Caricef®

(Cefixime Trihydrate)

1. NAME OF THE PRODUCT

Caricef® (Cefixime Trihydrate) Capsules (400mg)
Caricef® (Cefixime Trihydrate) 200mg Tablets
Caricef® (Cefixime Trihydrate) Suspension (100mg/5ml)
Caricef®DS (Cefixime Trihydrate) Suspension (200mg/5ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Caricef® Capsules (400mg)
Each capsule contains:
Cefixime Trihydrate equivalent to Cefixime.....400mg

Caricef® 200mg Tablets
Each film coated tablet contains:
Cefixime Trihydrate equivalent to Cefixime.....200mg

Caricef® Suspension (100mg/5ml)
Each 5ml contains (reconstituted):
Cefixime Trihydrate eq. to Cefixime.....100mg

Caricef®DS Suspension (200mg/5ml)
Each 5ml of reconstituted suspension contains:
Cefixime Trihydrate eq. to Cefixime.....200mg

3. PHARMACEUTICAL FORM

Capsule / Tablet / Suspension

Appearance:
Caricef® Capsules (400mg): Off white to yellowish granular powder, hard gelatin capsules having turquoise blue (Ferozi) cap, off white body **Caricef®** 400mg capsules printed on cap and SAMI logo on body in black color.
Caricef® 200mg Tablets: White to off White oblong film coated tablet embossed with SAMI on one side while other side is plain.
Caricef® Suspension (100mg/5ml): White to off white colored granular free flowing powder having no lumps and foreign particles with characteristic odor of banana.
Caricef®DS 200mg Suspension (200mg/5ml): White to yellow colored granular free flowing powder having no lumps and foreign particles with characteristic odor of banana.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Caricef® is an orally active cephalosporin antibiotic which has marked in vitro bactericidal 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 (caused by *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Streptococcus pyogenes*.); and other URTI e.g. Pharyngitis and Tonsillitis (caused by *Streptococcus pyogenes.*) 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. Acute exacerbations of chronic bronchitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae.*

Uncomplicated Gonorrhoea (cervical/urethral): Uncomplicated Gonorrhoea (cervical/urethral) caused by *Neisseria gonorrhoeae* (penicillinase-and non-penicillinase-producing isolates).

Urinary Tract Infections: e.g. cystitis, cystourethritis, uncomplicated pyelonephritis. 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. **Caricef®** 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, 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: The recommended dose of cefixime is 400mg daily. For the treatment of uncomplicated cervical/ urethral gonococcal infections, a single oral dose of 400mg is recommended. In the treatment of infections due to *Streptococcus pyogenes,* a therapeutic dosage of cefixime should be administered for at least 10 day.

Tablet:

Adults and Children over 10 years or weighing more than 50kg: The recommended dose is 200 – 400mg daily according to the severity of infection, given either as a single dose or in two divided doses.

Children under 10 years: **Caricef**® Tablets 200mg are not recommended for use in children under 10 years old.

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

Suspension:

Children (6 months or older): The recommended dosage for children in this age group is 8mg/kg body weight/day administered as a single dose or in two divided doses, as 4mg/kg every 12 hours.

PAEDIATRIC DOSAGE CHART			
		100mg/5ml	**200mg/5ml**
Patient Weight (kg)	**Dose/Day (mg)**	**Dose/Day (ml)**	**Dose/Day (ml)**
5 to 6.2	50	2.5	1.25
6.3 to 12.5	100	5	2.5
12.6 to 18.8	150	7.5	3.75
18.9 to 25	200	10	5
25.1 to 31.3	250	12.5	6.25
31.4 to 37.5	300	15	7.5
37.6 to 43.8	350	17.5	8.75
43.9 to 50	400	20	10

Children weighing more than 50kg or older than 12 years should be treated with the recommended adult dose. Otitis media should be treated with the suspension. Therefore, the tablet or capsule should not be substituted for the suspension in the treatment of otitis media. In the treatment of infections due to *Streptococcus pyogenes,* a therapeutic dosage of cefixime should be administered for at least 10 days.

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.

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 20ml/min or greater. In patients whose creatinine clearance is less than 20ml/min, it is recommended that a dose of 200mg 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 20ml/min. The dose of cefixime should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and haemodialysis (HD). Patients on dialysis should be monitored carefully.

Method for administration:

For oral administration. Absorption of **Caricef®** is not significantly modified by the presence of food.

DIRECTION FOR RECONSTITUTION:

For Suspension (30ml & 60ml): Shake bottle to loosen the mass. Add freshly boiled and cooled water below the mark given on bottle label then shake to make homogeneous suspension. Add further same water upto the mark of bottle label and shake vigorously to form uniform suspension.

4.3. CONTRAINDICATIONS:

Cefixime is contraindicated in patients with known allergy to cefixime or other cephalosporin.

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 (SCARS) including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS) drug rash with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with cefixime. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of skin hypersensitivity. 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.

Risk of Seizure/ neurotoxicity: Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Paediatric use: Safety of cefixime in premature or newborn infant has not been established.

Antibiotic-associated colitis: 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's, 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.

Coagulation Effects: Cephalosporins, including cefixime, may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment, or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

Development of Drug-Resistant Bacteria: Prescribing cefixime in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Carbamazepine: Elevated carbamazepine levels have been reported in post marketing experience when cefixime is administered concomitantly. Drug monitoring may be of assistance in detecting alterations in carbamazepine plasma concentrations.

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

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Cefixime has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Pregnancy: Category B. 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.

Breast-feeding: It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing nursing temporarily during treatment with this drug.

