Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

ZEFLET DRY SUSPENSION (Cefixime for Oral Suspension USP 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution each 5 mL contains:
Cefixime USP as Trihydrate
Eq. to Anhydrous Cefixime…100 mg

For full excipients see Section 6.1

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

They are limited, in children over 6 months, to infections due to germs defined as sensitive, when these infections allow oral antibiotic therapy and in particular:

- bronchial and pulmonary infections,
- Acute otitis media, especially recurrent,
- Acute pyelonephritis following parenteral antibiotic therapy for at least 4 days,
- Lower urinary tract infections in children over 3 years old and outside of severe infectious states.

Official recommendations for the appropriate use of antibacterial should be considered.

4.2 Posology and method of administration

Dosage:
The dosage of Cefixime for Oral Suspension 100 mg/5 ml, powder for oral suspension in a vial in children (above 6 months) is 8 mg/kg/day in two administrations, 12 hours apart, i.e. 4 mg/kg and per dose.

The drinkable suspension is to be reconstituted by adding water up to the mark to obtain a total volume of 40 ml and to be shaken before use.

Recommended Presentations According to Age – Cefixime for oral Suspension	
6 to 30 months	Infants 40 mg/5ml, powder for oral suspension in bottle Cefixime for oral

	suspension 100mg/5ml
30 months to 12 years	Powder for Oral suspension in bottle, Cefixime for oral suspension 100mg/5ml
> 12 years and adults	Cefixime Tablets 200mg
The dose per intake is indicated, according to the weight of the child, on the piston of the pipette graduated in kg. It is therefore read directly on the graduations of the pipette. Thus, the point indicated corresponds to the dose for one intake. Two doses per day are necessary. For example, the 10 kg graduation corresponds to the dose to be administered per dose for a 10 kg child, twice a day.	

In Renal insufficiency
When creatinine clearance values are above 20 ml/min, there is no need to modify the dosage. For lower values, including in hemodialysis patients, the dosage of Cefixime should not exceed 4 mg/kg/day, in one administration.

In hepatic insufficiency

It is not necessary to change the dosage

Mode of Administration
Oral Route

4.3 Contraindications

Hypersensitivity to Cefixime or to a cephalosporin antibiotic, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings
The occurrence of any allergic manifestation requires discontinuation of treatment.

- The prescription of cephalosporins requires a prior examination. Since penicillin allergy is crossed with that of cephalosporins in 5 to 10% of cases:

- The use of cephalosporins must be extremely cautious in penicillin-sensitive patients; strict medical supervision is necessary from the first administration,

- The use of cephalosporins should be strictly prohibited in subjects with a history of immediate-type allergy to cephalosporins. In case of doubt, the presence of the doctor with the patient is essential for the first administration, in order to treat the possible anaphylactic accident,

The hypersensitivity reactions (anaphylaxis) observed with these two types of substances can be serious and sometimes fatal.

- Cases of colitis related to the administration of an antibacterial product and pseudomembranous colitis have been reported with almost all antibacterial products, including Cefixime, with severity ranging from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or after administration of Cefixime. Discontinuation of Cefixime treatment and administration of specific treatment for Clostridium difficile should be considered. Any administration of peristalsis inhibitors should be avoided.

  Serious skin reactions:

  Serious skin reactions such as toxic epidermal necrolysis (TEN, also called Lyell's syndrome), Stevens- Johnson syndrome (SSJ), drug hypersensitivity syndrome with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (PEAG) have been reported in patients treated with Cefixime. Patients should be informed of the signs and symptoms of serious skin manifestations and should be closely monitored. Cefixime treatment should be discontinued immediately at the first appearance of rash, mucosal lesions or any other sign of skin hypersensitivity.

- Serious cases of haemolytic anaemia, including fatalities, have been reported in patients receiving cephalosporin class Antibacterials (class effect). The reappearance of haemolytic anemia after reintroduction of a cephalosporin in a patient with a history of haemolytic anemia under cephalosporin, including Cefixime, has also been described. If a patient develops anemia on Cefixime, the diagnosis of cephalosporin-associated anemia should be considered and Cefixime discontinued until the etiology is established (see section 4.8).

  Beta-lactams including Cefixime predispose the patient to the risk of encephalopathy (which may include convulsions, confusion, disturbances of consciousness or abnormal movements) and, particularly, in the event of overdose or impairment of renal function.

  Excipients with known effect:

- This medicine contains sucrose. Its use is not recommended in patients with fructose intolerance, glucose- galactose malabsorption syndrome or sucrose/isomaltase deficiency (rare hereditary diseases).
- This medicine contains an azo coloring agent (cochineal red 4R) and may cause allergic reactions.
- This medicinal products contains less than 1mmol sodium (23 mg) vial i.e. essentially ‘Sodium Free’.

