery averaged 21% after a 400 mg dose was given every 12 hours for 15 days. Other pharmacokinetic parameters were unchanged relative to those observed in healthy younger subjects.

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

Clavulanic acid: As this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

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
Clinical trials:
Film-coated tablets (multiple doses):
In reported clinical trials using multiple doses of cefpodoxime proxetil film-coated tablets, patients were treated with the recommended dosages of cefpodoxime (100 to 400 mg Q 12 hours). There were no deaths or permanent disabilities thought related to drug toxicity. 2.7% patients discontinued medication due to adverse events thought possibly or probably related to drug toxicity. 52% of the patients who discontinued therapy (whether thought related to drug therapy or not) did so because of gastrointestinal disturbances, nausea, vomiting, or diarrhea. The percentage of cefpodoxime proxetil-treated patients who discontinued study drug because of adverse events was significantly greater at a dose of 800 mg daily than at a dose of 400 mg daily or at a dose of 200 mg daily. Adverse events thought possibly or probably related to cefpodoxime in multiple-dose clinical trials were:
Incidence Greater Than 1%:

Adverse Events	**Incidence**
Diarrhea*	7.0 %
Nausea	3.3 %
Vaginal Fungal Infections	1.0 %
Vulvovaginal Infections	1.3 %
Abdominal Pain	1.2 %
Headache	1.0 %

*Diarrhea or loose stools were dose-related: decreasing from 10.4% of patients receiving 800 mg per day to 5.7% for those receiving 200 mg per day. Of patients with diarrhea, 10% had C. difficile organism or toxin in the stool (see WARNINGS).
Incidence Less Than 1%:
By body system in decreasing order:
Adverse events thought possibly or probably related to cefpodoxime proxetil that occurred in less than 1% of patients
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, tooth disorders, increased thirst, oral lesions, tenesmus, dry throat, toothache
Blood and Lymphatic- anemia
Metabolic and Nutritional- dehydration, gout, peripheral edema, weight increase.
Musculo-skeletal- myalgia

Nervous- dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paresthesia, 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.
Special Senses - taste alterations, eye irritation, taste loss, tinnitus
Urogenital - hematuria, 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 thought related to drug toxicity in these studies. Adverse events thought possibly or probably related to cefpodoxime in single-dose clinical trials conducted by the innovator in the United States were:
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.

Laboratory changes
Significant laboratory changes that have been reported in adult and pediatric patients in clinical Trials of cefpodoxime proxetil, without regard to drug relationship, were:
Hepatic: Transient increases in AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, bilirubin, and LDH
Hematologic: Eosinophilia, leukocytosis, lymphocytosis, granulocytosis, basophilia, monocytosis, thrombocytosis, decreased hemoglobin, decreased hematocrit, leukopenia, neutropenia, lymphocytopenia, thrombocytopenia, thrombocythemia, positive Coombs' test, and prolonged PT, and PTT
Serum Chemistry: Hyperglycemia, hypoglycemia, hypoalbuminemia, hypoproteinemia, hyperkalemia, and hyponatremia
Renal: Increases in BUN and creatinine
Most of these abnormalities were transient and not clinically significant.

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 reaction, 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.

Clavulanic Acid

Hepatic adverse events

Amoxycillin/clavulanic acid combination has also been reported to cause hepatic injury especially cholestatic hepatitis. Amoxycillin/clavulanic acid combination induced hepatotoxicity usually manifests 2-4 weeks after starting treatment and many cases first symptoms of liver injury may appear long after completion of course of antibiotic. Immunoallergic mechanisms have been implicated in amoxycillin/clavulanic acid combination induced hepatotoxicity. There is indirect evidence to support the central role of clavulanic acid in these cases. Several patients who had experienced hepatitis induced by amoxycillin/clavulanic acid combination tolerated the subsequent administration of amoxycillin alone. Moreover, amoxycillin alone has not been associated with an excess risk of acute liver injury. In addition, similar cases of cholestasis have been reported after ticarcillin/clavulanic acid combination administration, while no such cases have been reported with use of ticarcillin alone.

