1.6 Product Information

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. Name of the Medicinal Product

1.1 Trade Name : **CEFAZIM-DS** (Cefixime for Oral Suspension USP 100 mg)

1.2 Strength : 100 mg

1.3 Pharmaceutical Form : *"Powder for Oral Suspension"*

2. Qualitative and Quantitative Composition

S. No	Name of Ingredients	Quantity/ 30 (mL)
Active Substance		
1	Cefixime Trihydrate Eq. to anhydrous Cefixime*	0.67
Inactive Substance		
2	Colloidal Anhydrous Silica	0.09
3	Sodium Benzoate	0.06
4	Xanthan Gum	0.075
5	Aspartame	0.15
6	Sucrose	13.71
7	Colour Sunset Yellow	0.015
8	Trusil Orange Special Powder Flavor	0.23
	Total	**15.00 g**

Note:

*Molecular weight of Cefixime Trihydrate = 507.50

Molecular weight of Cefixime = 453.46

100 mg Cefixime is Eq. to 112 mg of Cefixime Trihydrate

3. Pharmaceutical Form

'*Powder for Oral Suspension*

Light orange colored free flowing powder granules when reconstituted it gives light orange colored 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, Cefixime Suspension 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. Cefixime Suspension 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. Cefixime Suspension is generally effective in the eradication of S. pyogenes from the nasopharynx; however, data establishing the efficacy of Cefixime Suspension 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 (penicillinaseand 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.

4.2 Posology and method of administration

Posology:

Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension.

Serum Levels of Cefixime after Administration of Oral Suspension (mcg/mL)							
DOSE	1h	2h	4h	6h	8h	12h	24h
100 mg	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200 mg	1.2	2.1	2.8	2	1.3	0.5	0.07
400 mg	1.8	3.3	4.4	3.3	2.2	0.8	0.07

Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. In animal studies, it was noted that cefixime is also excreted in the bile in excess of 10% of the administered dose. Serum protein binding is concentration independent with a bound fraction of approximately 65%. In a multiple dose study conducted with a research formulation which is less bioavailable than suspension, there was little accumulation of drug in serum or urine after dosing for 14 days. The serum half-life of cefixime in healthy subjects is independent of dosage form and averages 3-4 hours but may range up to 9 hours in some normal volunteers. Average AUCs at steady state in elderly patients are approximately 40% higher than average AUCs in other healthy adults. In subjects with moderate impairment of renal function (20 to 40 mL/min creatinine clearance), the average serum half-life of cefixime is prolonged to 6.4 hours. In severe renal impairment (5 to 20 mL/min creatinine clearance), the half-life increased to an average of 11.5 hours. The drug is not cleared significantly from the blood by hemodialysis or peritoneal dialysis. However, a study indicated that with doses of 400 mg, patients undergoing hemodialysis have similar blood profiles as subjects with creatinine clearances of 21-60 mL/min. There is no evidence of metabolism of cefixime in vivo. Adequate data on CSF levels of cefixime are not available.

Method of administration

Cefixime powder for oral suspension is for oral administration. The powder should be reconstituted with water.

4.3 Contraindication

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

4.4 Special warnings and special precautions for use

• Prolonged use of an anti-infective may result in overgrowth of non-susceptible organisms. With an oral medication the normal colonic flora may be altered allowing the overgrowth by Clostridia with consequent pseudomembranous colitis.

• 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.

• Emergence of resistance to cefixime has not to date been shown to be clinically significant. Nevertheless it is recommended that newer antibiotics such as cefixime should usually be reserved for infections which are recurrent or resistant to other agents.

• Particular care should be exercised in patients with severe gastrointestinal disturbances involving vomiting and diarrhoea. The product should be discontinued if severe diarrhoea develops.

• 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.

• The product should be used with caution in patients with renal functional impairment. Renal function should be monitored with particular care when combining cefixime with aminoglycoside antibiotic, polymyxin B, colistin or high-dosed loop diuretics (e.g. furosemide). This is applied especially to patients with pre-existing renal impairment.

• Cross allergenicity may exist between cephalosporins and penicillins. Use of the product should be cautious in patients allergic to penicillins.

• Particular care should be exercised in patients with poor oral nutrition, patients receiving parenteral nutrition, elderly patients or patients in a debilitated state.

• Particular care should be exercised in patients with a personal or familial predisposition to allergic reaction such as bronchial asthma, rash or urticaria.

