CEFIXIME

ULTRAXIME®

100 mg/5 mL Granules for Suspension
20 mg/mL Granules for Suspension (Oral Drops)

ANTIBACTERIAL

FORMULATIONS

Each 5 mL (1 teaspoonful) suspension contains:
Cefixime ....100 mg
Each mL suspension (oral drops) contains:
Cefixime .... 20 mg

PRODUCT DESCRIPTIONS

Cefixime (Ultraxime®) 100 mg/5 mL suspension and 20 mg/mL suspension (oral drops) are off-white to cream colored granules for reconstitution into off-white to cream, strawberry-flavored homogeneous suspensions.

PHARMACODYNAMICS

Cefixime is a third generation cephalosporin with antibacterial activity similar to penicillins, carbacephems and cephamycins.

Cefixime exerts its bactericidal activity by interfering with the synthesis of the bacterial cell wall. It binds to specific penicillin-binding proteins responsible for the synthesis of peptidoglycan, a heteropolymeric structure that gives the cell wall its mechanical stability. The final stage of peptidoglycan synthesis involves completion of the cross-linking of the terminal glycine residue of the pentaglycine bridge to the fourth residue of the pentapeptide. The transpeptidase that catalyzes this step is inhibited by cephalosporins. Thus, inhibition of the transpeptidase interrupts peptidoglycan synthesis, causing formation of defective cell walls and osmotically unstable spheroplasts and lysis of the bacteria.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Cefixime is active against the following organisms, both *in vitro* and in clinical infections:

Gram-positive organisms	Gram-negative organisms
Streptococcus pneumoniae *Streptococcus pyogenes*	*Haemophilus influenzae* (ß-lactamase positive and negative strains) *Moraxella catarrhalis* (most of which are ß-lactamase positive) *Escherichia coli* *Proteus mirabilis* *Neisseria gonorrhoeae* (including penicillinase- and nonpenicillinase-producing strains) *Salmonella* spp. including *S. typhi* *Shigella* spp.

Cefixime has been shown to be active *in vitro* against most strains of Gram-positive organisms such as *Streptococcus agalactiae* and most strains of Gram-negative organisms such as *Haemophilus parainfluenzae* (ß-lactamase positive and negative strains), *Neisseria meningitidis, Proteus vulgaris, Klebsiella pneumoniae, Klebsiella oxytoca, Pasteurella multocida, Providencia spp., Bordetella pertussis, Citrobacter freundii, Citrobacter amalonaticus, Citrobacter diversus, Helicobacter pylori,* and *Serratia marcescens*; however, clinical efficacy has not been established.

Pseudomonas spp., 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

About 30% to 50% of a single oral dose of cefixime is absorbed. Food decreases the rate but generally does not affect the extent of drug absorption. When cefixime oral suspension at a single dose of 4, 6, or 8 mg/kg body weight was administered to children 6 months to 6 years old or older, mean serum concentrations (C_{max}) attained 3.5 to 4.5 hours after the dose were 2.18 to 2.44, 3.55 to 4.07, and 3.4 to 3.91 µg/mL, respectively. Serum concentrations of cefixime are not directly dose proportional at doses of 4 to 8 mg/kg body weight in children. Little or no accumulation of cefixime occurs after multiple dosing.
After oral administration, cefixime is distributed into bile, sputum, tonsils, maxillary sinus mucosa, middle ear discharge, blister fluid, and prostatic fluid. Sputum concentrations may be 2% to 10% of concurrent serum concentrations; in one study, a single 200 mg oral dose of cefixime resulted in sputum concentrations of 0.03 to 0.12 µg/mL. It is not known whether cefixime is distributed into CSF after oral administration.
In children 3 months to 5 years old with acute otitis media with effusion or with otitis media with effusion that required tympanostomy tube placement, a single 8 mg/kg body weight oral dose of cefixime resulted in middle ear fluid mean concentrations averaging 1.3 to 1.4 mg/mL at 3 to 5 hours after the dose; concurrent C_{max} were 2.5 to 3.2 µg/mL.
About 65% to 75% of cefixime is bound to serum proteins, principally albumin, and such binding is not concentration-dependent over the range of 0.5 to 30 µg/mL. The fraction of free cefixime in plasma may be slightly greater in patients with renal impairment than in those with normal renal function.

