(MAL) XXXXX

For the use of a Qualified Health Provider or Hospital only

IXIME

(Cefixime for Oral suspension USP)

DESCRIPTION
Off white to pale yellow coloured powder forming off white to yellow suspension with characteristic fruity colour on constitution.

COMPOSITION
Each 5 ml of reconstituted suspension contains Cefixime USP equivalent to anhydrous Cefixime 100 mg

CLINICAL PHARMACOLOGY

MICROBIOLOGY
The bactericidal action of Cefixime, as with other Cephalosporins results from inhibition of cell wall synthesis. Cefixime is highly stable in the presence of ß lactamase enzymes.

As a result, many organisms resistant to Penicillins and some Cephalosporins due to the presence of ß lactamases, may be susceptible to Cefixime.

Cefixime has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections

GRAM-POSITIVE ORGANISMS
Streptococcus pneumoniae
Streptococcus pyogenes

GRAM-NEGATIVE ORGANISMS
Haemophilus influenzae (ß lactamase positive & negative strains)
Moraxella catarrhalis (mostly lactamase positive)
Escherichia coli
Proteus mirabilis
Salmonella typhi
Neisseria gonorrhoeae (including Penicillinase & Non Penicillinase Producing strains)

CEFIXIME has been shown to be active *in vitro* against most strains of the following organisms, however, clinical efficacy has not been established.

GRAM-POSITIVE ORGANISMS
Streptococcus agalactiae

GRAM-NEGATIVE ORGANISMS
Haemophilus parainfluenzae (ß lactamase positive & negative strains)
Proteus vulgaris,
Klebsiella pneumoniae
Klebsiella oxytoca
Pasteurella multocida
Providencia species
Shigella species
Citrobacter amalonaticus
Citrobacter diversus
Serratia marcescens

NOTE
Pseudomonas species, strains of group D streptococci (including Enterococci), *Listeria monocytogenes*, most strains of Staphylococci (including Methicillin Resistant Strains) and most strains of *Enterobacter* are resistant to Cefixime.
In addition, most strains of *Bacteroides fragilis* and *Clostridia* are resistant to Cefixime.

PHARMACOKINETICS
Cefixime given orally is about 40-50% absorbed whether administered with or without food, however, time to maximal absorption is increased approximately 0.8 hours when administered with food.

The oral suspension produces average peak concentrations approximately 25-50% higher than the tablets, when tested in normal adult volunteers.

200 mg and 400 mg doses of oral suspension produced average peak concentrations of 3*µg/ml* (range 1 to 4.5 *µg/ml*) and 4.6 *µ*g/ml (range 1.9 to 7.7 *µ*g/ml), respectively, when tested in normal adult volunteers.

The area under the time versus concentration curve 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.
Cross over studies of tablet versus suspension have not been performed in children.

Peak serum concentrations occur between 2 and 6 hours following oral administration of 400 mg of Cefixime suspension.
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 *(µg/ml)*							
Dose *(mg)*	**1 hour**	**2 hours**	**4 hours**	**6 hours**	**8 hours**	**12 hours**	**24 hours**
100	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200	1.2	2.1	2.8	2.0	1.3	0.5	0.07
400	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%.
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.
In a multiple dose study conducted with a research formulation which was less bioavailable than the tablet or 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 to 4hours 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.

Cefixime is predominantly eliminated as the unchanged drug in the urine.
Glomerular filtration is the predominant mechanism of elimination and metabolites have not been isolated either from human serum or urine.
Cefixime 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.

INDICATIONS
Cefixime 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 & Proteus mirabilis*

Otitis Media caused by *Haemophilus influenzae* (beta lactamase positive & negative strains), *Mora xella catarrhalis* (most of which are beta lactamase positive) and *Streptococcus pyogenes*

Pharyngitis and Tonsillitis caused by *Streptococcus pyogenes*

NOTE
Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections, including the prophylaxis of Rheumatic Fever.

Cefixime is generally effective in the eradication of *Streptococcus pyogenes* from the nasopharynx, however, data establishing the efficacy of Cefixime in the subsequent prevention of Rheumatic Fever are not available.

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

Uncomplicated Multidrug Resistant and Quinolone Resistant Typhoid Fever caused by *Salmonella typhi.*

Uncomplicated Gonorrhea (cervical/urethral) caused by both Penicillinase and Non Penicillinase Producing Strains of *Neisseria gonorrhoeae*

DOSAGE
CHILDREN
The recommended dose of the suspension is ***8mg/kg bodyweight/day*** which may be administered as a single daily dose or may be given in two divided doses, as ***4 mg/kg every 12 hours***.