Gastrointestinal adverse events

Gastrointestinal side-effects such as nausea, vomiting and diarrhoea, are seen more commonly with amoxycillin/clavulanic acid combination than with amoxycillin alone Incidence of gastrointestinal side effects associated with amoxycillin/clavulanic acid combination has been found to be related to the dose of clavulanic acid in the combination. In a clinical study evaluating the efficacy of amoxycillin/clavulanic acid combination for the treatment of urinary tract infections, patients were treated with either 2:1 or 4:1 combination of amoxycillin/clavulanic acid combination. Upper digestive intolerance (nausea, vomiting, and gastric pain) were found to be more common (5/10 patients) in the high-dose (500 mg amoxycillin/250 mg clavulanic acid) group as compared to the low-dose (500 mg amoxycillin/125 mg clavulanic acid) group (2/14 patients).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose

Cefpodoxime

In acute rodent toxicity studies, a single 5 g/kg oral dose produced no adverse effects. In the event of 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.

Clavulanic Acid

The molecular weight, degree of protein binding, and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by hemodialysis.

5. Pharmacological properties

5.1 Mechanism of Action

Cefpodoxime proxetil is a β-lactam antibiotic, a 3rd generation oral cephalosporin. It is the prodrug of cefpodoxime. Following oral administration, cefpodoxime proxetil is taken up by the gastrointestinal wall where it is rapidly hydrolyzed to cefpodoxime, a bactericidal antibiotic, which is then absorbed systemically. The mechanism of action of cefpodoxime is based on inhibition of bacterial cell wall synthesis. Cefpodoxime has been shown to possess in vitro bactericidal activity against numerous gram-positive and gram-negative bacteria. Cefpodoxime is stable in the presence of β-lactamase enzymes. As a result, many organisms resistant to penicillins and cephalosporins, due to their production of β-lactamase, may be susceptible to cefpodoxime. Cefpodoxime is inactivated by certain extended spectrum β-lactamases. Clavulanic acid is a β-lactam, structurally related to the penicillins, which possesses the ability to inactivate a wide range of β-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance. It blocks the destructive hydrolytic activity of β-lactamases sparing cefpodoxime from hydrolysis. The presence of clavulanic acid in the cefpodoxime + clavulanic acid dry syrup effectively extends the antibiotic spectrum of cefpodoxime to include many bacteria normally resistant to it and to other β-lactam antibiotics. Thus, cefpodoxime + clavulanic acid dry syrup (FDC Cefpodoxime + Clavulanic Acid) possess the properties of a broad- spectrum antibiotic and a β-lactamase inhibitor.

5.2 Pharmacodynamic properties

While in vitro studies of cefpodoxime have demonstrated the susceptibility of most strains of the Following organisms, clinical efficacy for infections other than those included in the indications section has not been documented. Cefpodoxime + clavulanic acid is usually effective against 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 β-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 following microorganisms. 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 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

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

5.3 Pharmacokinetic properties

Cefpodoxime:
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 to 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 film-coated tablets were administered with food. Following a 200 mg tablet dose taken with food, the AUC was 21 to 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 dosedependency; dose-normalized Cmax and AUC decreased by up to 32% with increasing dose. Over the recommended dosing range, the Tmax was approximately 2 to 3 hours and the T½ ranged from 2.09 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 Q 12 hours.

Cefpodoxime Plasma Levels (µg/mL) in Fasted Adults after Film-Coated Tablet Administration (Single Dose)							
Dose	Time after oral ingestion						
(Cefpodoxime equivalents)	1 hr	2 hr	3 hr	4 hr	6 hr	8 hr	12 hr
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 minimum inhibitory levels (MIC) 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 2.8 µg/ml, respectively. Skin blister fluid cefpodoxime levels at 12 hours after dosing averaged 0.2 and 0.4µg/ml for the 200 mg and 400 mg multiple dose regimens, respectively.