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:

Blood and lymphatic system disorders: Eosinophilia, hypereosinophilia, agranulocytosis, leucopenia, neutropenia, granulocytopenia, haemolytic anemia, thrombocytopenia, thrombocytosis.

Gastrointestinal disorders: Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, flatulence.

Hepatobiliary disorders: Jaundice, hepatitis.

Infections and infestations: Pseudomembranous colitis, vaginitis, candidiasis.

Investigations: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, SGPT increased, SGOT increased, alkaline phosphatase increased.

Nervous system disorders: Dizziness, headache, cases of convulsions have been reported with cephalosporins including cefixime (frequency not known) 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), seizures (less than 2%).

Respiratory, thoracic and mediastinal disorders: Dyspnoea.

Renal and urinary disorders: Acute renal failure with tubulointerstitial nephritis.
Immune system disorders: Anaphylactic reaction, angio-oedema, serum sickness-like reaction.
Skin and subcutaneous tissue disorders: Drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, stevens-johnson syndrome, toxic epidermal necrolysis, urticaria. Rash, pruritus, acute generalized exanthematous pustulosis (AGEP), erythema multiforme, Genital pruritus.
General disorders and administrative site conditions: Drug Fever, arthralgia, pyrexia, face oedema, genital pruritus, angioedema, serum sickness-like reactions.
Risk of Seizure/ neurotoxicity: Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced. If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated. Diarrhoea has been more commonly associated with higher doses. Cefixime should be discontinued if marked diarrhoea occurs.

4.9. OVERDOSE:
Cefixime is not removed from the circulation in significant quantities by dialysis. No specific antidote exists. General supportive measures are recommended. Gastric lavage may be indicated.

5. PHARMACOLOGICAL PROPERTIES
5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Third generation cephalosporin.
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. Typically, the peak serum levels following the recommended adult or pediatric doses are between 1.5–3mcg/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 400mg doses once daily for 5 days. 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:

Comparative clinical trials of otitis media were conducted in nearly 400 children between the ages of 6 months to 10 years. *Streptococcus pneumoniae* was isolated from 47% of the patients, *Haemophilus influenzae* from 34%, *Moraxella catarrhalis* from 15% and *S. pyogenes* from 4%. The overall response rate of *Streptococcus pneumoniae* to cefixime was approximately 10% lower and that of *Haemophilus influenzae or Moraxella catarrhalis* approximately 7% higher (12% when beta-lactamase positive isolates of *H. influenzae* are included) than the response rates of these organisms to the active control drugs. In these studies, patients were randomized and treated with either cefixime at dose regimens of 4mg/kg twice a day or 8mg/kg once a day, or with a comparator. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks post-treatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *Haemophilus influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2 to 4 week follow-up, a total of 30%-31% of patients had evidence of either treatment failure or recurrent disease.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Caricef® Capsules (400mg):

- Magnesium stearate

- Sodium lauryl sulphate
- Hard gelatin capsules

Caricef® 200mg Tablets:

- Micro crystalline cellulose PH 102
- Poly vinyl pyrrolidone K-30
- Silicon dioxide fumed
- Magnesium stearate

Caricef® Suspension (100mg/5ml):

- Sucrose (White refined cane sugar)
- Sodium benzoate
- Silicon dioxide fumed/Colloidal silicon dioxide
- Xanthan gum
- Sodium saccharin
- Banana powder flavor.

Caricef® DS Suspension (200mg/5ml):

- Sucrose (White refined cane sugar)
- Sodium benzoate
- Silicon dioxide fumed/ Colloidal silicon dioxide
- Xanthan gum
- Sodium saccharin
- Tartrazine yellow color
- Banana powder flavor.

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
For Suspension: The reconstituted suspension should be kept at 2 - 8°C, so that potency of the product remains stable and be used within 7 days.

6.5. NATURE AND CONTENTS OF CONTAINER:

Caricef® Capsules (400mg): Alu/Alu blister, pack size of 5 capsules.
Caricef® 200mg Tablets: Alu/Alu blister, pack size of 2 x 5 tablets.
Caricef® Suspension (100mg/5ml): Amber glass bottle, tamper-proof aluminium cap with conical plug, bottle size 60ml and 90ml for pack size 30ml & 60ml, respectively.

Caricef®DS Suspension (200mg/5ml): Amber glass bottle, tamper-proof aluminium cap with conical plug, bottle size 60ml for pack size 30ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
No special requirement.

6.7. DRUG PRODUCT SPECIFICATIONS:
Caricef® Capsules (400mg): SAMI's Specs.
Caricef® 200mg Tablets: USP Specs.
Caricef® Suspension (100mg/5ml): USP Specs.
Caricef®DS Suspension (200mg/5ml): USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured for:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com

by:
Healthtek (Pvt.) Limited
Plot No. 14, Sector 19, Korangi Industrial Area Karachi - Pakistan

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)
Caricef® Capsules (400mg): 022416
Caricef® 200mg Tablets: 070790
Caricef® Suspension (100mg/5ml): 022415
Caricef®DS Suspension (200mg/5ml): 044340

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Caricef® Capsules (400mg): 31st December 1998
Caricef® 200mg Tablets: 18th August 2011
Caricef® Suspension (100mg/5ml): 31st December 1998
Caricef®DS Suspension (200mg/5ml): 8th November 2006

10. DATE OF REVISION OF THE TEXT

سیری سیف کیپسول / ٹیبلٹ / سسپینشن

(سیفکزائم ٹرائی ہائیڈریٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔

برائے سسپینشن: تیار شدہ سسپینشن کو ۲ سے ۸ ڈگری سینٹی گریڈ پر رکھیں تا کہ دوا کی تاثیر برقرار رہے اور ۷ یوم کے اندر استعمال کر لیں۔