1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

CEFIXIME 400MG

INN (GENERIC NAME)

Cefixime USP 400 mg Tablets

1.2 Strength: - 400 mg

1.3 Pharmaceutical form: - Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEFIXIME 400MG
(Cefixime Tablets USP 400 mg)
Each film coated tablet contains:
Cefixime Trihydrate USP
Equivalent to Cefixime (anhydrous) (400 mg)
Approved colour used. (-)
Excipients: (0 QS)
Batch Size: 5,05,000 Tablets

Sr. No.	Ingredients	Specification	Label amount mg	% Overages	Qty. / Tablet mg	Reason for Inclusion
1.	Cefixime Trihydrate*	USP	400	4.5%	468.00	Active

USP = United State Pharmacopoeia

3. PHARMACEUTICAL FORM:

Pink coloured, elongated, biconvex, film coated tablets, having a break line on one side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Cefixime is indicated for the treatment of the following infections when caused by susceptible organisms:
Acute exacerbations of chronic bronchitis
Community-acquired Pneumonia
Lower urinary tract infections
Pyelonephritis
In the treatment of:
Otitis media
Sinusitis
Pharyngitis
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration:

Posology
Adults: The recommended adult dosage is 400 mg daily, given either as a single dose or in two divided doses of 200 mg every 12 hours.
Older people
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”).

Adolescents 12 years of age and older
should be treated with the recommended adult dose (400 mg daily, given either as a single dose or in two divided doses of 200 mg every 12 hours).
Children younger than 12 years of age
The pharmaceutical form tablet is not suitable for children younger than 12 years.
Renal insufficiency
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.
There are insufficient data regarding use of cefixime in pediatric and adolescent age groups in the presence of renal insufficiency. Therefore, the use of cefixime in these patient-groups is not recommended.
Duration of treatment
The usual course of treatment is 7 days. This may be continued for up to 14 days according the severity of the infection.
For acute uncomplicated cystitis in women, the treatment period is 1-3 days.
Method of administration
Cefixime tablets are for oral administration only. Cefixime should be taken with a sufficient amount of water. Cefixime may be taken with or without food.

4.3 Contraindications:
Hypersensitivity to the active substance, to other cephalosporin antibiotic.
Previous, immediate and/or severe hypersensitivity reaction to penicillin or any beta-lactam antibiotic.
4.4 Special warnings and precautions for use:
Cefixime should be given with caution to patients who have shown hypersensitivity to other drugs. Cephalosporins should be given with caution to penicillin-sensitive patients, as there is some evidence of partial cross-allergenicity between the penicillin and cephalosporins.

Patients have had severe reactions (including anaphylaxis) to both classes of drugs. Special care is indicated in patients who have experienced any allergic reaction to penicillin or any other beta-lactam antibiotics as cross-reactions may occur.

If severe hypersensitivity reactions or anaphylactic reactions occur after administration of cefixime, the use of cefixime should be discontinued immediately and appropriate emergency measures should be initiated.

Renal insufficiency
Cefixime should be administered with caution in patients with creatinine clearance < 20 ml / min. There are insufficient data regarding use of cefixime in the pediatric and adolescent age group in the presence of renal insufficiency. Therefore, the use of cefixime in these patient- groups is not recommended.

Renal function is to be monitored under a combination therapy with cefixime preparations and aminoglycoside antibiotics, polymyxin B, colistin or high-dose loop diuretics (e.g. furosemide) because of the probability of additional renal impairment. This applies particularly for patients with already restricted renal function.

Treatment with cefixime at the recommended (400 mg) dose can significantly alter the normal flora of the colon and lead to overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of antibiotic-associated diarrhea. In patients who develop severe persistent diarrhea during or after use of cefixime, the risk of life-threatening pseudomembranous colitis should be taken into account. The use of cefixime should be discontinued and appropriate treatment measures should be established. The use of medicinal products inhibiting the intestinal peristalsis is contraindicated.
Prolonged use of cefixime may result in the overgrowth of non-susceptible organisms.
Severe skin reactions such as drug hypersensitivity syndrome (DRESS) or bullous skin reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome) have been reported in patients treated with cefixime. If such reactions occur, cefixime should be immediately stopped.

