## MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

### 1.3 Product Information

### 1.3.1 Summary of Product Characteristics (SmPC)

**1. Name of the medicinal product:**

**Generic Name/INN Name:** Cefuroxime Axetil Tablets USP 500 mg

**Brand Name:** CEFUNAT- 500

**Strength:**

Each film coated tablet contains:

Cefuroxime Axetil USP (Amorphous) eq. to

Anhydrous Cefuroxime…… 500 mg

Excipients ……q.s.

Colour: Titanium Dioxide

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### 2. Qualitative and Quantitative Composition

| Sr. No. | Ingredients | Specification | Label Claim (mg). | Std. Qty. / Tab (In mg) | % w/w | Function |
|---|---|---|---|---|---|---|
| | **Dry Mixing** | | | | | |
| 1. | Cefuroxime Axetil (Amorphous)* | USP | 500.00 | 500.00 | 46.51 | Active |
| 2. | Microcrystalline Cellulose-102** | BP | | 295.00 | 27.44 | Diluent |
| 3. | Croscarmellose sodium | BP | | 90.00 | 8.37 | Disintegrant |
| 4. | Low Substituted Hydroxy Propyl Cellulose | BP | | 10.00 | 0.93 | Disintegrant |
| 5. | Polacrillin Potassium | USP | | 40.00 | 3.72 | Disintegration improving agent |
| 6. | Sodium Lauryl Sulphate | BP | | 8.00 | 0.74 | Solubilizer |
| 7. | Colloidal slicon Dioxide | BP | | 6.00 | 0.56 | Glidant |
| 8. | Calcium stearate | BP | | 5.00 | 0.47 | Lubricant |
| | **Lubrication** | | | | | |
| 9. | Croscarmellose sodium | BP | | 30.00 | 2.79 | Disintegrant |
| 10. | Polacrillin Potassium | USP | | 10.00 | 0.93 | Disintegration improving agent |
| 11. | Microcrystalline Cellulose-102 | BP | | 30.00 | 2.79 | Diluent |
| 12. | Sodium lauryl sulfate | BP | | 6.00 | 0.56 | Solubilizer |
| 13. | Colloidal silicon Dioxide | BP | | 15.00 | 1.40 | Glidant |
| 14. | Calcium stearate | BP | | 5.00 | 0.47 | Lubricant |
| **Total weight of uncoated tablet** | | | | 1050.00 | --- | --- |
| | **Film Coating** | | | | | |
| 15. | Isopropyl alocohol*** | BP | | 149.80 | --- | Solvent |
| 16. | Methylene Chloride (Dichloromethane)*** | BP | | 278.20 | --- | Solvent |
| 17. | H.P.M.C.E-15(premium) | BP | | 8.74 | 0.81 | Film foarming agent |
| 18. | H.P.M.C.E-5 | BP | | 8.74 | 0.81 | Film foarming agent |
| 19. | Titanium Dioxide | BP | | 3.11 | 0.29 | Coating agent |
| 20. | Propylene Glycol | BP | | 3.41 | 0.32 | Solvent |
| 21. | Col. Instaglow-IG001 | In-House | | 1.00 | 0.09 | Coating agent |
| **Total weight of coated tablet** | | | | 1075.00 | 100.00 | --- |

**Note:**
* Add the calculated quantity based on the Assay (potency) and Water content of Cefuroxime Axetil.
** Quantity of Microcrystalline Cellulose-102 will vary as per the quantity of the APIs.
*** Solvents that evaporated during the process

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**3. Pharmaceutical form:**

**Dosage Form:** Solid dosage form (Tablet)

**Visual & Physical characteristics of the product:** A white colored, capsule shape, biconvex, film coated tablets, having embossed "EMP" on one side and mark "CFT500" on other side of the tablets.

**4. Clinical particulars:**

**4.1 Therapeutic indications:**

Cefuroxime axetil is indicated for the treatment of the infections listed below in adults and children from the age of 3 months.

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

**4.2 Posology and method of administration:**

Route of administration: Oral

**Posology**

Course of therapy is seven days (may range from five to ten days).

Dosage schedule for tablets: Table 1. Adults and children (≥40 kg)

| **Indication** | **Dosage** |
|---|---|
| Acute otitis media | 500 mg twice daily |
| Acute exacerbations of chronic bronchitis | 500 mg twice daily |
| Cystitis | 250 mg twice daily |
| Pyelonephritis | 250 mg twice daily |
| Uncomplicated skin and soft tissue infections | 250 mg twice daily |
| Lyme disease | 500 mg twice daily for 14 days (range of 10 to 21 days) |

Table 2. Children (<40 kg)

| Indication | Dosage |
|---|---|
| Acute tonsillitis and pharyngitis, acute bacterial sinusitis | 10 mg/kg twice daily to a maximum of 125 mg twice daily |
| Children aged two years or older with otitis media or, where appropriate, with more severe infections | 15 mg/kg twice daily to a maximum of 250 mg twice daily |
| Cystitis | 15 mg/kg twice daily to a maximum of 250 mg twice daily |
| Pyelonephritis | 15 mg/kg twice daily to a maximum of 250 mg twice daily for 10 to 14 days |
| Uncomplicated skin and soft tissue infections | 15 mg/kg twice daily to a maximum of 250 mg twice daily |
| Lyme disease | 15 mg/kg twice daily to a maximum of 250 mg twice daily for 14 days (10 to 21 days) |

There is no experience of using Cefuroxime axetil in children under the age of 3 months.

