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

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Cefuroxime Axetil for Oral Suspension USP
(Brand Name: ENGEL® Dry Syrup)

2. Qualitative and Quantitative Composition

Each 5 ml of reconstituted suspension contains:
Cefuroxime Axetil IP equivalent to Cefuroxime ……..… 125 mg.
Excipients …….. q.s.
(In a flavoured base)
Colour: Erythrosine.

3. Dosage Form and Strength

Dosage Form: Dry powder for oral suspension.
Dosage Strength: Cefuroxime axetil 125 mg per 5 ml of reconstituted suspension.

4. Clinical Particulars

4.1 Therapeutic Indication

ENGEL Dry Syrup is indicated for the treatment of following infections when caused by susceptible strains of microorganisms in adults and children above 3 months of age.

- Acute streptococcal tonsillitis and pharyngitis.
- Acute bacterial sinusitis.
- Acute otitis media.
- Acute exacerbations of chronic bronchitis.
- Cystitis.
- Pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Early Lyme disease.

4.2Posology and Method of Administration

For oral administration.
There is no experience of using cefuroxime axetil in children below 3 months of age.

I. Recommended Dosage in Children Between 3 Months to 12 Years of Age (below 40 kg):

Dosage Based on Body Weight

- Mild to Moderate Infections: 10 mg/kg twice daily to a maximum of 125 mg twice daily.
- Severe Infections: 15 mg/kg twice daily to a maximum of 250 mg twice daily.

Dosage Based on Age Group (Usual Dose)

- **3 to 6 Months:** 2.5 ml twice daily.
- **6 Months to 2 Years:** 2.5 to 5 ml twice daily.
- **2 to 12 Years:** 5 ml twice daily.

Dosage Based on Age Group (For Otitis Media and More Serious Infections)

- **3 to 6 Months:** 2.5 ml twice daily.
- **6 Months to 2 Years:** 5 to 7.5 ml twice daily.
- **2 to 12 Years:** 7.5 to 10 ml twice daily.

II. Usual Recommended Dosage in Adults and Adolescents or Children Weighing >40 kg:

- Mild to Moderate Infections: 250 mg twice daily.
- Severe Infections: 500 mg twice daily.
- Uncomplicated Urinary Tract Infections: 125 mg twice daily, dose may be doubled in pyelonephritis.
- Gonorrhoea: 1 gram as a single dose.

For optimal absorption, cefuroxime axetil suspension should be taken with food. Duration of therapy is 5 to 10 days, depending on type and severity of infections.
Or, as prescribed by the physician.

Directions for Reconstitution of Dry Syrup

Shake the bottle to loosen the powder. Remove the cap. Slowly add boiled and cooled water up to the arrow mark on the label and shake well. Add more water, if necessary, to adjust the volume up to the arrow mark, to make 30 ml of reconstituted suspension. Replace the cap. Invert the bottle and shake vigorously so that water rises through the powder. Then, turn the bottle upright and shake vigorously for at least one minute.

Usage and Storage of Reconstituted Suspension

Shake the oral suspension well before each use.
Replace cap securely after each opening.
Store the reconstituted suspension in a refrigerator between 2 to 8 °C (36 to 46 °F).
Discard the reconstituted suspension, if any after 7 days.

4.3Contraindications

ENGEL Dry Syrup is contraindicated in the following:

- Patients with known hypersensitivity to cefuroxime axetil or to any component of this formulation.
- History of severe hypersensitivity (e.g., anaphylactic reaction) to other beta-lactam antibacterial agents (penicillins, cephalosporins, monobactams, and carbapenems).

4.4Special Warnings and Precautions for Use

Hypersensitivity: As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported with cefuroxime axetil. Before therapy with cefuroxime axetil is instituted, careful enquiry should be made to determine whether the patient has had previous hypersensitivity reaction to cefuroxime, other cephalosporins, penicillins, or other beta-lactam drugs (as there is a risk of cross-sensitivity). If a clinically significant allergic reaction occurs, discontinue the drug and institute appropriate therapy. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Jarisch-Herxheimer Reaction: The Jarisch-Herxheimer reaction has been seen following cefuroxime axetil treatment of Lyme disease. It results directly from the bactericidal activity of cefuroxime axetil on the causative bacteria of Lyme disease, the spirochaete *Borrelia burgdorferi*. Patients should be educated that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of Non-Susceptible Microorganisms (Pseudomembranous Colitis): As with other antibiotics, use of cefuroxime axetil may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible microorganisms (e.g., enterococci and *Clostridium difficile*), which may require interruption of treatment. Antibiotic-associated pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime and may range in severity from mild to life threatening. This diagnosis should be considered in patients with diarrhoea during or subsequent administration of cefuroxime. Moreover, cefuroxime axetil should be prescribed with caution in individuals with a history of colitis. The safety and effectiveness of cefuroxime axetil have not been established in patients with gastrointestinal malabsorption.