Tonsil tissue: Following a single, oral 100 mg cefpodoxime proxetil film-coated tablet, 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 concentrations of cefpodoxime exceeded the MIC90 of S. 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 S. pneumoniae and H. influenzae.

CSF: Adequate data on CSF levels of cefpodoxime are not available.

Clavulanic acid:

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 clavulanic acid after the oral administration of co-amoxiclav is 1.0 hour. Approximately 25% to 40% of the clavulanic acid is excreted unchanged in urine during the first 6 hours after administration. Concurrent administration of probenecid does not delay renal excretion of clavulanic acid.

Mean* clavulanate potassium pharmacokinetic parameters		
Dose† and regimen Co-amoxiclav	AUC0-24 (μg·hr/mL) (±S.D.)	Cmax (μg/mL) (±S.D.)
250/125 mg q8h	12.6 ± 3.25	1.5 ± 0.70
500/125 mg q12h	8.6 ± 1.95	1.8 ± 0.61
500/125 mg q8h	15.7 ± 3.86	2.4 ± 0.83
875/125 mg q12h	10.2 ± 3.04	2.2 ± 0.99

* = 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

Clavulanic acid has been found to be approximately 25% bound to human serum. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound is well distributed in body tissues. The disposition of clavulanic acid is also characterized by an initial rapid phase, indicating easy distribution to the peripheral compartment. The short t½ β (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 faeces, in the urine and through the lungs, with 20-60% of the dose being excreted in urine in the form of the parent drug. Plasma and renal clearance values of 14.9 and 6.3 L/h/1.73m2, respectively, have been reported for clavulanic acid after intravenous administration to healthy subjects.

Pharmacokinetics in special population
Renal disease
Cefpodoxime: 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 hours hemodialysis procedure.

Clavulanic acid: As this drug is known to be substantially excreted by the kidney, and the risk of Toxic reactions to this drug may be greater in patients with impaired renal function.

Hepatic disease
Cefpodoxime: Absorption was somewhat diminished and elimination unchanged in patients with cirrhosis. The mean cefpodoxime T½ 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.

Elderly patients

Cefpodoxime: Elderly subjects do not require dosage adjustments unless they have diminished renal function. In healthy geriatric subjects, cefpodoxime half-life in plasma averaged 4.2 hours (vs 3.3 in younger subjects) and urinary recovery averaged 21% after a 400 mg dose was administered every 12 hours. Other pharmacokinetic parameters (Cmax, AUC and Tmax) were unchanged relative to those observed in healthy young subjects.

Clavulanic acid: As this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

6. Nonclinical properties

Carcinogenesis, Mutagenesis, Impairment of Fertility

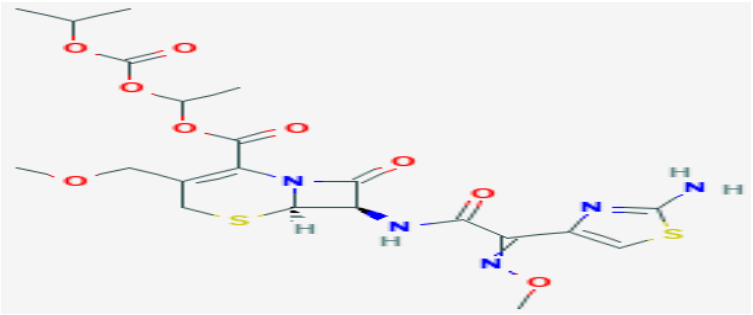
Long-term animal carcinogenesis studies of cefpodoxime proxetil have not been performed. Mutagenesis studies of cefpodoxime, including the Ames test both with and without metabolic activation, the chromosome aberration test, the unscheduled DNA synthesis assay, mitotic recombination and gene conversion, the forward gene mutation assay and the in vivo micronucleus test, were all negative. No untoward effects on fertility or reproduction were noted when 100 mg/kg/day or less (2 times the human dose based on mg/m2) was administered orally to rats.

