CEFIXIME CAPSULES 200/400mg

GRAMOCEF-O 200/400

13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
GRAMOCEF-O-200 (Cefixime Capsules 200mg)

13.1 Strength:
200/400mg

13.2 Pharmaceutical form
Capsules

14. Quality and Quantitative Composition
Each Capsule Contains:
Cefixime USP as Trihydrate equivalent to anhydrous Cefixime……. 200 mg
Cefixime USP as Trihydrate equivalent to anhydrous Cefixime……. 400 mg

15. Pharmaceutical Form
Capsules

16. Clinical Particulars
16.1 Therapeutic indications
Cefixime is an orally active cephalosporin antibiotic which has marked *in vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.
It is indicated for the treatment of the following acute infections when caused by susceptible micro-organisms:
Upper Respiratory Tract Infections (URTI): e.g. otitis media; and other URTI where the causative organism is known or suspected to be resistant to other commonly used antibiotics, or where treatment failure may carry significant risk.
Lower Respiratory Tract Infection: e.g. bronchitis.
Urinary Tract Infections: e.g. cystitis, cystourethritis, uncomplicated pyelonephritis.
Clinical efficacy has been demonstrated in infections caused by commonly occurring pathogens including *Streptococcus pneumoniae, Streptococcus pyogenes, Escherichia coli, Proteus mirabilis, Kliebsiella* species, *Haemophilus influenzae* (beta-lactamase positive and negative), *Branhamella catarrhalis* (beta-lactamase positive and negative) and *Enterobacter* species. Cefixime 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 meticillin-resistant strains) are resistant to Cefixime. In addition, most strains of *Pseudomonas, Bacteriodes fragalis, Listeria monocytogenes* and *Clostridia* are resistant to Cefixime.

16.2 Posology and method of administration
Absorption of Cefixime is not significantly modified by the presence of food. The usual course of treatment is 7 days. This may be continued for up to 14 days if required.
Adults and Children over 10 Years: The recommended adult dosage is 100-200 mg daily according to the severity of infection, given either as a single dose or in two divided doses.
The Elderly: Elderly patients may be given the same dose as recommended for adults. Renal function should be assessed and dosage should be adjusted in severe renal impairment.

Children weighing more than 50 kg or older than 10 years should be treated with the recommended adult dose (100 - 200 mg daily depending on the severity of infection).
The safety and efficacy of Cefixime has not been established in children less than 6 months.

16.3 Method of administration
For oral use

16.4 Contraindications
Patients with known hypersensitivity to cephalosporin antibiotics or any of the other components of the product.

16.5 Special warning and precautions
Severe cutaneous adverse reactions: Severe cutaneous adverse reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in some patients on Cefixime. When severe cutaneous adverse reactions occur, Cefixime should be discontinued and appropriate therapy and/or measures should be taken.
Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs.
Hypersensitivity to penicillins
As with other cephalosporins, Cefixime should be given with caution to patients with a history of hypersensitivity to penicillin, as there is some evidence of partial cross-allergenicity between the penicillins and cephalosporins.
Patients have had severe reactions (including anaphylaxis) to both classes of drugs. If an allergic effect occurs with Cefixime, the drug should be discontinued and the patient treated with appropriate agents if necessary.
Renal failure acute
As with other cephalosporins, Cefixime may cause acute renal failure including tubulointerstitial nephritis as an underlying pathological condition. When acute renal failure occurs, Cefixime should be discontinued and appropriate therapy and/or measures should be taken.
Renal impairment
Cefixime should be administered with caution in patients with markedly impaired renal function *Pediatric use*
Safety of Cefixime in premature or newborn infant has not been established.
Treatment with broad spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of antibiotic-associated diarrhoea. Pseudo membranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillin's, lincosamides and cephalosporin's); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Symptoms of pseudo membranous colitis may occur during or after antibiotic treatment.
Management of pseudo membranous colitis should include sigmoidoscopy, appropriate bacteriologic studies, fluids, electrolytes and protein supplementation. If the colitis does not improve after the drug has been discontinued, or if the symptoms are severe, oral vancomycin is the drug of choice for antibiotic-associated pseudo membranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

16.6 Paediatric population
None

16.7 Interaction with other medicinal products and other forms of interactions
Anticoagulants
In common with other cephalosporins, increases in prothrombin times have been noted in a few patients. Care should therefore be taken in patients receiving anticoagulation therapy.
Cefixime should be administered with caution to patients receiving coumarin-type anticoagulants, e.g. warfarin potassium. Since Cefixime may enhance effects of the *anticoagulants, prolonged prothrombin time with or without bleeding may occur.*

Other forms of interaction
A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions, but not with tests based on enzymatic glucose oxidase reactions. A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics, therefore it should be recognized that a positive Coombs test may be due to the drug.

