MODULE 1- ADMINISTRATIVE PARTICULARS OF THE PRODUCT

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

Generic Name/INN Name: Cefixime for Oral Suspension USP 100mg/5ml
Trade Name: CHEMIXIM SUSPENSION

Strength:

Each 5ml of reconstituted Suspension contains:
Cefixime Trihydrate USP eq. to
Anhydrous Cefixime 100 mg
Excipients q.s.
Colour: Col. Tartrazine Supra

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2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Spec	Label Claim (mg/5ml)	Std. Qty. (mg/5ml)	%w/w	Function
1.	Cefixime Trihydrate * eq. to Cefixime anhydrous	USP	100.000	100.000	16.67	Active Pharmaceutical Ingredient
2.	Microcrystalline Cellulose with Carboxymethylcellulose Sodium	USP	----	30.000	5.00	Suspending agent
3.	Sodium Citrate	BP	----	4.000	0.67	Buffering agent
4.	Sodium Benzoate	BP	----	2.000	0.33	Preservative
5.	Neomalt A-200 X	In-House	----	15.000	2.50	Sweetening agent
6.	Flav. Banana Dry Flavour STR DM 9019	In-House	----	10.000	1.67	Flavouring Agent
7.	Xanthan Gum	BP	----	8.000	1.33	Suspending agent
8.	Lactose Monohydrate	BP	----	240.000	40.00	Diluent
9.	Microcrystalline Cellulose PH-112**	BP	----	180.601	30.10	Suspending agent
10.	Col. Tartrazine Supra	In-house	----	0.399	0.07	Coloring agent
11.	Colloidal Anhydrous Silica	BP	----	10.000	1.67	Suspending agent
Total				**600.00mg**	**100.00%**	

Note:

*The quantity of the Cefixime Trihydrate USP has to be calculated as per the Assay & Water content.

** Quantity of Microcrystalline Cellulose PH-112 will vary as per the quantity of the API.

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3. Pharmaceutical form:

Dosage Form:

Powder for oral Suspension

Visual & Physical characteristics of the product:

An off white colored free flowing powder filled in HDPE bottle which after reconstituted gives yellow colored suspension.

4. Clinical particulars:

4.1 Therapeutic indications:

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

- Indicated in the treatment of adults and pediatric patients six months of age or older with uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis.
- Indicated in the treatment of adults and pediatric patients six months of age or older with otitis media caused by susceptible isolates of Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pyogenes.
- Pharyngitis and Tonsillitis, caused by S. pyogenes.
- 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).

4.2 Posology and method of administration:

Adults: The recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg daily or as 200 mg every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

In the treatment of infections due to Streptococcus pyogenes, a therapeutic dosage of Cefixime should be administered for at least 10 days.

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Pediatric Patients (6months or older): 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 (Doses are suggested for each weight range)		
Patient Weight (kg)	**Dose/ day (mg)**	**100mg/ 5ml**
		Dose/ day(ml)
5 to 7.5*	50	2.5
7.6 to 10*	80	4
10.1 to 12.5	100	5
12.6 to 20.5	150	7.5
20.6 to 28	200	10
28.1 to 33	250	12.5
33.1 to 40	300	15
40.1 to 45	350	17.5
45.1 or greater	400	20

* The preferred concentrations of oral suspension to use are 100 mg/5 mL or 200 mg/5 mL for pediatric patients in these weight ranges.

Children weighing more than 45 kg or older than 12 years should be treated with the recommended adult dose. Otitis media should be treated with the chewable tablets or suspension. Therefore, the tablet or capsule should not be substituted for the chewable tablets or 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.

Renal Impairment: Cefixime for oral suspension 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. Neither haemodialysis nor peritoneal dialysis removes significant amounts of drug from the body.

Doses for Adults with Renal Impairments	
Renal Dysfunction	**100 mg/ 5ml**
Creatinine clearance (ml/min)	***Dose/Day (ml)***
60 or greater	Normal Dose
21 to 59* OR Renal haemodialysis*	13
20 or less OR continuous peritoneal dialysis	8.6

* The preferred concentration of oral suspension to use is 200 mg/5 mL for patients with this renal dysfunction.

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Reconstitution directions for Oral Suspension

Strength	Bottle Size	Reconstitution Directions
100 mg/ 5ml and 200 mg/ 5ml	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.

Method of administration:

For oral use.

Absorption of Cefixime is not significantly modified by the presence of food. Cefixime may be taken with water before during or after the meal. 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:

Cefixime for Oral Suspension is contraindicated in patients with known allergy to cefixime and the cephalosporin group of antibiotics.

4.4 Special warnings and precautions for use:

Hypersensitivity Reactions

Anaphylactic/anaphylactoid reactions (including shock and fatalities) have been reported with the use of Cefixime. Before therapy with Cefixime for oral suspension 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 antibacterial drugs has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction to Cefixime for oral suspension occurs, discontinue the drug.

Clostridium difficile-Associated Diarrhea (CDAD)

CDAD has been reported with use of nearly all antibacterial agents, including Cefixime for oral suspension and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C.difficile.

