# National Agency for Food & Drug Administration &

# Control (NAFDAC)

# Registration & Regulatory Affairs (R & R)

# Directorate

# SUMMARY OF PRODUCT CHARACTERISTICS

**ARCERIN TABLETS**

## 1. NAME OF THE MEDICINAL PRODUCT

Cefixime Tablets USP 400 mg

**Strength**

Cefixime 400 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Cefixime (As Trihydrate) USP
Eq. to Anhydrous Cefixime……400 mg
Excipients……..….q.s.
Colour: Titanium Dioxide BP

| Sr. No. | Ingredient | Specification | Quantity in mg/ Tablet |
|---|---|---|---|
| 1. | Cefixime (As Trihydrate) eq.to Anhydrous Cefixime | USP | 400 |
| 2. | **Microcrystalline Cellulose PH-102) | BP | 340.00 |
| 3. | Croscarmellose Sodium | BP | 16.00 |
| 4. | Crospovidone | BP | 20.00 |
| 5. | Purified Talc | BP | 6.00 |
| 6. | Magnesium Stearate | BP | 10.00 |
| 7. | Colloidal Anhydrous Silica | BP | 8.00 |
| 8. | # Microcrystalline Cellulose (PH-102) | BP | 20.00 |
| 9. | Hypromellose (E-5) | BP | 3.00 |
| 10. | Ethyl Cellulose | USP/NF | 1.5 |
| 11. | Titanium Dioxide | BP | 5.00 |

| | | | |
|---|---|---|---|
| 12. | Hypromellose (E-15) | BP | 9.00 |
| 13. | Dibutyl Phthalate | BP | 1.00 |
| 14. | Purified Talc | BP | 1.00 |
| 15. | Isopropyl Alcohol | BP | 117.74 |
| 16. | Dichloromethane | BP | 399.20 |

*The quantity of API may vary depending on potency/Assay/% LOD/water/Moisture content
**The Qty. of Microcrystalline Cellulose (PH-102) may vary according to API.
# Extra Microcyrstalline Cellulose (PH-102) added due to loss on drying

## 3. PHARMACEUTICAL FORM

Oral Solid Dosage Form
Off white colour oblong shape, biconvex film coated tablets having breakline on one side and other side plain.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Cefixime is an orally active cephalosporin antibiotic which has marked in vitro bacteriocidal 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 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 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.

**4.2 Posology and Method of administration**

The usual course of treatment is 7 days. This may be continued for up to 14 days if required.

Posology

***Adults and Children over 10 Years or weighing more than 50 kg*:**

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.

***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 (See "Dosage in Renal Impairment").

***Children under 10 Years*:**

Cefixime Tablets 200 mg are not recommended for use in children under 10 years old.

The safety and efficacy of cefixime has not been established in children less than 6 months.

***Renal Impairment*:**

Cefixime 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 for administration

For oral administration.

Absorption of Cefixime is not significantly modified by the presence of food.

**4.3 Contraindications**

Hypersensitivity to cephalosporin antibiotics or to any of the excipients .

**4.4 Special Warnings and Precautions for use**

**Encephalopathy**

Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment.

**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.

**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.

**Acute renal failure**

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 (See section 4.2).

**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 interaction**
**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 Fertility, 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. Cefixime 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 machines**

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**
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<br>Hypereosinophilia<br>Agranulocytosis<br>Leucopenia<br>Neutropenia<br>Granulocytopenia<br>Haemolytic anaemia<br>Thrombocytopenia<br>Thrombocytosis |

| | |
|---|---|
| Gastrointestinal disorders: | Abdominal pain<br>Diarrhoea*<br>Dyspepsia<br>Nausea<br>Vomiting<br>Flatulance |
| Hepatobiliary disorders: | Jaundice |
| Infections and infestations: | Pseudomembranous colitis |
| Investigations: | Aspartate aminotransferase increased<br>Alanine aminotransferase increased<br>Blood bilirubin increased<br>Blood urea increased<br>Blood creatinine increased |
| Nervous system disorders: | Dizziness<br>Headache<br>Cases of convulsions have been reported with cephalosporins including cefixime (frequency not known)**<br>Beta-lactams, including cefixime, predispose the patient to encephalopathy risk (which may include convulsions, confusion, impairment of consciousness, movement disorders), particularly in case of overdose or renal impairment (frequency not known)** |
| 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<br>Serum sickness-like reaction<br>Drug rash with eaosinophilia and systemic symptoms (DRESS)<br>Pruritus<br>Rash<br>Drug Fever<br>Arthralgia<br>Erythema multiforme<br>Stevens-Johnson syndrome<br>Toxic epidermal necrolysis<br>Angio-oedema<br>Urticaria<br>Pyrexia<br>Face oedema<br>Genital pruritus |

| | |
|---|---|
| | Vaginitis |

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

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

**Pharmacotherapeutic group**: third generation cephalosporin,

**ATC code**: J01DD08

**Mechanism of resistance:**

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

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.

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.

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.

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.

### 5.3 Preclinical safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the Summary of Product Characteristics.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Microcrystalline cellulose (pH-102)
Croscarmellose sodium
Crospovidone
Purified Talc
Magnesium Stearate
Colloidal Anhydrous Silica
Hypromellose (E-5)
Ethyl Cellulose
Titanium Dioxide
Hypromellose (E-15)
Dibutyl phthalate
Purified talc
Isopropyl Alcohol
Dichloromethane

### 6.2 Incompatibilities

None

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in dry place, protected from light.

### 6.5 Nature and contents of container

Alu- Alu blister pack of 1x10 tablets packed in a carton along with a package insert.

**6.6 Special precautions for disposal**

No special requirements

## 7. APPLICANT/MANUFACTURER

**MARKETING AUTHORISATION HOLDER**
JB PHARMACEUTICALS
40B, COMMERCIAL AVENUE,
P.O. BOX 1828, SABO-YABA,
LAGOS, NIGERIA

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