  <u>Special precautions for use</u>

~ In patients allergic to other beta-lactam antibiotics, the possibility of cross-allergy should be taken into account. In case of severe renal insufficiency, it may be necessary to adjust the daily dose according to creatinine clearance (see sections 4.2 and 5.2).

~ In children under 6 months, to date, in the absence of specific studies, it is recommended not to use Cefixime.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs interactions

No clinically significant interactions have been reported during clinical trials. In pharmacokinetics, it has been shown that the combination of 1 g of probenecid with Cefixime leads to a 25% reduction in the total clearance of the product. In humans, the combination of an antacid does not reduce the absorption of Cefixime.

Interaction with laboratory tests

- False positive reactions when looking for ketones in the urine (by nitroprusside method).
- False positive reactions when looking for glycosuria (preferably use assay methods using glucose oxidase).
- A false positive Coombs test has been described during treatment with cephalosporin.

Special problems of INR imbalance

Numerous cases of increased activity of oral anticoagulants have been reported in patients receiving antibiotics. The marked infectious or inflammatory context, the patient's age and general condition appear to be risk factors. In these circumstances, it seems difficult to distinguish between the infectious pathology and its treatment in the occurrence of the INR imbalance. However, certain classes of antibiotics are more implicated: these include fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Due to the expected benefit, the use of Cefixime may be considered during pregnancy if necessary. Indeed, although the clinical data are insufficient, the animal data have not revealed any malformative or foetotoxic effect.

Feeding with milk

There are no data on whether Cefixime passes into breast milk. However, breastfeeding is possible when taking this antibiotic.

Nevertheless, breast-feeding (or treatment) should be discontinued and a doctor should be consulted immediately, if diarrhea, candidiasis or rash occurs in infants

4.7 Effects on ability to drive and use machines

If adverse reactions such as encephalopathy (which may include seizures, confusion, altered consciousness or abnormal movements) occur (see sections 4.4, 4.8, 4.9), the patient should not drive or use machinery.

4.8 Undesirable effects

Frequencies are determined as follows: very common (ÿ 1/10); common (ÿ 1/100, < 1/10); uncommon (ÿ1/1,000 to <1/100); rare (ÿ 1/10,000, < 1/1,000); very rare (<1/10,000) and frequency not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Hypereosinophilia, thrombocytosis, thrombocytopenia, leukopenia, neutropenia, granulocytopenia and agranulocytosis.

- Very rare cases of hemolytic anemia (see section 4.4).

Gastrointestinal disorders

Abdominal pain, diarrhea (see section 4.4), nausea, vomiting, dyspepsia, flatulence.

General disorders and administration site conditions

• Fever.

Infections and infestations

Pseudomembranous colitis, vaginitis.

Immune system disorders

- Rare cases of anaphylactic reactions such as urticaria or angioedema, serum sickness.

Investigations

Moderate and transient elevation of AST and ALT transaminases and alkaline phosphatase.

- Weak increase in blood urea and serum creatinine.
- Increased bilirubin in the blood.

Hepatobiliary disorders

Jaundice, hepatitis.

Nervous system disorders

Headaches, dizziness.

Unknown frequency: cases of seizures have been reported with cephalosporins including Cefixime.

Beta-lactams including Cefixime predispose the patient to the risk of encephalopathy (which may include convulsions, confusion, disturbances of consciousness or abnormal movements) and, particularly, in the event of overdose or impairment of renal function.

Respiratory, thoracic and mediastinal disorders

Dyspnea.

Kidney and urinary disorders

Acute renal failure due to interstitial nephritis.

Skin and subcutaneous tissue disorders

Rash, pruritus,
Very rare cases of bullous eruptions (erythema multiforme, Stevens-Johnson syndrome (SSJ), toxic epidermal necrolysis (TEN, also called Lyell's syndrome)), drug hypersensitivity syndrome with eosinophilia and systemic symptoms (DRESS), pustulosis acute generalized exanthematous (AGEP) (see section 4.4).

Reporting of suspected adverse reactions

The reporting of suspected adverse reactions after authorization of the medicinal product is important. It allows continuous monitoring of the benefit/ risk ratio of the medicinal product. Health professionals report any suspected adverse effects via below mentioned contact
www.zimlab.in

4.9 Overdose

Beta-lactams including Cefixime predispose the patient to the risk of encephalopathy and, particularly, in the event of overdose or impairment of renal function.
If large quantities of Cefixime are ingested, symptomatic treatment should be initiated. There is no specific antidote. Hemodialysis or peritoneal dialysis does not remove Cefixime from plasma

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibiotic of the beta-lactam family, of the group of the cephalosporin of 3 Like generation – ATC code: J01DD08

The other cephalosporin, the mechanism of action of Cefixime is based on the inhibition of the synthesis of the bacterial walls.

Cefixime has bactericidal activity in vitro against many Gram-positive and Gram-negative germs.