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CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C.difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial drug treatment of C.difficile, and surgical evaluation should be instituted as clinically indicated.

Coagulation Effects

Cefixime for oral suspension 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.

Adverse Reactions

The following adverse reactions have been reported following the post-approval use of Cefixime.

Gastrointestinal	Several cases of documented pseudomembranous colitis were identified in clinical trials. 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 System	Transient thrombocytopenia, leukopenia, neutropenia, prolongation in prothrombin time, elevated LDH, pancytopenia, agranulocytosis, and eosinophilia.
Abnormal Laboratory Tests	Hyperbilirubinemia.
Other Adverse Reactions	Genital pruritus, vaginitis, candidiasis, toxic epidermal necrolysis.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant intake with potentially nephrotoxic substances (such as aminoglycoside antibiotics, colistin, polymyxin and viomycin) and strong acting diuretics (e.g. ethacrynic acid or furosemide) induce in increased risk of impairment of renal function.

Administration of Cefixime may reduce the efficacy of oral contraceptive. It is therefore recommended to take supplemental non-hormonal contraceptive measures.

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.

Influence on laboratory diagnostic test

May cause false-positive urine glucose test results with Benedict solution, Fehling solution, or Clinitest tablets, but not with glucose test based on enzymatic glucose oxidase reactions (eg, Clinistix , Tes-tape); false-positive test results for ketones in the urine may occur with tests using nitroprusside but not nitroferricyanide; false-positive direct Coombs test has been reported during treatment with other cephalosporins.

4.6 Fertility, Pregnancy and lactation:

Pregnancy

Category B: Reproduction studies in mice & rats at doses up to 40 times the human dose has not demonstrated a foetal risk but there are no 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.

Lactation:

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:

No untoward effects reported as yet.

4.8 Undesirable effects:

Stomach upset/pain, diarrhea, nausea, gas, headache, or dizziness may occur. Many people using this medication do not have serious side effects.

Rare but very serious side effects includes : severe stomach/abdominal pain, persistent nausea/vomiting, yellowing eyes/skin, dark urine, unusual tiredness, new signs of infection (e.g., persistent sore throat, fever), easy bruising/bleeding, change in the amount of urine, mental/mood changes (such as confusion).This medication may rarely cause a severe intestinal condition (Clostridium difficile-associated diarrhea) due to a resistant bacteria. This condition may occur weeks to months after treatment has stopped.

Following side effects may develop: persistent diarrhea, abdominal or stomach pain/cramping, or blood/mucus in your stool.

Use of this medication for prolonged or repeated periods may result in oral thrush or a new vaginal yeast infection (oral or vaginal fungal infection).

Symptoms of a serious allergic reaction may include: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

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 properties:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Third generation semi-synthetic cephalosporin antibacterial drug.

ATC code: J01DD08.

Mode of action: Third-generation oral cephalosporin with broad activity against gram-negative bacteria. By binding to one or more of the penicillin-binding proteins, it arrests bacterial cell wall synthesis and inhibits bacterial growth.

5.2 Pharmacokinetic properties:

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Absorption

Cefixime tablets and suspension, given orally, are about 40% to 50% absorbed whether administered with or without food; however, time to maximal absorption is increased approximately 0.8 hours when administered with food.

A single 200 mg tablet of Cefixime produces an average peak serum concentration of approximately 2 mcg/mL (range 1 to 4 mcg/mL); a single 400 mg tablet produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The oral suspension produces average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal adult volunteers. Two hundred and 400 mg doses of oral suspension produce average peak concentrations of 3 mcg/mL (range 1 to 4.5 mcg/mL) and 4.6 mcg/mL (range 1.9 to 7.7 mcg/mL), respectively, when tested in normal adult volunteers. The area under the time versus concentration curve (AUC) is greater by approximately 10% to 25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal adult volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Because of the lack of bioequivalence, tablets should not be substituted for oral suspension in the treatment of otitis media.

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 400 mg of Cefixime suspension. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg of suspension.

Distribution

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 the tablet or suspension, there was little accumulation of drug in serum or urine after dosing for 14 days.

Metabolism & Excretion

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. The serum half-life of Cefixime in healthy subjects is independent of dosage form and averages 3 to 4 hours but may range up to 9 hours in some normal volunteers.

In 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.

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, invivo and invitro studies did not yield any indication of a potential to cause mutagenicity. Long-term studies on carcinogenicity have not been conducted.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Microcrystalline Cellulose with Carboxymethylcellulose Sodium
Sodium Citrate
Sodium Benzoate
Neomalt A-200 X
Flav. Banana Dry Flavour STR DM 9019
Xanthan Gum
Lactose Monohydrate
Microcrystalline Cellulose PH-112
Col. Tartrazine Supra
Colloidal Anhydrous Silica

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special precautions for storage:

Store at a temperature not exceeding 30°C. Protect from Moisture.

6.5 Nature and contents of container:

Primary Pack: 100 ml HDPE bottle

Secondary Pack: Such one bottle packed in one monocarton along with pack insert.

6.6 Special precautions for disposal:

No special requirements.

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

7. Applicant:

Chez Resources Pharmaceutical Limited

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Manufacturer:

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