Teratogenic Effects

Cefpodoxime proxetil was neither teratogenic nor embryocidal when administered to rats during organogenesis at doses up to 100 mg/kg/day (2 times the human dose based on mg/m2) or to rabbits at doses up to 30 mg/kg/day (1 to 2 times the human dose based on mg/m2).

7. Description

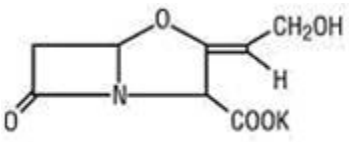
UVA CEF CV 50 dry syrup is a fixed-dose combination of cefpodoxime proxetil and potassium clavulanate. Cefpodoxime proxetil is chemically 1-propan-2-yloxycarbonyloxyethyl (6R,7R)-7-[[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyiminoacetyl]amino]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate having molecular weight of 557.6 g/mol and molecular formula is $C_{21}H_{27}N_5O_9S_2$. The chemical structure is



Potassium Clavulanate

Potassium Clavulanate molecular formula is $C_8H_8KNO_5$, and the molecular weight is 237.25. Chemically, Potassium Clavulanate is potassium (Z)-(2R,5R)-3-(2-

hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate, and may be represented structurally as:



Potassium Clavulanate is white to off-white, crystalline hygroscopic powder which is freely soluble in water; slightly soluble in ethanol (95%); very slightly soluble in acetone.

Cefpodoximie Proxetil 50 mg and Potassium Clavulanate 31.25 mg Dry syrup is Sunset Yellow Supra colour oral suspension.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

U.V.A. CEF - CV 50 Dry Syrup is available in combi pack containing one bottle and one ampoule in a carton.

8.4 Storage and handing instructions

Store in a cool (below 25°C) & dry place, Protect from light.

Keep all medicines out of reach of children.

9. Patient counselling information

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• Keep all medicines out of reach of children

• If you have any further questions, ask your doctor or pharmacist.

• **This medicine has been prescribed for you only.** Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1.What U.V.A. CEF - CV 50 DRY SYRUP is and what it is used for

9.2.What you need to know before you take U.V.A. CEF - CV 50 DRY SYRUP

9.3.How to take U.V.A. CEF - CV 50 DRY SYRUP

9.4.Possible side effects

9.5.How to store U.V.A. CEF - CV 50 DRY SYRUP

9.6.Contents of the pack and other information

9.1 What U.V.A. CEF - CV 50 DRY SYRUP is and what it is used for

Cefpodoxime and Potassium Clavulanate is an antibiotic medicine (a medicine used to treat bacterial infections).

- Cefpodoxime + Clavulanic acid dry syrup (FDC Cefpodoxime + Clavulanic Acid) are indicated for the treatment of lower and upper respiratory tract infection and urinary tract infection.

9.2 What you need to know before you take U.V.A. CEF - CV 50 DRY SYRUP

Do not take U.V.A. CEF - CV 50 DRY SYRUP

- If you are allergic to Cefpodoxime Proxetil and Potassium Clavulanate or any of the other ingredients of this medicine

Warnings and precautions

- Talk to your doctor before taking U.V.A.CEF-CV

- If you suffer from kidney problems, follow your doctor's instructions. He/she may decide if your dose should be adjusted.

- Antibacterial drugs including U.V.A. CEF - CV 50 DRY SYRUP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).

- Although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by U.V.A. CEF - CV 50 DRY SYRUP or other antibacterial drugs in the future.

- Diarrhoea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, you should contact their physician as soon as possible.

Infants

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

Other medicines and U.V.A. CEF - CV 50 DRY SYRUP

- Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Pregnancy and breast-feeding

- If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor for advice before taking this medicine.

