



**National Agency for Food & Drug Administration
& Control (NAFDAC)**

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)



1. NAME OF THE MEDICINAL PRODUCT

Gramocef O 400

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Capsule Contains:

Cefixime USP as Trihydrate equivalent to anhydrous Cefixime.....200 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Purple/white colored 'C' Size plain capsules containing white to light yellow granular powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Uncomplicated Urinary Tract Infections

Cefixime is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated urinary tract infections caused by susceptible isolates of *Escherichia coli* and *Proteus mirabilis*.

Otitis Media

Cefixime is indicated in the treatment of adults and pediatric patients six months of age or older with otitis media caused by susceptible isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes*. (Efficacy for *Streptococcus pyogenes* in this organ system was studied in fewer than 10 infections.)

Note: For patients with otitis media caused by *Streptococcus pneumoniae*, overall response was approximately 10% lower for cefixime than for the comparator.

Pharyngitis and Tonsillitis

Cefixime is indicated in the treatment of adults and pediatric patients six months of age or older with pharyngitis and tonsillitis caused by susceptible isolates of *Streptococcus pyogenes*. (Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections. Cefixime is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx; however, data establishing the efficacy of Cefixime in the subsequent prevention of rheumatic fever is not available.)



Acute Exacerbations of Chronic Bronchitis

Cefixime is indicated in the treatment of adults and pediatric patients six months of age or older with acute exacerbations of chronic bronchitis caused by susceptible isolates of *Streptococcus pneumoniae* and *Haemophilus influenzae*.

Uncomplicated Gonorrhea (cervical/urethral)

Cefixime is indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated gonorrhea (cervical/urethral) caused by susceptible isolates of *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing isolates).

Usage

To reduce the development of drug resistant bacteria and maintain the effectiveness of Cefixime and other antibacterial drugs, Cefixime should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration:

Adults

The recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg tablet or capsule daily every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended. The capsule and tablet may be administered without regard to food.

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

Therefore, the tablet or capsule should not be substituted for the suspension in the treatment of otitis media.

In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of cefixime should be administered for at least 10 days.

Method of administration: Orally



4.3 Contraindications:

Cefixime is contraindicated in patients with known allergy to cefixime or other cephalosporins.

4.4 Special warning and precautions:

Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Before therapy with Cefixime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefixime occurs, discontinue the drug.

Clostridium difficile-Associated Diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including Cefixime, and may range in severity from mild diarrhoea 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 isolates 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, on-going 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.

Dose Adjustment in Renal Impairment

The dose of Cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis (HD). Patients on dialysis should be monitored carefully.

***Coagulation Effects***

Cephalosporins, including Cefixime, 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.

Development of Drug-Resistant Bacteria

Prescribing Cefixime (cefixime) in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5 Interactions with Other Medicaments***Carbamazepine***

Elevated carbamazepine levels have been reported in post marketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

Warfarin and Anticoagulants

Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is administered concomitantly.

Drug/Laboratory Test Interactions

A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of cefixime may result in a false-positive reaction for glucose in the urine using Clinitest® **, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix® ** or TesTape® **) be used. A false-positive direct Coombs test has been reported during treatment with other cephalosporins; therefore, it should be recognized that a positive Coombs test may be due to the drug.

4.6 Fertility, pregnancy and lactation***Pregnancy***



Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 40 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies 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.

Labor and Delivery

Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Lactation

It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A pharmacokinetic study in the elderly detected differences in pharmacokinetic parameters [see Clinical Pharmacology (12.3)]. These differences were small and do not indicate a need for dosage adjustment of the drug in the elderly.

Renal Impairment

The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully.

4.7 Effects on ability to drive and use machine:

In the case of side effects such as encephalopathy (which may include convulsion, confusion, impairment of consciousness, movement disorders), the patient should not operate machines or drive a vehicle.

4.8 Undesirable effects:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.



The most commonly seen adverse reactions in U.S. trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the twice daily or the once daily regimen. Five percent (5%) of patients in the U.S. clinical trials discontinued therapy because of drug-related adverse reactions. Individual adverse reactions included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 4%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients receiving tablets.

Post-marketing Experience

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%).