***Clostridium Difficile*-Associated Diarrhea (CDAD):** CDAD has been reported with use of nearly all antibacterial agents, including cefuroxime axetil, 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*. 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, specific antibiotic treatment for *C. difficile*, and surgical evaluation should be instituted as clinically indicated. Medicinal products that inhibit gastric peristalsis should not be given.

Antibiotic Resistance: Prescribing cefuroxime axetil 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.

Anticoagulant Therapy: Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

4.5Drug Interactions

Probenecid: Cefuroxime is excreted by glomerular filtration and tubular secretion. Concurrent administration of probenecid significantly increases the peak concentration, area under the plasma concentration time curve and elimination half-life of cefuroxime. Thus, co-administration of probenecid with cefuroxime axetil is not recommended.

Antacids, H_2-Antagonists, and Proton Pump Inhibitors - PPIs: Drugs that reduce gastric acidity may result in a lower bioavailability of cefuroxime with that of fasting state and tend to cancel the effect of enhanced absorption after food.

Oral Contraceptives: In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral estrogen/progesterone contraceptives. It is advised that patients to consider alternative supplementary (non-hormonal) contraceptive measures during treatment with cefuroxime.

Aminoglycosides: When cephalosporins are given with aminoglycoside antibacterial agents, there is increased risk of nephrotoxicity; thus, concomitant use should be avoided.

Anticoagulants: Cephalosporins possibly enhance anticoagulant effect of coumarin derivatives. It is recommended that the international normalised ratio (INR) should be monitored frequently during and shortly after co-administration of cefuroxime with an oral anti-coagulant agent.

Drug/Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with copper reduction tests (e.g., Benedict's or Fehling's solution), but not with enzyme-based tests for glycosuria.

Also, a false-negative result for plasma glucose may occur with ferricyanide tests in subjects receiving cefuroxime axetil. Thus, it is recommended that either the glucose oxidase or hexokinase methods are used to determine plasma glucose levels in patients receiving cefuroxime axetil.

The presence of cefuroxime does not interfere with the assay of plasma and urine creatinine by the alkaline picrate method.

The development of a positive Coomb's Test associated with the use of cefuroxime may interfere with cross matching of blood.

4.6Use in Special Populations

Pregnant Women

Pregnancy Category B. There are limited data with regard to use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal development. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, cefuroxime axetil should be used during pregnancy only if clearly needed (i.e., when benefit outweighs the risk).

Lactating Women

Cefuroxime is excreted in human milk in small quantities. Thus, caution should be exercised when cefuroxime axetil is administered to nursing mother. Adverse effects at therapeutic doses are not expected, although a risk of diarrhoea and fungus infection of the mucous membranes cannot be excluded. Breastfeeding might have to be discontinued due to these effects. The possibility of sensitization should be taken into account. Cefuroxime axetil should only be used during breastfeeding after benefit/risk assessment by the physician.

Paediatric Patients

Safety and efficacy of cefuroxime axetil has not been established in infants below 6 months of age. Cefuroxime axetil can be administered in children between 3 months to 12 years of age. For dosage, please refer 'Posology and Method of Administration' section.

Geriatric Patients

No overall differences in safety or effectiveness were observed between elderly and younger subjects. No special precaution is necessary in the elderly patients with normal renal function at dosage up to maximum of 1 gram per day. Cefuroxime is substantially excreted by the kidney, and the risk of adverse reactions 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 (dose should be adjusted in accordance with the renal function), and it may be useful to monitor renal function.

Renal Impairment Patients

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established. Cefuroxime is primarily excreted by the kidneys. Thus, reduction in the dosage of cefuroxime is recommended for adult patients with severe renal impairment (creatinine clearance < 30 ml/min). Cefuroxime is effectively removed by dialysis.

Hepatic Impairment Patients

No dosage adjustment is generally required in patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on dosing of cefuroxime axetil.

4.7Effect on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. However, as this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

4.8Undesirable Effects

The safety profile for cefuroxime axetil in children is consistent with the profile in adults. Following are the adverse reactions reported in the adults.

Clinical Trials Experience

The following adverse events have been reported with the use of cefuroxime axetil:

Incidence ≥ 1%: Diarrhea/loose stools (3.7%), nausea/vomiting (3.0%), transient elevation in liver enzymes such as aspartate aminotransferase - AST (2.0%) and alanine aminotransferase - ALT (1.6%), eosinophilia (1.1%), transient elevation in lactate dehydrogenase - LDH (1.0%).

