1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. **Name of the proprietary product: CEFIXIME POWDER FOR ORAL SUSPENSION**

   Name of the nonproprietary International Product: Cefixime for oral suspension USP 100 mg/5ml)

   Route of Administration: Oral

2. **Qualitative and Quantitative composition:**

Batch size: 10,000 Bottles

SR. No	Ingredients	Specification	Qty/ 5ml (mg)	Qty/ Bottle (gm)	Overages	Qty/ batch (kg)	Reason for inclusion
1.	Cefixime Trihydrate	USP	100.000	1.000	--	10.000	Active
2.	Sucrose (Pharma grade Sugar)	BP	1462.692	17.552	--	175.523	Sweetner
3.	Magnesium Stearate	BP	13.167	0.158	--	1.580	Lubricant
4.	Sodium Carboxy Methyl Cellulose (Carmellose Sodium)	BP	29.667	0.356	--	3.560	Viscosity modifier
5.	Sodium Benzoate	BP	6.942	0.083	--	0.833	Preservative
6.	Purified Talc	BP	13.750	0.165	--	1.650	Lubricant (soapstone)
7.	Colloidal Anhydrous silica	BP	10.667	0.128	--	1.280	Fining agent
8.	Mango Dry Flavour	IH	8.333	0.100	--	1.000	Flavouring agent

9.	Quinoline yellow WS Colour	IH	0.167	0.002	--	0.020	Colouring agent
10.	Anhydrous Citric Acid	BP	5.500	0.066	--	0.660	Acidifier
11.	Sodium Methyl Paraben	BP	4.167	0.050	--	0.500	Presevative

Where, USP – United state Pharmacopiea

BP- British Pharmacopiea

IH- In-House

3. Pharmaceutical Form: Oral Suspension

4. Clinical Particulars:

4.1 Therapeutic Indications:

To reduce the development of drug resistant bacteria and maintain the effectiveness of (cefixime) and other antibacterial drugs, should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antimicrobial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis.

Otitis Media caused by Haemophilus influenzae (beta-lactamase positive and negative strains), Moraxella (Branhamella) catarrhalis, (most of which are beta-lactamase positive) and S. pyogenes*.

Pharyngitis and Tonsillitis, caused by S. pyogenes.

Note: Penicillin is the usual drug of choice in the treatment of S. pyogenes infections, including the prophylaxis of rheumatic fever. is generally effective in the eradication of S. pyogenes from the nasopharynx; however, data establishing the efficacy of in the subsequent prevention of rheumatic fever are not available.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis, caused by Streptococcus pneumoniae and Haemophilus influenzae (beta-lactamase positive and negative strains).

Uncomplicated gonorrhea (cervical/urethral), caused by Neisseria gonorrhoeae (penicillinase-and non-penicillinase- producing strains).

Appropriate cultures and susceptibility studies should be performed to determine the causative organism and its susceptibility to cefixime; however, therapy may be started while awaiting the results of these studies. Therapy should be adjusted, if necessary, once these results are known.

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

4.2 Posology and method of administration:

Children: The recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours.

PEDIATRIC DOSAGE CHART 100 mg/5 mL

Patient Weight (kg)	Dose/Day mg	Dose/Day mL	Dose/Day tsp of Suspension
6.25	50	2.5	½
12.5	100	5	1
18.75	150	7.5	1½
25	200	10	2
31.25	250	12.5	2½
37.5	300	15	3

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose.

Otitis media should be treated with the suspension. Clinical studies of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the suspension in the treatment of otitis media.

Efficacy and safety in infants aged less than six months have not been established. In the treatment of infections due to S. pyogenes, a therapeutic dosage of should be administered for at least 10 days.

Renal Impairment

may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 60 mL/min or greater. Patients whose clearance is between 21 and 60 mL/min or patients who are on renal hemodialysis may be given 75% of the standard dosage at the standard dosing interval (i.e., 300 mg daily). Patients whose clearance is < 20 mL/min, or patients who are on continuous ambulatory peritoneal dialysis may be given half the standard dosage at the standard dosing interval (i.e., 200 mg daily). Neither hemodialysis nor peritoneal dialysis remove significant amounts of drug from the body.

Reconstitution Directions for Oral Suspension

Strength	Bottle Size	Reconstitution Directions
100 mg/5 mL and 200 mg /5 mL	100 ml	To reconstitute, suspend with 68 mL water. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
100 mg/5 mL and 200 mg /5 mL	75 ml	To reconstitute, suspend with 34 mL water. Method: Tap the bottle Several times to loosen powder contents prior to reconstitution. Add Approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.

100 mg/5 mL and 200 mg /5 mL	50 ml	To reconstitute, suspend with 34 mL water. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
200 mg/5 mL	37.5 ml	To reconstitute, suspend with 26 mL water. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.
200 mg/5 mL	25 ml	To reconstitute, suspend with 17 mL water. Method: Tap the bottle several times to loosen powder contents prior to reconstitution. Add approximately half the total amount of water for reconstitution and shake well. Add the remainder of water and shake well.

