*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 Tablets IP

(Brand Name: ENGEL® - 250 mg / ENGEL® - 500 mg Tablets)

## 2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Cefuroxime Axetil IP equivalent to Cefuroxime ……..… 250 mg / 500 mg.

Excipients …….. q.s.

Colours: Titanium Dioxide IP.

## 3. Dosage Form and Strength

Dosage Form: Tablet.

Dosage Strength: Cefuroxime axetil 250 mg per tablet; Cefuroxime axetil 500 mg per tablet.

## 4. Clinical Particulars

### 4.1 Therapeutic Indication

ENGEL-250 / ENGEL-500 Tablets are indicated for the treatment of following infections when caused by susceptible strains of microorganisms:

- Upper respiratory tract infections such as acute otitis media, sinusitis, tonsillitis, and pharyngitis.
- Lower respiratory tract infections such as acute bronchitis and acute exacerbations of chronic bronchitis (AECB).
- Uncomplicated urinary tract infections such as cystitis and pyelonephritis.
- Uncomplicated skin and soft tissue infections.
- Early Lyme disease.
- Uncomplicated gonorrhoea.

### 4.2Posology and Method of Administration

For oral administration.

**Usual Recommended Dosage in Adults and Adolescents**

- 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.

Duration of therapy is 5 to 10 days, depending on type and severity of infections. ENGEL-250 / ENGEL-500 Tablets should be preferably administered with or after food (as food increases bioavailability of cefuroxime axetil). The tablet should be swallowed whole with water and not to be cut, crushed or chewed.
Or, as prescribed by the physician.

## 4.3Contraindications

ENGEL-250 / ENGEL- 500 Tablets are 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**

Cefuroxime axetil can be administered in children between 3 months to 12 years of age. As there is no dosage feasibility with this formulation, ENGEL Tablets are not recommended for use in children below 12 years of age. Children between 3 months to 12 years of age should use paediatric formulations of cefuroxime axetil such as suspension.

**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

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice. The following adverse events have been reported with the use of cefuroxime axetil in multiple-dose clinical trials:

**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, fixed drug eruption (FDE).
**Urologic:** Renal dysfunction.
**Laboratory Abnormalities:** Increased prothrombin time.

## 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

**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 2.4 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

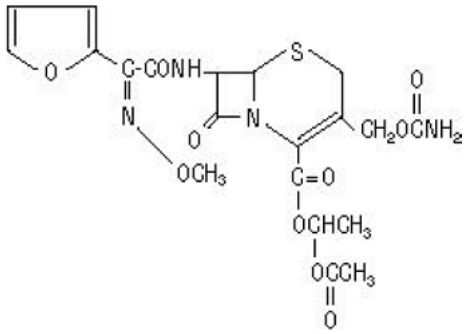
Carcinogenesis and Mutagenesis: Although lifetime studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic activity was found for cefuroxime axetil in a battery of bacterial mutation tests. Positive results were obtained in an *in vitro* chromosome aberration assay; 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-250 Tablets are white coloured capsule shaped, biconvex, film coated tablets plain on both sides.
ENGEL-500 Tablets are off white coloured capsule shaped, biconvex, film coated tablets plain on both sides.

ENGEL-250 Tablets contains 250 mg of cefuroxime axetil per tablet for oral administration.
ENGEL-500 Tablets contains 500 mg of cefuroxime axetil per tablet 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: $C_{20}H_{22}N_4O_{10}S$.
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-250 Tablet contain Microcrystalline Cellulose, Hydrogenated Castor Oil, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Hydroxy Propyl Methyl Cellulose, Methacrylic Acid Polymer with Divinyl Benzene and Acrylic Acid Potassium, Titanium Dioxide, Talc, and Propylene Glycol.

Inactive ingredients (excipients) of ENGEL-500 Tablet contain Microcrystalline Cellulose, Hydrogenated Castor Oil, Colloidal Silicon Dioxide, Sodium Lauryl Sulphate, Hydroxy Propyl Methyl Cellulose, Crosscarmellose Sodium, Titanium Dioxide, Talc, and Propylene Glycol.

## 8. Pharmaceutical Particulars

### 8.1 Incompatibilities

None known.

### 8.2Shelf-life

24 months.

### 8.3Packaging Information

10 tablets per strip.

### 8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of reach of children.

## 9. Patient Counseling Information

Administration Instructions to Patients

- Patients 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 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 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.

- Pregnant women and lactating mothers should use this medicine only if essential and in consultation with their doctor.

## 10. Details of Manufacturer

Twenty First Century Pharmaceutical Pvt. Ltd.
Unit – II: Khasra No. 282, Nalheri Dehviran, Puhana –
Iqbalpur Road, Roorkee – 247 668. Dist. Haridwar. Uttarakhand.

## 11. Details of Permission or License Number with Date

Mfg. Lic. No. : 11/UA/SC/P-2010; Date of FDA Product Permission: 19/02/2015.

## 12. Date of Revision

September 2022.