Spectrum of Antibacterial Activity
Critical concentrations separate susceptible strains from strains of intermediate sensitivity and the latter from resistant strains: S ≤1 mg/l and R > 2 mg/l the prevalence of acquired resistance may vary according to geography and time for some species.
It is therefore useful to have information on the prevalence of local resistance, especially for the treatment of severe infections. These data can only provide an orientation on the probabilities of the sensitivity of a bacterial strain to this antibiotic.

When the variability of the prevalence of resistance in France is known for a bacterial species, it is indicated in the table below categories

	Frequency of resistance acquired in France (> 10%) (extreme values)
SENSITIVE SPECIES	
Gram-positive aerobes	
Streptococcus	
Streptococcus pneumoniae	30 – 70 %
Gram-negative aerobes	
Branhamella catarrhalis	
Citrobacter koseri	
Escherichia coli	5-15 %
Haemophilus influenzae	
Klebsiella	0-20%
Neisseria gonorrhoeae	
Pasteurella	
Proteus mirabilis	
Proteus vulgaris	
Providence	
Anaerobes	
Fusobacterium	10-20 %
Prevotella	30-70 %
RESISTANT SPECIES	
Gram-positive aerobes	
Corynebacterium diphtheriae	
Enterococci	
Listeria	
Staphylococcus	
Gram-negative aerobes	
Acinetobacter	
Citrobacter freundii	
Pseudomonas	
Serratia	
Anaerobes	
Except for Prevotella and Fusobacterium	

5.2 Pharmacokinetic properties

Pharmacokinetic studies have demonstrated the bioequivalence of the tablet and granule forms.

In adults:

Absorption

After oral administration, in a single dose of 200 mg, the maximum serum concentrations (Cmax) are, on average, 3 micrograms/ml and are reached (Tmax) in approximately 3 to 4 hours. After administration of a 400 mg dose, the maximum serum concentrations are higher (3.4-5 micrograms/ml) but not proportionally to the increase in doses.

After repeated administrations for 15 days of doses of 400 mg/day in one or two administrations, the serum concentrations and the bioavailability are not modified, thus reflecting the absence of accumulation of the active principle.

The bioavailability of Cefixime is approximately 50% at a dose of 200 mg. It is not modified by taking a meal. However, the time to peak serum concentrations is delayed by approximately one hour.

Distribution

The apparent volume of distribution is of the order of 15 liters. In animals, Cefixime diffuses into the vast majority of tissues studied, with the exception of the brain. In humans, after doses of 200 mg at 12-hour intervals, the pulmonary concentrations, 4 and 8 hours after the last dose, are of the order of 1 microgram/g of tissue, these concentrations being higher than the MICs 90% of sensitive germs, responsible for lung infections.

Elimination

- The elimination of Cefixime is characterized by a half-life (T½) of between 3 and 4 hours (mean: 3.3 hours). The product is eliminated via the kidneys in unchanged form (16 to 20% of the ingested dose), extra-renal elimination is essentially biliary (25%).

- No metabolites, serum or urinary, could be demonstrated in animals as in humans.

- In case of severe renal insufficiency (creatinine clearance < 20 ml/min), the increase in plasma elimination half- life and maximum serum concentrations make it necessary to reduce the daily dosage from 400 to 200 mg /d.

In hepatic insufficiency, elimination is slowed down (T½ = 6.4 hours), but it is not necessary to modify the dosage.

Binding to serum proteins is about 70% and is mainly on albumin, regardless of the concentration (at therapeutic doses).

The pharmacokinetic characteristics of Cefixime are very slightly modified in the elderly. The slight increase in maximum serum concentrations, bioavailability and the slight decrease in the quantity excreted (15 to 25%) do not require any reduction in dosage in this population.

In the child

The serum concentrations obtained after administration, in a single dose, of 4 mg/kg of Cefixime (granulated) vary from 1.7 to 2.5 micrograms/ml.

Five hours after taking 4 mg/kg of Cefixime, the concentrations in the non-fibrous tonsils are on average C 6 at 0.8 micrograms/g for a concomitant serum concentration of 1.24 ± 0.94 micrograms/ml

5.3 Preclinical safety data

Not Applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Anhydrous Silica
Sodium Benzoate
Xanthan Gum
Aspartame
Sucrose
Trusil Orange Special Powder Flavor
Colour Sunset Yellow

6.2 Incompatibilities

None

6.3 Shelf-life

2 Years from the date of Manufacture.
For 30 ml: After reconstitution use within 7 days.
For 60 ml: After reconstitution use within 14 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.
Keep out of the reach of children.

6.5 Nature and content of container

For 30 ml: Dry powder for oral suspension packed in 30 mL HDPE Bottle.
For 60 ml: Dry powder for oral suspension packed in 60 mL HDPE Bottle.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zim Laboratories Limited.
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India.

8. MARKETING AUTHORISATION NUMBERS

07852/09255/NMR/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/10/2022

10. DATE OF REVISION OF THE TEXT

04/07/2023