Cefixime crosses the placenta and is distributed in low concentrations into amniotic fluid and cord serum; cord serum concentrations may be 15% to 50% of concurrent maternal plasma concentrations. No data are available on secretion of cefixime into human milk.
The half-life ($t_{1/2}$) of cefixime is about 3 to 4 hours and is not dose-dependent. It is excreted renally via glomerular filtration and to a lesser extent by tubular secretion. Metabolites of cefixime have not been isolated from human serum or urine. About 7% to 41% of a single oral dose of the drug is excreted unchanged in urine within 24 hours. The remainder of the dose (up to 60%) is eliminated by nonrenal mechanism. In animal studies, it was noted that up to 10% of a single oral dose of cefixime is excreted unchanged in bile.
Cefixime is not removed to a significant degree by either hemodialysis or peritoneal dialysis.

INDICATIONS

For the treatment of the following infections due to susceptible microorganisms:

- Acute bronchitis, acute exacerbations of chronic bronchitis, bronchiectasis with infection, secondary infections in chronic respiratory tract diseases, pneumonia
- Urinary tract infections including pyelonephritis, cystitis and cystourethritis
- Uncomplicated gonorrhea (cervical/urethral)
- Cholecystitis, cholangitis
- Scarlet fever
- Sinusitis, tonsillitis, pharyngitis, otitis media
- Typhoid fever (enteric fever) including multi-drug resistant typhoid fever

DOSAGE AND ADMINISTRATION

Cefixime (Ultraxime®) 100 mg/5 mL suspension and
Cefixime (Ultraxime®) 20 mg/mL suspension (oral drops)
Usual Recommended Dose in Children:

Total daily dose: 8 mg/kg body weight given as a single dose or divided into two equal doses every 12 hours (except for urinary tract infections where once daily dosing must be used, since twice daily dosing was shown to be not as effective in clinical trials).

USUAL RECOMMENDED DOSE IN CHILDREN

AGE GROUP	Cefixime (Ultraxime®) 20 mg/mL suspension (oral drops)		Cefixime (Ultraxime®) 100 mg/5 mL suspension	
	Dose in mL		Dose in mL (Dose in teaspoonful)	
	Given once a day	Given every 12 hours	Given once a day	Given every 12 hours
6 to 11 months	2.5 to 5 mL	1.25 to 2.5 mL	_	_
1 to 2 years	2.5 to 5 mL	1.25 to 2.5 mL	2.5 to 5 mL (1/2 to 1 teaspoonful)	1.25 to 2.5 mL (1/4 to 1/2 teaspoonful)
3 to 6 years	–	–	5 to 10 mL (1 to 2 teaspoonsful)	2.5 to 5 mL (1/2 to 1 teaspoonful)
7 to 12 years	–	–	10 to 15 mL (2 to 3 teaspoonsful)	5 to 7.5 mL (1 to 1 1/2 teaspoonsful)
Children over 12 years old and Adults	–	–	20 mL (4 teaspoonsful)	10 mL (2 teaspoonsful)

- **Usual duration of treatment:** 7 to 14 days
- Infections due to *Streptococcus pyogenes*: at least 10 days
- Or, as prescribed by a physician.