- You should not stop your treatment without discussing this with your doctor.

Driving and using machines

- Dizziness has been reported during treatment with cefpodoxime and may affect the ability to drive and use machines.

9.3 How to take U.V.A. CEF - CV 50 DRY SYRUP

For pediatric use only.
Dosage: As directed by the Physician
Shake well before use.
Direction for reconstitution:
1. Shake the bottle to loosen the powder.
2. Twist to open the ampoule of sterile water given with the pack.
3. Add 2/3rd of sterile water into bottle which contains powder.
4. Put the cap and shake the bottle vigorously.
5. Adjust the volume up to the ring mark on the bottle by adding more sterile water if required and shake well. Allow the suspension to stand for 5 mins.
6. Store the reconstituted suspension in a refrigerator. Content to be consumed within 7 days. Any extra portion left to be thrown away.

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

U.V.A. CEF - CV 50 DRY SYRUP should be administered orally with food to enhance absorption.

If you take more U.V.A. CEF - CV 50 DRY SYRUP than you should contact your doctor if you took more syrup than you should. Your doctor will establish the best possible treatment of overdose.

The possible side effects of an overdose of U.V.A. CEF - CV 50 DRY SYRUP are nausea, vomiting, pain or discomfort right below your ribs in the area of your upper abdomen (epigastric distress), and diarrhoea.

If you forget to take U.V.A.CEF-CV:

Contact your doctor if you have missed one or more doses.

Do not take a double dose to make up for a forgotten dose.

If you stop taking U.V.A. CEF - CV 50 DRY SYRUP

Should your doctor decide to stop your U.V.A. CEF - CV 50 DRY SYRUP treatment, he/she will instruct you about the gradual withdrawal of U.V.A.CEF-CV.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately or contact the casualty department at your nearest hospital, if you get any of the following serious side effects:

- weakness, feel light-headed or dizzy or have difficulty breathing, as these may be signs of a serious allergic (anaphylactic) reaction
- gastrointestinal disturbances, nausea, vomiting, or diarrhoea
- dehydration, gout, peripheral oedema, weight increase
- Muscle Pain
- Dizziness, insomnia, somnolence, anxiety, shakiness, nervousness, cerebral infarction, change in dreams, impaired concentration, confusion, nightmares, paraesthesia, vertigo.
- asthma, cough, epistaxis, rhinitis, wheezing, bronchitis, dyspnoea, pleural effusion, pneumonia, sinusitis
- urticaria, rash, pruritus non-application site, diaphoresis, maculopapular rash, fungal dermatitis, desquamation, dry skin non-application site, hair loss, vesiculobullous rash, sunburn
- Taste alterations, eye irritation, taste loss, tinnitus.
- hematuria, urinary tract infections, metrorrhagia, dysuria, urinary frequency, nocturia, penile infection, proteinuria, vaginal pain.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How **to store U.V.A. CEF - CV 50 DRY SYRUP**

Store in a cool (below 25°C) & dry place, Protect from light.

Keep all medicines out of reach of children

9.6 Contents of the pack and other information

What **U.V.A.CEF-CV 50 DRY SYRUP** contains
• The active substances are Cefpodoxime and Clavulanic acid.
Cefpodoxime Proxetil I.P. equivalent to Cefpodoxime…....50 mg
Potassium Clavulanate Diluted I.P. equivalent to Clavulanic acid….31.25 mg

• U.V.A. CEF - CV 50 Dry Syrup is available in combi pack containing one bottle and one ampoule in a carton.

10. Details of manufacturer

Manufactured in India by:

Hetero Labs Limited (Unit - I)

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,

Distt: Solan, Himachal Pradesh – 173205.

11. Details of permission or licence number with date

Mfg. Lic. No. MB/05/194 issued on 24.09.2015

12. Date of revision

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/U.V.A. CEF - CV 50 DRY SYRUP /APR-20/01/PI