16.8 Additional information on special populations
None

16.9 Paediatric population
None

16.10 Fertility, pregnancy and lactation
16.10.1 General principles
16.10.2 Women of childbearing potential / Contraception in males and females
Not known

16.10.3 *Pregnancy*
Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus due to Cefixime. In the rabbit, at doses up to 4 times the human dose, there was no evidence of a teratogenic effect; there was a high incidence of abortion and maternal death which is an expected consequence of the known sensitivity of rabbits to antibiotic-induced changes in the population of the micro flora of the intestine.

16.10.4 *Lactation*
There are no adequate and well-controlled studies in pregnant women. Gramocef should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

16.4.5 *Fertility*
None

16.11 Effects on ability to drive and use machine
None

16.12 Undesirable effects
Cefixime is generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.
The following adverse reaction (Preferred term# or equivalent) will be considered listed:

Blood and lymphatic system disorders:	Eosinophilia Hypereosinophilia Agranulocytosis Leucopenia Neutropenia Granulocytopenia Haemolytic anaemia Thrombocytopenia Thrombocytosis

Gastrointestinal:	Abdominal pain Diarrhoea Dyspepsia Nausea Vomiting Flatulence
Hepatobiliary disorders:	Jaundice
Infections and infestations:	Pseudomembranous colitis
Investigations:	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased
Nervous system disorders:	Dizziness Headache
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Renal and urinary disorders:	Renal failure acute including tubulointerstitial nephritis as an underlying pathological condition
Immune System disorders, administrative site conditions, skin and subcutaneous tissue disorders:	Anaphylactic reaction Serum sickness-like reaction Drug rash with eosinophilia and systemic symptoms (DRESS) Pruritus Rash Drug Fever Arthralgia Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Angio-oedema Urticaria Pyrexia Face oedema Genital pruritus Vaginitis

The above mentioned listed adverse reactions have been observed during clinical studies and/or during marketed use.

Diarrhoea has been more commonly associated with higher doses. Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Cefixime should be discontinued if marked diarrhoea occurs

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

16.13 Overdose

There is no experience with overdoses with Cefixime.

Adverse reactions seen at dose levels up to 2 g Cefixime in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Cefixime is not removed from the circulation in significant quantities by dialysis.

No specific antidote exists. General supportive measures are recommended.

17. Pharmacological Properties

17.1 Pharmacodynamic Properties

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 meticillin-resistant strains) are resistant to Cefixime. In addition, most strains of *Pseudomonas, Bacteroides fragilis, Listeria monocytogenes* and *Clostridia* are resistant to Cefixime.

17.2 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 Cmax.

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.

17.3 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.

17.4 Environmental Risk Assessment (ERA)
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

18. Pharmaceutical Particulars
18.1 List of excipients
Dibasic Calcium Phosphate (Anhydrous)
Colloidal silicon Dioxide (Aerosil 200)
Talc
Sodium Lauryl Sulphate
Magnesium Stearate
HEG Cap 2 Light Green Dark Green Micro/Micro printed

18.2 Incompatibilities
None

18.3 Shelf life
36 months from the date of manufacturing.

18.4 Special precautions for storage
Store below 30°C. Keep out from the reach of children

18.5 Nature and contents of container
10 Capsules are packed in ALU/ ALU Blisters.
Such 1 Blisters is then packed in a printed outer carton along with a pack insert

18.6 Special precautions for disposal and other handling
None

19. Marketing Authorization Holder and Manufacturing Site Addresses
No.121-124, 4th Phase, K.I.A.D.B, Bommasandra Industrial Area,
Bangalore, India

20. Marketing Authorisation Number
FDA-HMP-MA-0093

21. Date of First Registration/Renewal of the registration
5th August 2021

22. Date of revision of the text
August 2021

23. DOSIMETRY
Not applicable

24. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
Not applicable