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

Pediatric Dosage Chart			
Patient Weight *(kg)*	**Dose / Day *(mg)***	**Dose / Day *(ml)***	**Dose /Day *(teaspoon)***
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

RABRO ADVERTISING & MARKETING			
Market/Customer :-	Malaysia	**Location**	Mandideep
Prepared On	28/02/2k20	**Version No**	0
Product name	Ixime Suspension (Malaysia)		
Material code	XXXXX	**Supercedes Material code**	261561
Open Size	150 x 226 mm (W x H)	**Pharmacode value**	NA
Folded Size	75 x 56.5 mm (W x H) ± 2 mm	**Component**	Leaflet
No. of Folds	V1 x H2	**GSM :**	54 ± 10% gsm Creamwove Paper
Pantone Colours	Black		
Reason of Revision:	Incorporated 'Pregnancy & Lactation' details, change in Description as suggested by the customer		

Rabro Advertising & Marketing
Artwork Same Size
Size: 150 x 226 mm (W x H)
D:\Jobs\Lupin-Ltd\UAE\Packins\Ixime Suspension (Malaysia) Feb-2020 PI XXXXX
1st Laser Proof 28/02/2k20

The recommended dose of Cefixime for Uncomplicated Multidrug Resistant and Quinolone Resistant Typhoid Fever is ***20mg /kg body weight / 24 hours*** in divided BID doses for 7 days.

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

RENAL IMPAIRMENT
Cefixime may be administered in the presence of impaired renal function as follows

Creatinine Clearance	**Dose**
>60ml/min	400 mg daily
21-60ml/min	300 mg daily
<20ml/min	200 mg daily

RECONSTITUTION DIRECTIONS FOR ORAL SUSPENSION
Tap the bottle several times to loosen powder contents prior to reconstitution.
Add boiled and cooled water. Add water up to half of the ring mark and shake vigorously.
Further add water up to the ring mark of the bottle and shake vigorously to obtain an evenly dispersed suspension. Shake the bottle to ensure uniformity.
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.

CONTRAINDICATION
Cefixime is contraindicated in patients with known allergy to the Cephalosporin group of antibiotics.

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.

DRUG INTERACTIONS

CARBAMAZEPINE
Elevated carbamazepine levels have been reported in postmarketing experience when Cefixime was 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 was administered concomitantly.
Care should therefore be taken in patients receiving anticoagulation therapy

PROBENECID
Concomitant administration of Probenecid increases peak serum concentrations and the AUC while decreasing the renal clearance and volume of distribution of Cefixime

OTHER DRUGS
Concomitant administration of Cefixime and Nifedipine increases the oral bioavailability of Cefixime as a result of higher peak plasma concentrations and area under the plasma concentration time curve.

In vitro, in pooled serum, Acetaminophen, Heparin, Phenytoin, Diazepam, Ibuprofen or Furosemide had no clinically important effects on the protein binding of Cefixime.

LABORATORY TEST INTERFERENCES

TESTS FOR URINARY GLUCOSE
Cefixime, like most Cephalosporins may cause false positive results in urinary glucose determinations, using cupric sulphate as in Benedict's solution, Clinitest or Fehling's slolution, but enzymatic Glucose Oxidase methods are unaffected.

IMMUNOHEMATOLOGY TESTS
A false positive direct Coombs test has been reported during treatment with Cephalosporin antibiotics, therefore it should be recognised that this reaction may interfere with hematologic studies or transfusion cross matching procedures and should be considered in patients receiving Cefixime

URINARY KETONES
Cefixime may cause false positive results for urinary ketones when tests using nitroprusside are used but not with tests using nitroferricyanide

WARNING
Before therapy with Cefixime is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to Cephalosporins, Penicillins or other drugs.

PRECAUTIONS
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 cases, careful observation of the patient is essential and if superinfection occurs during therapy appropriate measures should be taken.

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

SIDE EFFECTS
Cefixime is generally well tolerated.
The majority of adverse reactions observed in clinical trials were mild and self-limiting in nature.

Gastrointestinal Disturbances
The most frequent side effects seen with Cefixime are diarrhoea and stool changes with diarrhoea being been more commonly associated with higher doses.
Some cases of moderate to severe diarrhoea have been reported; this has occasionally warranted cessation of therapy. Ixime should be discontinued if marked diarrhoea occurs. Other gastrointestinal side effects seen less frequently are nausea, abdominal pain, dyspepsia, vomiting and flatulence. Pseudomembranous colitis has been reported.

Central Nervous System
Headache and dizziness
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.

Hypersensitivity Reactions
Allergies in the form of rash, pruritus, urticaria, drug fever and arthralgia have been observed.
These reactions usually subsided upon discontinuation of therapy.
Rarely Erythema multiforme, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported

Haematological and Clinical Chemistry
Thrombocytopenia, leukopenia and eosinophilia have been reported though these reactions were infrequent and reversible.
Mild transient changes in liver and renal function tests too have been observed.

Hepatic Disorders
Transient rises in liver transaminases, alkaline phosphatase and jaundice can also occur

Miscellaneous
Other possible reactions include genital pruritus and vaginitis

OVERDOSAGE
Gastric lavage may be indicated; otherwise there is no specific antidote.
Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis.

PEDIATRIC USE
Safety and Effectiveness of Cefixime in children aged less than 6 months have not been determined.
The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools in pediatric patients receiving the suspension was comparable to the incidence seen in adult patients on tablets.

PRESENTATION
50 ml HDPE bottle.

Keep all the medicines out of reach of children.
Shake well before use.

STORAGE

Prior to reconstitution :
Store the drug powder at 20-25°C

After reconstitution :
Store at room temperature or under refrigeration.
Keep the bottle tightly closed.

SHELF LIFE
24 months

Date of Revision : 28.02.2020

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