Typhoid Fever in Children:
Total daily dose: 15 to 20 mg/kg body weight given as a single dose or divided into two equal doses every 12 hours for 7 to 14 days.
Maximum dose: 400 mg/day

DIRECTIONS FOR RECONSTITUTION

Cefixime (Ultraxime®) dosage format	Volume of Distilled Water to be added	Directions
Cefixime (Ultraxime®) 20 mg/mL suspension (oral drops) (10 mL)	6.8 mL	Tap the bottle several times to loosen the granules before reconstitution. Add the required amount of distilled water in two portions and shake vigorously until all contents are evenly suspended. Keep bottle tightly closed. Shake well before use.
Cefixime (Ultraxime®) 100 mg/5 mL suspension (30 mL)	19.8 mL	
Cefixime (Ultraxime®) 100 mg/5 mL suspension (60 mL)	39.6 mL	

Protect from light. Store for not more than 7 days at 25°C – 30°C (Room) or not more than 14 days at 4°C - 8°C (Refrigerator). Discard unused portion after 7 or 14 days depending on how the reconstituted product is stored.

CONTRAINDICATION

Known hypersensitivity to cefixime or other cephalosporins, to penicillins or any component of the product.

WARNINGS AND PRECAUTIONS

- A thorough inquiry about the patient's previous hypersensitivity history should be made. Cefixime, like other cephalosporins, penicillins and other drugs, may cause serious hypersensitivity reactions and should be used with caution in any patient who has demonstrated some allergy to any drug. Although it has not been established, allergic reactions to antibiotics may occur more frequently in atopic individuals. Serious acute hypersensitivity reactions may require treatment with Epinephrine and other emergency measures including oxygen, intravenous fluids and intravenous antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.
- *Clostridium difficile*-associated diarrhea (CDAD) and colitis have been reported with the use of nearly all antibacterial agents, including cefixime, and may range in severity from mild to life threatening. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.
- As with other broad-spectrum antibiotics, cefixime should be given with caution in individuals with a history of colitis. The safety and efficacy of cefixime have not been established in patients with gastrointestinal malabsorption.
- Cephalosporins may be associated with a fall in prothrombin activity. Patients who are at risk are those with kidney or liver 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.
- Seizures have been reported with several cephalosporins (e.g., cefuroxime, ceftazidime), particularly in patients with renal impairment in whom dosage of the drug was not reduced. If seizures occur during treatment with a cephalosporin, the drug should be discontinued and anticonvulsant therapy initiated as clinically indicated.
- Prescribing cefixime in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of antibiotic resistance.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Studies have not been performed to date to evaluate the carcinogenic potential of cefixime. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage, or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to 125 times the adult therapeutic dose.

INTERACTIONS WITH OTHER MEDICAMENTS

- **Carbamazepine:** Elevated carbamazepine levels have been reported when administered concomitantly with cefixime. Drug monitoring when these drugs are given together is advised.
- **Chloramphenicol:** *In vitro* and *in vivo* antagonism have been noted between cephalosporins and chloramphenicol against a variety of Gram-positive and Gram-negative bacteria; therefore, it is recommended that combined therapy with chloramphenicol and a cephalosporin be avoided, particularly when bactericidal activity is considered important.
- **Nifedipine:** Concomitant administration of cefixime and nifedipine increases oral bioavailability of cefixime as a result of higher C_{max} and AUC.
- **Probenecid:** Concomitant administration of probenecid reportedly increases C_{max} and AUC of cefixime and decreases renal clearance and volume of distribution of the drug.
- **Salicylates:** Concomitant administration of 650 mg oral dose of aspirin and a 400 mg oral dose of cefixime in healthy adult men may result in a 20-25% decrease in C_{max} and AUC of cefixime but did not affect protein binding, serum $t_{1/2}$ or renal clearance. This effect may not be clinically important since serum concentrations of cefixime remained higher than the MIC values reported for most susceptible organisms. However, some clinicians state that this effect may be clinically important in certain infections.
- **Warfarin and other anticoagulants:** Increased prothrombin time, with or without clinical bleeding, has been reported when cefixime is given concomitantly.