Incidence < 1% but > 0.1%: Abdominal pain, abdominal cramps, flatulence, indigestion, headache, dizziness, candida overgrowth, vaginitis, vulvar itch, rash, hives, itch, dysuria, chills, chest pain, shortness of breath, mouth ulcers, swollen tongue, sleepiness, thirst, anorexia, and positive Coombs test.

Post-Marketing Experience

Following adverse events have been identified during clinical practice in patients treated with cefuroxime axetil and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

Gastrointestinal: Pseudomembranous colitis.

Hematologic: Hemolytic anemia, leukopenia, pancytopenia, thrombocytopenia, and increased prothrombin time.

Hepatic: Hepatic impairment including hepatitis and cholestasis, jaundice.

Immune System Disorders: Anaphylaxis, serum sickness-like reaction.

Neurologic: Seizure, encephalopathy.

Skin: Angioedema, rashes, pruritus, urticaria, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Urologic: Renal dysfunction.

Laboratory Abnormalities: Increased prothrombin time.

Adverse Reactions Reported for Cephalosporin-Class Drugs: Following adverse reactions have been reported for cephalosporin-class antibiotics: Renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, serum sickness-like reaction, hemorrhage, agranulocytosis, pancytopenia, fixed drug eruption (FDE) and purpura.

4.9Overdose

Overdose of cephalosporins can lead to neurological sequelae including encephalopathy, convulsions and coma. Symptoms of overdose can occur if the dose is not reduced appropriately in patients with renal impairment.

Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

5. Pharmacological Properties

5.1 Mechanism of Action

Cefuroxime is second generation cephalosporin class of beta-lactam antibiotic. Cefuroxime axetil is a prodrug; its active metabolite is cefuroxime. Cefuroxime axetil undergoes hydrolysis by esterase enzymes to the active antibiotic, cefuroxime. Cefuroxime inhibits bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death. Cefuroxime axetil has activity in the presence of some β-lactamases, both penicillinases and cephalosporinases, of gram-negative and gram-positive bacteria.

5.2Pharmacodynamic Properties

Cefuroxime axetil is a semisynthetic, cephalosporin class of beta-lactam antibacterial drug for oral administration. Cefuroxime has bactericidal activity against a wide range of common pathogens, including many beta-lactamase-producing strains. Cefuroxime is stable to many bacterial beta-lactamases, especially plasmid-mediated enzymes that are commonly found in enterobacteriaceae. Cefuroxime has been demonstrated to be active against most strains of the following microorganisms both *in vitro* and in clinical infections.

Gram-Positive Bacteria

- *Staphylococcus aureus* (including beta-lactamase-producing strains).
- *Streptococcus pneumonia.*
- *Streptococcus pyogenes.*

Gram-Negative Bacteria

- *Escherichia coli.*
- *Haemophilus influenzae* (including beta-lactamase-producing strains).
- *Haemophilus parainfluenzae.*
- *Klebsiella pneumonia.*
- *Moraxella catarrhalis* (including beta-lactamase-producing strains).
- *Neisseria gonorrhoeae* (including beta-lactamase-producing strains).

Spirochetes

- *Borrelia burgdorferi.*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefuroxime axetil of 1 mcg/ml. However, the efficacy of cefuroxime axetil in treating clinical infections due to these microorganisms has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

- *Staphylococcus epidermidis.*
- *Staphylococcus saprophyticus.*
- *Streptococcus agalactiae.*

Gram-Negative Bacteria

- *Morganella morganii.*
- *Proteus inconstans.*
- *Proteus mirabilis.*
- *Providencia rettgeri.*

Anaerobic Bacteria

- *Peptococcus niger.*

5.3Pharmacokinetic Properties

In older infants (aged > 3 months) and in children, the pharmacokinetics of cefuroxime are similar to that observed in adults.

The pharmacokinetics of cefuroxime is linear over the oral dosage range of 125 to 1000 mg. No accumulation of cefuroxime occurred following repeat oral doses of 250 to 500 mg.

Absorption: After oral administration, cefuroxime axetil is absorbed from the gastrointestinal tract (GIT) and rapidly hydrolyzed in the intestinal mucosa and blood to release cefuroxime into the circulation. Following oral administration of cefuroxime axetil tablets, peak plasma levels occur approximately 2 to 3 hours after dosing when administered with food. Optimum absorption occurs when cefuroxime is administered shortly after a meal (bioavailability of cefuroxime axetil increases from 37 % to 52 %).