4.5 Interaction with other medicinal products and other forms of interaction:
Concomitant intake with potentially nephrotoxic substances (such as aminoglycoside antibiotics, colistin, polymyxin and viomycin) and strong-acting diuretics (e.g. ethacrynic acid or furosemide) induce an increased risk of impairment of renal function.

Nifedipine, a calcium channel blocker, may increase bioavailability of cefixime up to 70 %.
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.

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

4.6 Pregnancy and lactation:

Pregnancy
There are no adequate data from the use of cefixime in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/ fetal development, parturition or postnatal development. As a precautionary measure,
Cefixime should not be used in pregnant mothers unless considered essential by the physician.

Breast-feeding

It is unknown whether cefixime is excreted in human milk. Non-clinical studies have shown excretion of cefixime in animal milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with cefixime should be made taking into account the benefit of breast-feeding to the child and the benefit of cefixime therapy to the woman. However, until further clinical experience is available, Cefixime should not be prescribed to breast-feeding mothers.

Fertility

Reproduction studies performed in mice and rats do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines:

Cefixime has no known influence on the ability to drive and use machines.

4.8 Undesirable Effects:

In this section, the following convention has been used for the classification of undesirable effects in terms 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 ≥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**	**Not known (cannot be estimated from the available data)**
Infections and infestations			Superinfection bacterial, superinfection fungal	Antibiotic associated colitis	
Blood and lymphatic system disorders			Eosinophilia	Leucopenia, agranulocytosis, pancytopenia, thrombocytopenia, haemolytic anaemia	THROMBOCYTOSIS, NEUTROPENIA
Immune system disorders			Hypersensitivity	Anaphylactic shock, serum sickness	
Metabolism and nutrition			Anorexia		

disorders					
Nervous system disorders		Headache	Vertigo	Psychomotor hyperactivity	
Gastrointestinal disorders	Diarrhea	Abdominal pain, nausea, vomiting	Flatulence		
Hepatobiliary disorders				Hepatitis, cholestatic jaundice	
Skin and subcutaneous tissue disorders		Rash	Angioneurotic oedema, pruritus	Stevens-Johnson syndrome, toxic epidermal necrolysis	Drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme
Renal and urinary disorders				Interstitial nephritis	
General disorders and administration site conditions			Mucosal inflammation, pyrexia		
Investigations		Hepatic enzyme increased (transaminase, alkaline phosphatase)	Blood urea increased	Blood creatinine increased.	Direct and indirect positive Coombs tests

4.9 OVERDOSE:

There is no experience with cefixime overdose.

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. Gastric lavage may be indicated in overdosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by hemodialysis or peritoneal dialysis.

5 Pharmacological Properties:

5.1 Pharmacodynamic properties:
Pharmacotherapeutic group: ATC code: J01DD08.

Mode of Action
Cefixime is an antibacterial agent of the cephalosporin class. Like other cephalosporins, cefixime exerts antibacterial activity by binding to and inhibiting the action of penicillin binding proteins involved in the synthesis of bacterial cell walls. This leads to bacterial cell lysis and cell death.

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

- Hydrolysis by extended-spectrum beta-lactamases and / or by chromosomally-encoded (AmpC) enzymes that may be induced or derepressed in certain aerobic gram-negative bacterial species
- Reduced affinity of penicillin-binding proteins
- Reduced permeability of the outer membrane of certain gram-negative organisms restricting access to penicillin-binding proteins
- Drug efflux pumps

More than one of these mechanisms of resistance may co-exist in a single bacterial cell. Depending on the mechanism(s) present, bacteria may express cross-resistance to several or all other beta-lactams and / or antibacterial drugs of other classes.