**Renal impairment**

The safety and efficacy of cefuroxime axetil in patients with renal failure have not been established.

Cefuroxime is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of cefuroxime should be reduced to compensate for its slower excretion. Cefuroxime is effectively removed by dialysis.

Table 3. Recommended doses for Cefuroxime axetil in renal impairment

| Creatinine clearance | $T_{1/2}$ (hrs) | Recommended dosage |
|---|---|---|
| ≥30 mL/min/1.73 m2 | 1.4–2.4 | No dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily) |
| 10-29 mL/min/1.73 m2 | 4.6 | Standard individual dose given every 24 hours |
| <10 mL/min/1.73 m2 | 16.8 | Standard individual dose given every 48 hours |
| Patients on haemodialysis | 2–4 | A further standard individual dose should be |

| | | |
|---|---|---|
| | | given at the end of each dialysis |

**Hepatic impairment**

There are no data available for patients with hepatic impairment. Since cefuroxime is primarily eliminated by the kidney, the presence of hepatic dysfunction is expected to have no effect on the pharmacokinetics of cefuroxime.

**Method of administration**

Oral use

Cefuroxime axetil tablets should be taken after food for optimum absorption.

Cefuroxime axetil tablets should not be crushed and are therefore unsuitable for treatment of patients who cannot swallow tablets. In children Cefuroxime axetil oral suspension may be used.

**4.3 Contraindications:**

Hypersensitivity to Cefuroxime or any of the cephalosporin antibiotics. Previous immediate and/or severe hypersensitivity reaction to penicillin or to any other type of beta-lactam drug.

**4.4 Special warnings and precautions for use:**

Hypersensitivity reactions

Special care is indicated in patients who have experienced an allergic reaction to penicillins or other beta-lactam antibiotics because there is a risk of cross-sensitivity. As with all beta-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with cefuroxime must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to cefuroxime, to other cephalosporins or to any other type of beta-lactam agent. Caution should be used if cefuroxime is given to patients with a history of non-severe hypersensitivity to other beta-lactam agents.

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 reassured that this is a common and usually self-limiting consequence of antibiotic treatment of Lyme disease.

Overgrowth of non-susceptible microorganisms

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.

Antibacterial agent–associated pseudomembranous colitis have 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 to the administration of cefuroxime. Discontinuation of therapy with cefuroxime and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Interference with diagnostic tests

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

As a false negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase methods are used to determine blood/plasma glucose levels in patients receiving cefuroxime axetil.

**4.5 Interaction with other medicinal products and other forms of interaction:**

Drugs which reduce gastric acidity may result in a lower bioavailability of cefuroxime axetil compared with that of the fasting state and tend to cancel the effect of enhanced absorption after food.

Cefuroxime axetil may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

Cefuroxime is excreted by glomerular filtration and tubular secretion. Concomitant use of probenecid is not recommended. Concurrent administration of probenecid significantly increases the peak concentration, area under the serum concentration time curve and elimination half-life of cefuroxime.

Concomitant use with oral anticoagulants may give rise to increased INR.

**4.6 Pregnancy and lactation:**

Pregnancy

There are limited data from the use of cefuroxime in pregnant women. Studies in animals have shown no harmful effects on pregnancy, embryonal or foetal development, parturition or postnatal

development. Cefuroxime axetil should be prescribed to pregnant women only if the benefit outweighs the risk.

Breastfeeding

Cefuroxime is excreted in human milk in small quantities. 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 sensitisation should be taken into account. Cefuroxime should only be used during breastfeeding after benefit/risk assessment by the physician in charge.

Fertility

There are no data on the effects of cefuroxime axetil on fertility in humans. Reproductive studies in animals have shown no effects on fertility.

**4.7 Effects on ability to drive and use machines**

There are no studies of the effect of cefuroxime axetil on the ability to drive and to handle machines. However, any effects are not to be expected.

**4.8 Undesirable effects:**

The most common adverse reactions are *Candida* overgrowth, eosinophilia, headache, dizziness, gastrointestinal disturbances and transient rise in liver enzymes.