Distribution: Approximately 50% of cefuroxime is bound to plasma proteins. Cefuroxime is distributed throughout the extracellular fluids. Concentrations of cefuroxime in excess of the minimum inhibitory levels for common pathogens can be achieved in the tonsilla, sinus tissues, bronchial mucosa, bone, pleural fluid, joint fluid, synovial fluid, interstitial fluid, bile, sputum and aqueous humor. Cefuroxime passes the blood-brain barrier when the meninges are inflamed. The apparent volume of distribution is around 50 liters.

Metabolism: Cefuroxime is not metabolised, however, the axetil moiety is metabolized to acetaldehyde and acetic acid.

Excretion: Cefuroxime is excreted unchanged in the urine. In adults, approximately 50% of the administered dose is recovered in the urine within 12 hours. The plasma half-life is between 1 to 1.5 hours.

6. Nonclinical Properties

6.1 Animal Toxicology

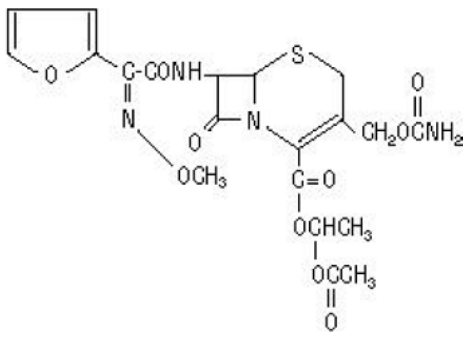
Carcinogenesis and Mutagenesis: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay; however, negative results were found in an *in vivo* micronucleus test at doses up to 1.5 g/kg. Impairment of Fertility: Reproduction studies in rats at doses up to 1,000 mg/kg/day (9 times the recommended maximum human dose based on body surface area) have revealed no impairment of fertility.

7. Description

ENGEL Dry Syrup is off-white coloured granular powder in 30 ml white HDPE bottle with induction seal having white coloured HDPE cap and 10 ml measuring cup. On reconstitution, it forms a pink colour suspension.

ENGEL Dry Syrup contains 125 mg of cefuroxime axetil per 5 ml of reconstituted suspension for oral administration.

Cefuroxime axetil is semi-synthetic, second generation cephalosporin class of beta-lactam antibiotic with bactericidal activity.
Cefuroxime axetil appears as white to almost white crystalline powder.
Molecular Weight: 510.48 g/mol.
Molecular Formula: C20H22N4O10S.
Chemical Name: (1-(acetyloxy) ethyl ester of cefuroxime) is (RS)-1- hydroxyethyl (6R,7R)-7-[2-(2-furyl)glyoxyl-amido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylate, 72-(Z)-(O-methyl-oxime), 1-acetate 3-carbamate.
Structural Formula:



Inactive ingredients (excipients) of ENGEL Dry Syrup contain Cross Linked Acrylic Copolymer, Sodium Benzoate, Sodium Carboxymethycellulose, Colloidal Silicon Dioxide, Sodium Citrate, Citric Acid Anhydrous, Butylated Hydroxy Anisole, Sucralose, Orange Flavour, Lemon Flavour, Sodium Bicarbonate, Magnesium Stearate, Talc, Sodium Lauryl Sulphate, Colour Erythrosine, Pharma Grade Sugar, and Neotame.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

18 months.

8.3Packaging Information

15g / 30 ml bottle with measuring cup.

8.4Storage and Handling Instructions

Store protected from light and moisture, at a temperature not exceeding 25°C.
Store the reconstituted suspension in a refrigerator.
The reconstituted suspension should be consumed within 7 days of preparation.
Keep out of reach of children.

9. Patient Counseling Information

Administration Instructions to Patients / Caregivers

- Patients/caregivers should be counseled that antibacterial drugs should only be used to treat bacterial infections; not to use this medicine to treat infections caused by viruses (such as common cold).
- Patients/caregivers should be told that 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 decrease the effectiveness of the treatment and increase the likelihood of developing antibiotic resistance.
- Inform patients/caregivers that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, 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 antibacterial. If this occurs, patients should inform their physician as soon as possible.
- This medicine should be avoided in children below 3 months of age.

- Pregnant women and lactating mothers should use this medicine only if essential and in consultation with their doctor.
- Shake suspension well before each use. Use reconstituted suspension within 7 days; thereafter, unused portion, if any, should be discarded.

10. Details of Manufacturer

Twenty First Century Pharmaceutical Pvt. Ltd.
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11. Details of Permission or License Number with Date

Mfg. Lic. No. : 11/UA/SC/P-2010; Date of FDA Product Permission: 18/07/2019.

12. Date of Revision

February 2023.

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