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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. Name of the Medicinal Product

(a) Product Name : FEXOPOXIME 400 TABLET
(b) Strength : 400 mg
(c) Pharmaceutical Dosage Form : Tablet

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Each Film Coated Tablet contains:
Cefixime Trihydrate U.S.P.
Equivalent to Anhydrous Cefixime 400 mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Ingredient	**Spec.**	**Claim**	**Overages**	**Qty./tab**	**Functions**
Active Ingredient					
Cefixime Trihydrate Eq. to Anhydrous Cefixime	U.S.P.	400 mg	1.0%	452.47 mg	Active
Inactive Ingredient					
Maize Starch	B.P.	---	---	95.40 mg	Binder
Microcrystallinecellulose	B.P.	---	---	106.61mg	Diluent
Methylparaben	B.P.	---	---	0.990 mg	Preservative
Propylparaben	B.P.	---	---	0.099 mg	Preservative
Magensium Stearate	B.P.	---	---	7.188 mg	Lubricant
Purified Talc	B.P.	---	---	36.00 mg	Glidant
Sodium Starch Glycolate	B.P.	---	---	14.00 mg	Disintegrant
Colloidal Silicon Dioxide	B.P.	---	---	7.207 mg	Glidant
Hydroxypropylmethylcellulose	B.P.	---	---	12.99 mg	Film former
Isopropyl Alcohol	B.P.	---	---	3.584 mg	Solvent
Ethylcellulose	B.P.	---	---	84.00 mg	Coating Agent
Methylene Chloride	B.P.	---	---	350.00 mg	Solvent
Titanium Dioxide	B.P.	---	---	8.079 mg	Colorant

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.: White colour, oblong biconvex and film coated tablet. One side smooth and other side mid divide line.

4. Clinical Particulars

4.1 Therapeutic indications:
FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) is an orally active cephalosporin antibiotic which has marked *in vitro* bactericidal activity against a wide variety of Gram-positive and Gram-negative organisms.

FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) 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 occuring 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 Trihydrate 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 Trihydrate. In addition, most strains of *Pseudomonas*, *Bacteriodes fragalis*, *Listeria monocytogenes* and *Clostridia* are resistant to Cefixime Trihydrate.

4.2 Posology and method of administration:
Posology
Absorption of FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) 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 200-400 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 (Use Paediatric Oral Suspension): The recommended dosage for children is 8 mg/kg/day administered as a single dose or in two divided doses. As a general guide for prescribing in children the following daily doses in terms of volume of Paediatric Oral Suspension are suggested:

6 months up to 1 year:	3.75 ml daily
Children 1-4 years:	5 ml daily
Children 5-10 years:	10 ml daily

Children weighing more than 50 kg or older than 10 years should be treated with the recommended adult dose (200 - 400 mg daily depending on the severity of infection).

The safety and efficacy of FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) has not been established in children less than 6 months.

Dosage In Renal Impairment: FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) may be administered in the presence of impaired renal function. Normal dose and schedule may be given in patients with creatinine clearances of 20 ml/min or greater. In patients whose creatinine clearance is less than 20 ml/min, it is recommended that a dose of 200 mg once daily should not be exceeded. The dose and regimen for patients who are maintained on chronic ambulatory peritoneal dialysis or haemodialysis should follow the same recommendation as that for patients with creatinine clearances of less than 20 ml/min.

Method of administration:
Oral use

4.3 Contraindications:
Hypersensitivity to the Cefixime or to any of the excipients of formulation.

4.4 Special warning and precautions for use:
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.

FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) 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 FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg), the drug should be discontinued and the patient treated with appropriate agents if necessary.

Haemolytic anaemia
Drug-induced haemolytic anaemia, including severe cases with a fatal outcome, has been described for cephalosporins (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporins in a patient with a history of cephalosporin (including cefixime) –associated haemolytic anaemia has also been reported.

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 Trihydrate should be administered with caution in patients with markedly impaired renal function.