The frequency categories assigned to the adverse reactions below are estimates, as for most reactions suitable data (for example from placebo-controlled studies) for calculating incidence were not available. In addition the incidence of adverse reactions associated with cefuroxime axetil may vary according to the indication.

Data from large clinical studies were used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e. those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than true frequency. Placebo-controlled trial data were not available. Where incidences have been calculated from clinical trial data, these were based on drug-related (investigator assessed) data. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Treatment related adverse reactions, all grades, are listed below by MedDRA body system organ class, frequency and grade of severity. The following convention has been utilised for the classification of frequency: very common ≥ 1/10; common ≥ 1/100 to < 1/10, uncommon ≥ 1/1,000

to < 1/100; rare ≥ 1/10,000 to < 1/1,000; very rare < 1/10,000 and not known (cannot be estimated from the available data).

| System organ class | Common | Uncommon | Not known |
|---|---|---|---|
| Infections and infestations | *Candida* overgrowth | | *Clostridium difficile* overgrowth |
| Blood and lymphatic system disorders | eosinophilia | positive Coomb's test, thrombocytopenia, leukopenia (sometimes profound) | haemolytic anaemia |
| Immune system disorders | | | drug fever, serum sickness, anaphylaxis, Jarisch-Herxheimer reaction |
| Nervous system disorders | headache, dizziness | | |
| Gastrointestinal disorders | diarrhoea, nausea, abdominal pain | vomiting | pseudomembranous colitis |
| Hepatobiliary disorders | transient increases of hepatic enzyme levels | | jaundice (predominantly cholestatic), hepatitis |
| Skin and subcutaneous tissue disorders | | skin rashes | urticaria, pruritus, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (exanthematic necrolysis) (see *Immune system disorders*), angioneurotic oedema |
| *Description of selected adverse reactions*<br>Cephalosporins as a class tend to be absorbed onto the surface of red cells membranes and react with | | | |

antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely haemolytic anaemia.

Transient rises in serum liver enzymes have been observed which are usually reversible.

*Paediatric population*

The safety profile for cefuroxime axetil in children is consistent with the profile in adults.

### 4.9 Overdose

Overdosage of cephalosporins may cause cerebral irritancy leading to convulsions. In case of overdosage cefuroxime serum levels can be reduced by haemodialysis and peritoneal dialysis.

## 5. Pharmacological properties:

### 5.1 Pharmacodynamic properties:

General properties:

ATC classification

Pharmacotherapeutic group: cephalosporins and related substances

ATC-Code: J01D C02

Mode of action

Cefuroxime axetil owes its in vivo bactericidal activity to the parent compound cefuroxime. All cephalosporins (β-lactam antibiotics) inhibit cell wall production and are selective inhibitors of peptidoglycan synthesis. The initial step in drug action consists of binding of the drug to cell receptors, called Penicillin-Binding Proteins. After a β-lactam antibiotic has bound to these receptors, the transpeptidation reaction is inhibited and peptidoglycan synthesis is blocked. Bacterial lysis is the end result.

Mechanism of resistance

Bacterial resistance to cefuroxime may be due to one or more of the following mechanisms:

• hydrolysis by beta-lactamases. Cefuroxime may be efficiently hydrolysed by certain of the extended-spectrum beta-lactamases (ESBLs) and by the chromosomally-encoded (AmpC) enzyme that may be induced or stably derepressed in certain aerobic gram-negative bacterial species

• reduced affinity of penicillin-binding proteins for cefuroxime

• outer membrane impermeability, which restricts access of cefuroxime to penicillin binding proteins in gram-negative organisms

• drug efflux pumps

Methicillin-resistant staphylococci (MRS) are resistant to all currently available β-lactam antibiotics including cefuroxime. Penicillin-resistant Streptococcus pneumoniae are cross-resistant to cephalosporins such as cefuroxime through alteration of penicillin binding proteins. Beta-lactamase negative, ampicillin resistant (BLNAR) strains of H. influenzae should be considered resistant to cefuroxime despite apparent in vitro susceptibility. Strains of Enterobacteriaceae, in particular Klebsiella spp. and Escherichia coli that produce ESBLs (extended spectrum β-lactamase) may be clinically resistant to therapy with cephalosporins despite apparent in vitro susceptibility and should be considered as resistant.

**Breakpoints:**

According to the NCCLS (National Committee on Clinical Laboratory Standards) in 2001 the following breakpoints have been defined for cefuroxime axetil:

Enterobacteriaceae: ≤ 4 µg/ml susceptible, ≥ 32 µg/ml resistant

Staphylococcus spp.: ≤ 4 µg/ml susceptible, ≥ 32 µg/ml resistant

Haemophilus spp.: ≤ 4 µg/ml susceptible; ≥ 16 µg/ml resistant

Streptococcus pneumoniae: ≤ 1 µg/ml susceptible, ≥ 4 µg/ml resistant

Streptococcus spp. other than S. pneumoniae:

Streptococcal isolates susceptible to penicillin (MIC90 ≤ 0.12 µg/ml) may be considered susceptible to cefuroxime.

