SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name:

Cefixime and Clavulanic Acid

1.2 Strength:

Cefixime 200 mg

Clavulanic Acid 125 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Cefixime Trihydrate USP

Label claim equivalent to Cefixime ……..200 mg

Diluted Potassium Clavulanate BP

equivalent to Clavulanic Acid ……125 mg

3. PHARMACEUTICAL FORM

Tablets

Oblong shaped white colored film coated tablets with ML embossing on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefixime-Clavulanate is indicated for the treatment of:

- Uncomplicated Urinary Tract Infections
- Otitis Media
- Pharyngitis and Tonsillitis
- Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis

- Uncomplicated gonorrhoeae (cervical/urethral)

4.2 Posology and method of administration

Adults and Children over 10 Years: One tablet twice daily

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

Route of administration: Orally one tablet twice daily

4.3 Contraindications

Patients with known hypersensitivity to cephalosporin antibiotics

4.4 Special warnings and precautions for use

Cefixime

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 penicillin's

As with other cephalosporin, 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 penicillin and cephalosporin.

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 cephalosporin (as a class). The recurrence of haemolytic anaemia after re-administration of cephalosporin in a patient with a history of cephalosporin (including Cefixime) –associated haemolytic anaemia has also been reported.

Renal failure acute

As with other cephalosporin, 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

Paediatric use

Safety of Cefixime in premature or new-born 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 penicillin, Lincosamides and cephalosporin); 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.

- Before therapy with Cefixime-Clav is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporin, penicillins or other drugs.

4.5 Interaction with other medicinal products and other forms of interaction

Carbamazepine: Elevated carbamazepine levels have been reported when Cefixime is administered concomitantly.

Warfarin and Anticoagulants: Increased prothrombin time, with or without clinical bleeding, has been reported when Cefixime is administered concomitantly.

Oral Contraceptives: Cefixime may interfere with the effectiveness of birth control pills.

Glucose Test: A false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with copper sulphate test tablets.

Coombs test: A false positive direct Coombs test has been reported during treatment with cephalosporin antibiotics.

4.6 Pregnancy and lactation

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

None

4.8 Undesirable effects

Cefixime and Clavulanate Potassium Tablets are generally well tolerated. The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

Gastrointestinal Disturbances: The most frequent side effects seen with are diarrhoea and stool changes; 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 and Clavulanate Potassium Tablets should be discontinued if marked diarrhoea occurs. Other gastrointestinal side effects seen less frequently are nausea, abdominal pain, dyspepsia, vomiting and flatulence. Pseudo membranous colitis has been reported.

Central Nervous System: Headache and dizziness.

Hypersensitivity Reactions: Allergies in the form of rash, pruritus, drug fever and arthralgia have been observed, including rare cases of urticaria or angioedema. These reactions usually subsided upon discontinuation of therapy. Rarely, erythema multiform, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.

Haematological and Clinical Chemistry: Thrombocytosis, thrombocytopenia, leucopenia, hyper eosinophilia, neutropenia and agranulocytosis have been reported. These reactions were infrequent and reversible. Mild transient changes in liver and renal function tests have been observed.

Hepatic Disorders: Transient rises in liver transaminase, alkaline phosphates and jaundice can also occur.

Miscellaneous: Other possible reactions include genital pruritus and vaginitis.

4.9 Overdose

Adverse reactions seen at dose levels up to 2 g in normal subjects did not differ from the profile seen in patients treated at the recommended doses. Gastric lavage may be indicated in over dosage. No specific antidote exists. Cefixime is not removed from the circulation in significant quantities by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

Clavulanic acid is an irreversible 'suicide' inhibitor of intracellular and extracellular β-lactamases, demonstrating concentration-dependent and competitive inhibition. It has a high affinity for the class A β-lactamases. This wide range of β-lactamases, which includes the plasmid-mediated TEM and SHV enzymes, is found frequently in members of the Enterobacteriaceae, *Haemophilus influenza* and *Neisseria gonorrhoeae*. The chromosomally mediated β-lactamases of *Kliebsiella pneumoniae*, *Proteus mirabilis*, *Proteus vulgaris*, *Bacteroides fragilis* and *Moraxella catarrhalis* are also inhibited, as are the extended-spectrum β-lactamases. The frequency of β-lactamase mediated resistance has continued to rise over the years, but the majority of clinically significant β-lactamases are inhibited by Clavulanate.

5.2 Pharmacokinetic properties

Combining Clavulanic acid with beta lactam antibiotic causes no appreciable alteration of the pharmacokinetics of either drug compared with their separate administration.

About 40-50% of Cefixime is absorbed slowly following oral administration from the GIT. Absorption is not significantly modified by the presence of food. 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 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.

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.

5.3 Preclinical safety data

Reproductive Toxicity

In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the adult therapeutic dose. Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to cefixime.

Mutagenic Potential

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.

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose

Talc

Colloidal silicon dioxide

Magnesium Stearate

Croscarmellose sodium

Povidone (K-30)

Maize Starch

HPMC 5 CPS

Diethyl phthalate

Titanium dioxide

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months from the date of manufacture.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Alu/Alu Blister pack of 10 Tablets, such 1 blister is packed in printed outer carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing Authorization Holder:

MICRO LABS LIMITED

Plot No. 121-124, KIADB,

Bommasandra Industrial Area,

4th Phase Anekal Taluk,

Bangalore 560 099

8. Marketing Authorization Numbers

Rwanda FDA-HMP-MA-0052

9. Date of First Registration/Renewal Of The Registration

17th March 2021

10. Date of revision of the text

July 2021

11. DOSIMETRY

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable