1.6 Product information:

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Cefixime Tablets USP 200 mg

1.1 Strength

200mg

1.2 Pharmaceutical form

Solid oral Dosage form-Film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Each film coated tablet contains:
Cefixime USP as Trihydrate
Eq. to Anhydrous Cefixime 200 mg
Excipients q.s.
Color: Approved colour used.

2.2 Quantitative declaration

S. No.	Ingredients	Specification	Qty. Req. per batch in Kg	Over ages	Actual Qty per batch	Actual Qty per Tablet (mg)	Function
ACTIVE PHARMACEUTICAL INGREDIENT							
1.	*Cefixime Trihydrate	USP	22.400	Nil	22.400	224.0	Cephalosporin Antibiotic
EXCIPIENTS							

2.	Microcrystalline Cellulose pH 102	USP	25.000	Nil	25.000	250.0	Diluent
3.	Maize Starch	USP	8.000	Nil	8.000	80.0	Diluent
4.	Colloidal Anhydrous Silica	USP	0.300	Nil	0.300	3.0	Glidant
5.	Magnesium Stearate	USP	1.300	Nil	1.300	13.0	Lubricant
6.	Purified Talc	USP	1.700	Nil	1.700	17.0	Lubricant
7.	Croscarmellose Sodium	USP	1.800	Nil	1.800	18.0	Super Disintegrant
8.	Tulsion 339 (Polacrillin Potassium)	USP	1.500	Nil	1.500	15.0	Disintegrant
9.	Sodium Starch Glycolate (Type A)	USP	3.000	Nil	3.000	30.0	Super Disintegrant
10.	**Microcrystalline Cellulose pH 102 (Additional)	USP	1.000	Nil	1.000	10.0	Diluent
COATING MATERIAL							
11.	Hypromellose	USP	1.540	Nil	1.540	15.4	Coating Agent
12.	Purified Talc	USP	0.220	Nil	0.220	2.2	Lubricant
13.	Polyethylene Glycol-6000	USP	0.220	Nil	0.220	2.2	Lubricant
14.	Titanium dioxide	USP	0.500	Nil	0.500	5.0	Opacifier

15.	Dichloromethane	USP	34.000	Nil	34.000	-----	Co-solvent
16.	Isopropyl Alcohol	USP	17.400	Nil	17.400	-----	Solvent

Note:- 223.8 mg of Cefixime Trihydrate is equivalent to 200 mg of Cefixime.

* To be dispensed on 100% assay on anhydrous basis and tablet weight to be adjusted by reducing the quantity of Microcrystalline Cellulose pH 102.

** Additional quantity to be added to compensate the loss during drying.

2.3 Salts and hydrates

Cefixime (as Trihydrate) equivalent to 200 mg anhydrous cefixime.

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable

2.6 Parenterals excluding powders for reconstitution

Not Applicable

2.7 Powders for reconstitution prior to Parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multidose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

Not Applicable

3. PHARMACEUTICAL FORM

Solid oral Dosage form-Film coated tablet.

Off white elongated, biconvex, film coated tablet having break line on one side and plain on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cefixime is indicated for the treatment of the following infections when caused by susceptible 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 Tablets 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 Tablets . In addition, most strains of *Pseudomonas, Bacteriodes fragalis, Listeria monocytogenes* and *Clostridia* are resistant to Cefixime Tablets.

4.2 Posology and method of administration

Posology

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 cefixime has not been established in children less than 6 months.

Dosage in Renal Impairment: Cefixime Tablets 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.

4.3 Method of administration

Route of Administration: Oral
Cefixime tablets are for oral administration only. Cefixime tablets should be taken with a sufficient amount of water. Cefixime may be taken with or without food.

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

4.4 Contraindications

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

4.5 Special warnings 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. 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.

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.

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.

4.6 Paediatric population

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.

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4.7 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 recognized that a positive Coombs test may be due to the drug.

4.8 Additional information on special populations

Not Applicable.

4.9 Paediatric population

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.

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4.10 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.

4.11 Effects on ability to drive and use machines

Cefixime has no known influence on the ability to drive and use machines. However, side effects may occur, which may influence the ability to drive and use machines.

4.12 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 and Flatulance.

Hepatobiliary disorders: Jaundice

Infections and infestations: Pseudomembranous colitis

Investigations: Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood urea increased and 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, Angiooedema, Urticaria, Pyrexia, Face oedema and Genital pruritus.

4.13 Overdose

There is no experience with overdoses with Cefixime Tablets. Adverse reactions seen at dose levels up to 2 g Cefixime Tablets 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

Pharmacotherapeutic group: Cephalosporins third generation; ATC code: J01DD08

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 methicillin-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 pediatric 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 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. 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 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 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 antibioticinduced changes in the population of the microflora of the intestine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose pH 102	USP
Maize Starch	USP
Colloidal Anhydrous Silica	USP
Magnesium Stearate	USP
Purified Talc	USP
Croscarmellose Sodium	USP
Tulsion 339 (Polacrillin Potassium)	USP
Sodium Starch Glycolate (Type A)	USP
Hypromellose	USP
Polyethylene Glycol-6000	USP
Titanium dioxide	USP

Dichloromethane	USP
Isopropyl Alcohol	USP

6.2 Incompatibilities

None

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store protected from light at a temperature not exceeding 30°C.

6.5 Nature and contents of container

10x1×10 Alu/Alu Blister.

6.6 Special precautions for disposal and other handling

None

7 Marketing Authorisation Holder And Manufacturing Site Addresses

Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

MANUFACTURING SITE ADDRESS
Scott-Edil Advance Research Laboratories & Education Limited.
Hill Top Ind. Area, Bhatoli Kalan,
Baddi-173205, Himachal Pradesh, INDIA

8 MARKETING AUTHORISATION NUMBER

Not Applicable

9 DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Not Applicable.

10 DATE OF REVISION OF THE TEXT

Not Applicable

11 DOSIMETRY

Not Applicable