**Susceptibility:**

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Cefuroxime is usually active against the following microorganisms in vitro.

| **Commonly susceptible species** |
|---|
| Gram-positive aerobes: |
| Staphylococcus aureus (methicillin susceptible)* |
| Coagulase negative staphylococcus (methicillin susceptible) Streptococcus pyogenes |

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| |
|---|
| Streptococcus agalactiae |
| Gram-negative aerobes:<br>Haemophilus influenzae<br>Haemophilus parainfluenzae<br>Moraxella catarrhalis |
| Spirochaetes:<br>Borrelia burgdorferi |
| **Microorganisms for which acquired resistance may be a problem** |
| Gram-positive aerobes:<br>Streptococcus pneumoniae |
| Gram-negative aerobes:<br>Citrobacter freundii<br>Enterobacter aerogenes<br>Enterobacter cloacae<br>Escherichia coli<br>Klebsiella pneumoniae<br>Proteus mirabilis<br>Proteus spp.(other than P. vulgaris)<br>Providencia spp. |
| Gram-positive anaerobes:<br>Peptostreptococcus spp.<br>Propionibacterium spp. |
| Gram-negative anaerobes:<br>Fusobacterium spp.<br>Bacteroides spp. |
| **Inherently resistant microorganisms** |
| Gram-positive aerobes:<br>Enterococcus faecalis |

| |
|---|
| Enterococcus faecium |
| Gram-negative aerobes:<br>Acinetobacter spp.<br>Campylobacter spp.<br>Morganella morganii<br>Proteus vulgaris<br>Pseudomonas aeruginosa<br>Serratia marcescens |
| Gram-negative anaerobes:<br>Bacteroides fragilis |
| Others:<br>Chlamydia spp.<br>Mycoplasma spp.<br>Legionella spp. |

**5.2 Pharmacokinetic properties**

**Pharmacokinetics**

**Absorption:** After oral administration cefuroxime axetil is absorbed from the gastrointestinal tract and rapidly hydrolysed in the intestinal mucosa and blood causing the release of the active compound cefuroxime into the circulation. Optimum absorption occurs when Cefuroxim axetil is taken shortly after a meal (50-60%). Under these circumstances maximum serum concentration is achieved after 2-3 hours.

**Distribution:** Cefuroxime is widely distributed in the body including pleural fluid, sputum, bone, synovial fluid, and aqueous humour, but only achieves therapeutic concentrations in the CSF when the meninges are inflamed. About 50% of cefuroxime in the circulation is bound to plasma proteins. It diffuses across the placenta and has been detected in breast milk.

**Metabolism:** Cefuroxime is not metabolised.

**Elimination:** Most of the dose of cefuroxime is excreted unchanged. About 50% is excreted by glomerular filtration and about 50% through renal tubular secretion within 24 hours, with the majority being eliminated within 6 hours; high concentrations are achieved in the urine. Small

amounts of cefuroxime are excreted in bile. Probenecid competes with cefuroxime for renal tubular secretion resulting in higher and more prolonged plasma concentrations of cefuroxime. The plasma half-life ranges between 60 and 90 minutes and is prolonged in patients with renal impairment and in neonates.

Dialysis causes the decrease of cefuroxime serum levels.

**5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development. No carcinogenicity studies have been performed; however, there is no evidence to suggest carcinogenic potential.

Gamma glutamyl transpeptidase activity in rat urine is inhibited by various cephalosporins, however the level of inhibition is less with cefuroxime. This may have significance in the interference in clinical laboratory tests in humans.

**6. Pharmaceutical particulars:**

**6.1 List of Excipients:**

Microcrystalline Cellulose

Croscarmellose Sodium

Low substituted Hydroxy Propyl Cellulose

Polacrillin Potassium

Sodium Lauryl Sulphate

Colloidal Anhydrous Silica

Calcium Stearate

Croscarmellose Sodium

H.P.M.C.E-15

H.P.M.C.E-5

Titanium Dioxide

Propylene Glycol

Col. Instaglow-IG001

**6.2 Incompatibilities:**

None

**6.3 Shelf life:**

24 months

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**6.4 Special precautions for storage:**

Store below 30°C in a dry place.

**6.5 Nature and contents of container:**

Primary Packing:

10 Tablets pack in ALU-ALU blister pack.

Secondary Packing:

Such one ALU-ALU blister pack in single unit printed mono carton along with pack insert.

**6.6 Special precautions for disposal:**

No special requirement.

**7. Registrant:**

**BHARAT PARENTERALS LTD.**

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