Paediatric 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. Pseudomembranous colitis is associated with the use of broad-spectrum antibiotics (including macrolides, semi-synthetic penicillins, lincosamides and cephalosporins); it is therefore important to consider its diagnosis in patients who develop diarrhoea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment.

Management of pseudomembranous 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 pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

4.5 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 or with copper sulphate test tablets, 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 recognised that a positive Coombs test may be due to the drug.

4.6 Pregnancy and Lactation:
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 microflora of the intestine.

There are no adequate and well-controlled studies in pregnant women.

FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) should therefore not be used in pregnancy or in nursing mothers unless considered essential by the physician.

4.7 Effects on ability to drive and use machine:
Not relevant.

4.8 Undesirable effects:
Cefixime Trihydrate 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, Flatulance

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 eaosinophilia 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 Trihydrate should be discontinued if marked diarrhoea occurs

4.9 Overdose
No case of overdose has been reported.

Adverse reactions seen at dose levels up to 2 g Cefixime Trihydrate 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

5 Pharmacological Properties

5.1 Pharmacodynamic Properties: General Pharmacodynamic Effect

Pharmacotherapeutic group: third-generation cephalosporins, ATC-Code: J01DD08

Mechanism of action
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.

5.2 Pharmacokinetic Properties:
Absorption and bioavailability
The absolute oral bioavailability of cefixime is in the range of 22-54%. Absorption is not significantly modified by the presence of food. Cefixime may therefore be given without regard to meals.

Distribution
From *in vitro* studies, serum or urine concentrations of 1 mcg/mL or greater were considered to be adequate for most common pathogens against which cefixime is active. Typically, the peak serum levels following the recommended adult or paediatric doses are between 1.5 and 3 mcg/ mL. Little or no accumulation of cefixime occurs following multiple dosing.

The pharmacokinetics of cefixime in healthy elderly (age > 64 years) and young volunteers (11-35) compared the administration of 400 mg doses once daily for 5 days. Mean C_{max} and AUC values were slightly greater in the elderly. Elderly patients may be given the same dose as the general population.

Metabolism

Serum protein binding is well characterised for human and animal sera; cefixime is almost exclusively bound to the albumin fraction, the mean free fraction being approximately 30%. Protein binding of cefixime is only concentration dependent in human serum at very high concentrations which are not seen following clinical dosing.

Transfer of ^{14}C-labelled cefixime from lactating rats to their nursing offspring through breast milk was quantitatively small (approximately 1.5% of the mothers' body content of cefixime in the pup). No data are available on secretion of cefixime in human breast milk. Placetal transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

Excretion

Cefixime is predominantly eliminated as unchanged drug in the urine. Glomerular filtration is considered the predominant mechanism. Metabolites of cefixime have not been isolated from human serum or urine.

5.3 Preclinical Safety Data:

Non-clinical data reveal no special hazard for humans based on 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.

6.0 Pharmaceutical Particulars

6.1 List of excipients:

Sr. No.	Name of the Materials	Specification
1	Maize Starch	B.P.
2	Microcrystallinecellulose	B.P.
3	Methylparaben	B.P.
4	Propylparaben	B.P.
5	Magensium Stearate	B.P.
6	Purified Talc	B.P.
7	Sodium Starch Glycolate	B.P.
8	Colloidal Silicon Dioxide	B.P.
9	Hydroxypropylmethylcellulose	B.P.
10	Isopropyl Alcohol	B.P.
11	Ethylcellulose	B.P.
12	Methylene Chloride	B.P.

13	Titanium Dioxide	B.P.

6.2 Incompatibilities:
Not applicable.

6.3 Shelf life:
The shelf of FEXOPOXIME 400 TABLET (Cefixime Tablets USP400 mg) from the date of manufacture is 36 Months.

6.4 Special precautions for storage:
Store protected from light and moisture at a temperature below 30°C. Keep medicine out of reach of children.

6.5 Nature and contents of container:
White colour, oblong biconvex and film coated tablet. One side smooth and other side mid divide line.
1×10 Tablets in ALU-ALU Blister pack.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 Applicant/Manufacturer

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