Interference with Laboratory Tests

- **Nitroprusside test:** A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.
- **Coombs' test:** A false-positive Coombs' test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs' test may be due to the drug, e.g., Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition or in hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed.
- **Clinitest®, Benedict's solution, Fehling's solution:** A false-positive reaction for glucose in the urine using Clinitest®, Benedict's solution, or Fehling's solution may result when done during therapy with cefixime. It is recommended that other tests based on enzymatic glucose oxidase reactions (e.g., Clinistix®) be used.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

- ***Pregnancy:*** (Pregnancy Category B). Reproduction studies performed in mice and rats up to 400 times the human dose have not revealed evidence of harm to the fetus. There are no adequate and well-controlled studies in pregnant women, and the drug should be used during pregnancy only when clearly needed.
- ***Labor and Delivery:*** The effect of cefixime in labor and delivery is unknown.
- ***Lactation:*** It is not known whether cefixime is excreted in human milk. Consideration should be given to discontinuing breastfeeding temporarily during treatment with cefixime.

- ***Use in Children:*** The safety and efficacy of cefixime in children less than six (6) months old have not been established. The incidence of GI adverse reactions such as diarrhea and loose stools, in children receiving cefixime suspension, was comparable to the incidence seen in adults receiving cefixime tablets.
- ***Use in Patients with Renal Impairment:*** Experience in children with renal impairment is very limited.

UNDESIRABLE EFFECTS

Most adverse effects reported with cefixime were similar to those reported with other oral cephalosporins and were usually mild and transient in nature.
Gastrointestinal Effects: Abdominal pain, anorexia, diarrhea, dry mouth, dyspepsia, flatulence, loose or frequent stools, nausea, vomiting, pseudomembranous colitis, pruritus ani.
Hypersensitivity Reactions: Anaphylactic/anaphylactoid reactions (including shock and fatalities), angioedema, arthralgia, drug fever, erythema multiforme, facial edema, pruritus, skin rashes, serum sickness-like reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Hepatic Effects: Transient elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin and lactate dehydrogenase (LDH); hepatitis, jaundice
Renal and Genitourinary Effects: Transient elevations in blood urea nitrogen (BUN) and serum creatinine levels, acute renal failure, dysuria, pyuria, genital pruritus, vaginitis, vaginal candidiasis
Central Nervous System Effects: Dizziness, headache, fatigue, insomnia, malaise, nervousness, seizures, somnolence
Hematologic Effects: Transient thrombocytopenia, thrombocytosis, leukopenia, leukocytosis, neutropenia, and eosinophilia; prolongation of prothrombin time and partial thromboplastin time, decreased hemoglobin concentration and hematocrit
Abnormal Laboratory Test: Hyperbilirubinemia
Other Adverse Effects: Increased serum amylase concentrations

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:

- Allergic reactions, hypersensitivity reactions including chills, joint pain or inflammation, hypotension; renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis; aplastic anemia, hemolytic anemia, epistaxis or hemorrhage, agranulocytosis, thrombocythemia, granulocytosis, monocytosis, lymphocytopenia, basophilia, hypoprothrombinemia (with or without bleeding), menstrual irregularities, tenesmus, epigastric pain, glossitis, candidiasis (oral thrush), taste alteration, decreased salivation, heartburn, colitis, nightmares, vertigo, chest pain, pleural effusion, pulmonary infiltrate, dyspnea or respiratory distress, cough, and rhinitis, increased or decreased serum glucose concentration, superinfection
- Abnormal Laboratory Tests: Positive Coombs' test, pancytopenia, transient increase in γ-glutamyl transferase, decreased serum albumin and/or total protein

OVERDOSE AND TREATMENT

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

STORAGE CONDITIONS

Keep the products out of sight and reach of children.
Store at temperatures not exceeding 30°C.

AVAILABILITY

Cefixime (Ultraxime®) 20 mg/mL Granules for Suspension (Oral Drops) in bottle of 10 mL.
Cefixime (Ultraxime®) 100 mg/5 mL Granules for Suspension in bottle of 30 mL and 60 mL.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

DATE OF REVISION OF THE PACKAGE INSERT: April 2012

Manufactured by
ASIAN ANTIBIOTICS, INC.
No. 130 Pioneer Street
Mandaluyong City, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City
Metro Manila, Philippines
Under License from:
Astellas Pharma Inc.
Tokyo, Japan