Breakpoints
Clinical minimum inhibitory concentration (MIC) breakpoints established by EUCAST (May 2009) for cefixime are:

- H.influenzae: sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L
- M.catarrhalis: sensitive ≤ 0.5 mg/L, resistant > 1.0 mg/L
- Neisseria gonorrhoeae: sensitive ≤ 0.12 mg/L, resistant > 0.12 mg/L
- Enterobacteriaceae: sensitive ≤ 1.0 mg/L, resistant > 1.0 mg/L (for uncomplicated urinary tract infections only).
- The breakpoints for Enterobacteriaceae will detect reduced susceptibility mediated by most clinically important beta-lactamases in Enterobacteriaceae. Occasional ESBL-producing strains will be reported susceptible. For purposes of infection control, epidemiology and surveillance, laboratories may wish to use specific tests to screen for and confirm ESBL-production.
- Non-species related breakpoints: insufficient evidence

*Isolates with MIC values above the susceptible breakpoint are very rare or not yet reported. The
identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the
result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC values above the current resistant breakpoint they should be reported resistant.

Susceptibility
The prevalence of resistance may vary geographically and over 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.

Commonly susceptible species
Aerobes, Gram positive: *Streptococcus pyogenes*
Aerobes, Gram negative: *Haemophilus influenzae* *Moraxella catarrhalis* *Neisseria gonorrhoeae* *Proteus mirabilis%*
Species for which resistance may be a problem
Aerobes, Gram positive: *Streptococcus pneumoniae* Aerobes, Gram negative: *Citrobacter freundii $* *Enterobacter cloacae $* *Escherichia coli % &* *Klebsiella oxytoca %* *Klebsiella pneumoniae %* *Morganella morgani $* *Serratia marcescens $*
Inherently Resistant species
Aerobes, Gram positives: *Enterococci* *Streptococcus pneumoniae* (Penicillin-intermediate and -resistant) *Staphylococcus spp.* Aerobes, Gram-negative
Pseudomonas species Other micro-organism *Chlamydia spp.* *Chlamydophila spp.* *Clostridium difficile* *Bacteroides fragilis* *Legionella pneumophila* *Mycoplasma spp.* *Staphylococcus aureus+*

+ Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin).
$ Natural intermediate susceptibility.
% Extended spectrum beta-lactamase (ESBL) producing strains are always resistant.
& Resistance rate <10% in isolates of female patients with uncomplicated cystitis, otherwise >10%.

5.2 Pharmacokinetic properties:
Absorption:

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:

Serum protein binding is well characterized 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.

From *in vitro* studies, serum or urine concentrations of 1 mg/L 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 pediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

Biotransformation and elimination:

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 Cmax 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.

Transfer of 14C-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.

Placental transfer of cefixime was small in pregnant rats dosed with labelled cefixime.

Pharmacokinetic/pharmacodynamic relationship

The time that the plasma concentration of cefixime exceeds the MIC of the infecting organism has been shown to best correlate with efficacy in PK/PD studies.

5.3 Preclinical safety data:

There are no findings from chronic toxicity investigations suggesting that any side effects unknown to date could occur in humans. Furthermore, *in vivo* and *in vitro* studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted. 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 fetus 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.

6 Pharmaceutical Particulars

6.1 List of Excipients.

Cefixime Trihydrate, Maize Starch. Sodium Starch Glyclate. Lactose. Methylene Chloride, P.V.P.K. 30, Purified Talc, Magnesium Sterate, Cross Carmellose Sodium, Colloidal Silicon Dioxide, H.P.M.C. E15 cps, Titanium Dioxide, Purified Talc, P.E.G. 4000, Propylene Glycol, Color Erythrosine Lake, Isopropyl Alcohol.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 Years

6.4 Special precautions for storage
Store in cool & dry place

6.5 Nature and contents of container
Blister pack of 10 tablets (10X1X10)

7. APPLICANT/ MANUFACTURER
APPLICANT:
HOMMAGE INTERNATIONAL SERVICES. LTD.
No. 35, Lusaka street, Wuse zone 6, Abuja , Nigeria.

MANUFACTURED BY:
MEDICO REMEDIES. LTD.
8 & 9 Dewan and Sons Udyog Nagar,
Lokmanya Nagar, Palgar (West), Dist, Palgar, Maharashtra, India.