• Adverse reactions to drugs are liable to occur more frequently in the elderly patients since they usually have physiological hypofunction. Bleeding tendency due to Vitamin K deficiency may occur in the elderly.

• The safety of cefixime in premature or newborn infant has not been established.

• 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.

4.5 Interaction with other medicinal products and other forms of interaction

• 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.

• A false positive direct Coomb's test may occur with cefixime.

• The administration of cefixime may result in false-positive results for glucose in the urine using Benedict's solution, Fehling's solution, or Clinitest. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (e.g. Tes-Tape) be used.

4.6 Pregnancy and lactation

Pregnancy: Safety of cefixime in pregnant women has not been established.

Lactation: It is not known whether cefixime is excreted in human milk.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that cefixime may have an effect on a patient's ability to drive or operate machinery.

4.8 The following adverse reaction will be considered listed **Undesirable effects**
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Blood and lymphatic system class: Eosinophilia, Granulocytopenia, Haemolytic anaemia, Thromocytopenia, Prolonged PT/Coagulation.
Gastrointestinal disorders: Abdominal pain, Diarrhoea, Dyspepsia, Nausea, Vomiting, Anorexia, Flatulence.
General disorders and administration site conditions: Pyrexia, Face oedema
Hepatobiliary disorders: Jaundice, Hepatitis.
Infections and infestations: Pseudomembranous colitis, Vaginitis
Investigations: Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood urea increased, 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
Skin and subcutaneous tissue disorders: Drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, pruritus, rash, stevens-johnson syndrome, toxic epidermal necrolysis, urticaria, genital pruritus.

4.9 Overdose
No specific antidote exists. General supportive measures are recommended.

5. Pharmacological Properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Anti-Bacterial Agents, Cephalosporins
ATC Code: J01DD08
Cefixime inhibits the cell wall synthesis of various bacteria. Cefixime has high affinity for penicillin binding proteins (PBP) 1 (1a, 1b and 1c) and 3 and prevents cross-linking reaction. Cefixime has broad spectrum activity against Gram-positive and Gram-negative bacteria. Sensitivity will vary according to area, and local prescribing guidelines should always be consulted. Where possible microbiological sensitivity tests should guide treatment as resistance can emerge. Its mechanism of action is bactericidal.

5.2 Pharmacokinetic properties
Absorption: Following oral administration of cefixime, peak serum concentrations are generally attained in 3 to 4 hours. In reported study after a single oral dose of 50, 100 and 200mg mean peak serum concentrations were 1.02, 1.46 and 2.63 mg/L respectively in 12 healthy volunteers of Western origin and 0.69, 1.13 and 1.95 mg/L respectively in 12 healthy Japanese volunteers.
Paediatric Populations: Following a single oral dose of 1.5, 3.0 and 6.0 mg/kg of cefixime in Japanese paediatric patients, maximum serum concentrations at around 3 to 4 hours were 1.14, 2.01 and 3.97 mg/L, respectively.

Distribution: In human plasma, cefixime is approximately 70% protein bound, a value not concentration dependent in the range 0.5 to 30mg/L. Cefixime is distributed to target organs/tissues such as tonsils, maxillary sinus mucosal tissue, lung tissue and gallbladder tissue.
Metabolism & Excretion: No biologically active metabolites of cefixime were identified in plasma or urine following oral administration to healthy volunteers. Around 20% of a 200mg dose of cefixime is recovered unchanged over 24 hours in the urine of healthy volunteers. The elimination half-life is 2-4 hours.

5.3 Preclinical safety data
There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of Package Insert.

6 Pharmaceutical Particulars

6.1 List of excipients
Colloidal Anhydrous Silica
Sodium Benzoate
Xanthan Gum
Aspartame
Sucrose
Colour Sunset Yellow
Trusil Orange Special Powder Flavour

6.2 Incompatibilities
None

6.3 Shelf life
Unopened bottle with dry powder: 2 years from the date of manufacture
Reconstituted suspension: 7 days.

6.4. Special precautions for storage
Before reconstitution do not store above 30°C. After reconstitution store the suspension at 5°C to 30°C.

6.5 Nature and contents of container
30 mL HDPE Bottle

6.6 Special precautions for disposal and other handling
Tap bottle to loosen the powder. Powder should be reconstituted with water.
Any unused product or waste material should be disposed off in accordance with the local requirements

7. Marketing Authorization Holder

ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

8. Marketing Authorization Number(S)

NA

9. Date of First Authorization/Renewal of the Authorization

NA

10. Date of Revision of the Text

02 Jun. 2019