Gastrointestinal

Several cases of documented pseudomembranous colitis were identified in clinical trials. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic

Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal

Transient elevations in BUN or creatinine, acute renal failure

Central Nervous System

Headaches, dizziness, seizures

Hemic and Lymphatic System

Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia

Abnormal Laboratory Tests

Hyperbilirubinaemia

Other Adverse Reactions

Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis



Adverse Reactions Reported for Cephalosporin-class Drugs

Allergic reactions, super infection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, haemorrhage, and colitis.

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.

4.9 Overdose:

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: third generation cephalosporin, ATC code: J01DD08

Cefixime is an oral third generation cephalosporin which has marked *in vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative),

Branhamella catarrhalis (beta -lactamase positive and negative) and *Enterobacter* species. It is highly stable in the presence of beta-lactamase enzymes.

Most strains of enterococci (*Streptococcus faecalis*, group D Streptococci) and Staphylococci (including coagulase positive and negative strains and methicillin-resistant strains) are resistant to Cefixime. In addition, most strains of *Pseudomonas*, *Bacteroides fragilis*, *Listeria monocytogenes* and *Clostridia* are resistant to Cefixime.

Mechanism of Action

As with other cephalosporins, the bactericidal action of cefixime results from inhibition of cell wall synthesis. Cefixime is stable in the presence of certain beta-lactamase enzymes. As a result, certain



organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases may be susceptible to cefixime.

Resistance

Resistance to cefixime in isolates of *Haemophilus influenzae* and *Neisseria gonorrhoeae* is most often associated with alterations in penicillin-binding proteins (PBPs). Cefixime may have limited activity against Enterobacteriaceae producing extended spectrum beta-lactamases (ESBLs). *Pseudomonas* species, *Enterococcus* species, strains of Group D streptococci, *Listeria monocytogenes*, most strains of staphylococci (including methicillin-resistant strains), most strains of *Enterobacter* species, most strains of *Bacteroides fragilis*, and most strains of *Clostridium* species are resistant to cefixime.

Antimicrobial Activity

Cefixime has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections

Gram-positive Bacteria

Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative Bacteria

Escherichia coli

Haemophilus influenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

Proteus mirabilis

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for cefixime against isolates of similar genus or organism group. However, the efficacy of cefixime in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive Bacteria

Streptococcus agalactiae

Gram-negative Bacteria

Citrobacter amalonaticus

Citrobacter diversus

Haemophilus parainfluenzae



Klebsiella oxytoca

Klebsiella pneumoniae

Pasteurella multocida

Proteus vulgaris

Providencia species

Salmonella species

Serratia marcescens

Shigella species

5.2 Pharmacokinetic Properties:

Absorption

The 100 mg capsule is bioequivalent to the 100 mg under fasting conditions. However, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on C_{max}.

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg, a single 400 mg or 400 mg of Cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension. Peak serum concentrations occur between 3 and 8 hours following oral administration of a single 400 mg capsule.

Distribution

Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. Adequate data on CSF levels of Cefixime are not available.

Metabolism

There is no evidence of metabolism of Cefixime in vivo.

Elimination

Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that Cefixime is also excreted in the bile in excess of 10% of the administered dose. The serum half-life of Cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours but may range up to 9 hours in some normal volunteers.



5.3 Preclinical safety Data:

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage in vitro and did not exhibit clastogenic potential in vivo in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by Cefixime at doses up to 25 times the adult therapeutic dose.



6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Dibasic Calcium Phosphate

Colloidal Silicon Dioxide-Aerosil

Talc

Sodium Lauryl Sulphate

Magnesium Stearate

HEG Capsules 'O' size purple/white printed plain

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

2 years

6.4 Special precautions for storage:

Store below 30° C. Keep away from the reach of children

6.5 Nature and contents of container:

Alu/Alu Blister pack of 1 x 10's

6.6 Special precautions for disposal

No special requirements

7. Marketing Authorization Holder:

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

INDIA

8. Marketing Authorization Numbers

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MICRO LABS LIMITED, INDIA

SUMMARY OF PRODUCT CHARACTERISTICS

CEFIXIME CAPSULES 200mg (GRAMOCEF O 400)



9. Date of first authorization

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10. Date of revision of the text

Jan 2021