After reconstitution the suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days.

4.3 Contraindications

is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use

Before therapy with is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. If this product is to be given to penicillin-sensitive patients, caution should be exercised because cross hypersensitivity among beta-lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of cefixime.

Antibiotics, including , should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Treatment with broad spectrum antibiotics, including , 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 severe antibiotic-associated diarrhea including pseudomembranous colitis.

Pseudomembranous colitis has been reported with the use of and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with the use of antibiotics. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life-threatening. Mild

cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, management should include 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.

PRECAUTIONS

General

Prescribing (Cefixime) in the absence of a proven or strongly suspected bacterial infection of a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

The possibility of the emergence of resistant organisms which might result in overgrowth should be kept in mind, particularly during prolonged treatment. In such use, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

The dose of should be adjusted in patients with renal impairment as well as those undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD). Patients on dialysis should be monitored carefully.

should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins 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.

Information for Patients

Patients should be counseled that antibacterial drugs, including , should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When is prescribed to treat a bacterial infection, patients should be told that although it is

common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by or other antibacterial drugs in the future.

4.5 Interaction with other medicinal products and other forms of interaction:

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

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

4.6 Pregnancy and Lactation:

Usage in Pregnancy

Pregnancy Category B. 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. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of cefixime in children aged less than six months old have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in the pediatric patients receiving the suspension, was comparable to the incidence seen in adult patients receiving tablets.

4.7 Effects on the 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.

4.8 Undesirable effects:

These symptoms usually responded to symptomatic therapy or ceased when cefixime was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of cefixime. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal : Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), skin rashes, urticaria, drug fever, pruritus, angioedema, and facial edema. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness-like reactions have been reported.

Hepatic: Transient elevations in SGPT, SGOT, alkaline phosphatase, hepatitis, jaundice.

Renal: Transient elevations in BUN or creatinine, acute renal failure.

Central Nervous System: Headaches, dizziness, seizures.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, neutropenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Abnormal Laboratory Tests: Hyperbilirubinemia.

Other: Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

In addition to the adverse reactions listed above which have been observed in patients treated with cefixime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse reactions: Allergic reactions, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, and colitis.

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.

4.9 Overdose

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of cefixime did not differ from the profile seen in patients treated at the recommended doses.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Antibiotic, is a third-generation cephalosporin.

ATC Code : J01DD08

Mechanism 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.

PK/PD 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.

Mechanism 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 de-repressed 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 data.

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 Proteus mirabilis
Species for which resistance may be a problem
Streptococcus pneumoniae Citrobacter freundii $ Enterobacter cloacae $ Escherichia coli % & Klebsiella oxytoca % Klebsiella pneumoniae % Morganella morganii $

Serratia marcescens $°
Resistant species
Chlamydia spp. Chlamydophila spp. Clostridium difficile Bacteroides fragilis Enterococci Legionella pneumophila Mycoplasma spp. Pseudomonas species Staphylococcus aureus + Streptococcus pneumoniae (Penicillin-intermediate and -resistant)

Cefixime has poor activity against staphylococci (regardless of susceptibility to methicillin) $ Natural intermediate susceptibility.% Extended spectrum beta-laktamase (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 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.

From in vitrostudies, 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 paediatric doses are between 1.5 and 3 mg/L. Little or no accumulation of cefixime occurs following multiple dosing.

Metabolism 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 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.

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

5.3 Pre-clinical Safety:

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 antibiotic-induced changes in the population of the microflora of the intestine.

6. Pharmaceutical Particulars:

List of Excipients:

Sucrose (Sugar)	BP
Magnesium Stearate	BP
Sodium Carboxy Methyl Cellulose (Carmellose Sodium)	BP
Sodium Benzoate	BP
Purified Talc	BP
Colloidal Anhydrous silica	BP
Mango Dry Flavour	IH
Quinoline yellow WS Colour	IH
Anhydrous Citric Acid	BP
Sodium Methyl Paraben	BP
Purified water	BP

6.2 Incompatibilities: Nil.

6.3 Shelf Life: Powder for Oral Suspension: 36 months

Reconstituted suspension: 7 days

6.4 Special Precautions for storage:

Powder for Oral Suspension: Stored below 30°C.

Reconstituted suspension: When Refrigerated between 2 and 8°C can be kept for up to 7 days.

6.5 Nature and contents of container:

100 ml Hdpe bottle packed in a printed carton along with pack inert and measuring cup.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder:

SIMPEC PHARMACEUTICAL LTD

8. Marketing Authorization Number: --

9. Date of first Authorization /renewal of the authorization: --

10. Date of revision of text: January 2018