PRODUCT MONOGRAPH

^{Pr}SUPRAX®

Cefixime tablets, Mfr. Std., 400 mg
Cefixime for oral suspension, Mfr. Std., 100 mg/5 mL

Antibiotic

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

SUPRAX (cefixime) exerts its bactericidal effect by attaching to penicillin-binding proteins and inhibiting peptidoglycan synthesis, thus causing damage to the bacterial cell wall.

Following oral dosing, SUPRAX attains peak serum levels in approximately 4 hours. The half-life is about 3 to 4 hours and is not dose dependent. Cefixime is excreted by renal and biliary mechanisms. About 50% of the absorbed dose is excreted unchanged in the urine within 24 hours. There is no evidence of metabolism of cefixime *in vivo*.

INDICATIONS AND USAGE

SUPRAX (cefixime) is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms:

Upper Respiratory Tract:
Pharyngitis and tonsillitis caused by *S. pyogenes*.

Middle Ear:
Otitis media caused by *S. pneumoniae, H. influenzae* (beta-lactamase positive and negative strains), *M. catarrhalis* (former *B. catarrhalis*) (beta-lactamase positive and negative strains) and *S. pyogenes*.

Paranasal sinuses:
Sinusitis caused by *S. pneumoniae, H. influenzae* (beta-lactamase positive and negative strains), and *M. catarrhalis* (former *B. catarrhalis*) (beta-lactamase positive and negative strains).

Lower Respiratory Tract:
Acute bronchitis caused by *S. pneumoniae, M. catarrhalis* (former *B. catarrhalis*) (beta-lactamase positive and negative strains) and *H. influenzae* (beta-lactamase positive and negative strains).

Urinary Tract:
Acute uncomplicated cystitis and urethritis caused by *E. coli, P. mirabilis*, and *Klebsiella* species.

Uncomplicated Gonorrhea
Uncomplicated gonorrhea (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including penicillinase (beta-lactamase-positive) and nonpenicillinase (beta-lactamase-negative) producing strains.

Appropriate cultures should be taken for susceptibility testing before initiating treatment with SUPRAX. If warranted, therapy may be instituted before susceptibility results are known; however, once these are obtained, therapy may need to be adjusted.

CONTRAINDICATIONS

SUPRAX (cefixime) is contraindicated in patients with known allergies to the cephalosporin or penicillin antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, SUPRAX (cefixime) SHOULD BE ADMINISTERED CAUTIOUSLY. PATIENTS MAY BE SENSITIVE TO PENICILLINS AND NOT TO CEPHALOSPORINS SUCH AS SUPRAX OR BE SENSITIVE TO BOTH. MEDICAL LITERATURE INDICATES THAT PATIENTS SENSITIVE TO CEPHALOSPORINS ARE VERY LIKELY TO BE PENICILLIN SENSITIVE.

Antibiotics, including SUPRAX (cefixime), should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including SUPRAX. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile. C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given

to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

PRECAUTIONS

General:
If an allergic reaction to SUPRAX (cefixime) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

The possibility of the emergence of resistant organisms, which might result in overgrowth, should be kept in mind, particularly during prolonged treatment. In such use, careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics such as SUPRAX should be prescribed with caution in individuals with a history of gastrointestinal disease.

Once daily dosing only must be used for urinary tract infections, since twice daily dosing was shown to be not as effective in clinical studies.

Do not use SUPRAX to treat *Staphylococcus aureus* as this strain of staphylococcus is resistant to cefixime.

Renal Impairment:
SUPRAX may be administered in the presence of impaired renal function, but dose modification is recommended for patients with moderate or severe renal impairment (i.e., creatinine clearance of < 40 mL/min). See **DOSAGE AND ADMINISTRATION** section.

Bioavailability Differences Between Tablet and Suspension:
The area under the time versus concentration curve is greater by approximately 26.4% and the C_{max} is greater by approximately 20.7% with the oral suspension when compared to the tablet after doses of 400 mg. 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 particularly in the treatment of otitis media where clinical trial experience with the suspension only is available. (See **DOSAGE AND ADMINISTRATION** section).

Drug/Laboratory Interactions:
A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

The administration of beta-lactams may result in a false-positive reaction for glucose in the urine using Clinitest*, Benedict's solution, or Fehling's solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix*) be used.

A false-positive direct Coombs test has been reported during treatment with cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Usage in Pregnancy:
The safety of SUPRAX in the treatment of infection in pregnant women has not been established.

Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefixime. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the likely benefits of using SUPRAX outweigh the potential risk to the fetus and/or the mother.

Labour and Delivery:
SUPRAX has not been studied for use during labour and delivery.

Nursing Mothers:
It is not known whether cefixime is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when cefixime is administered to a nursing woman.

Usage in Children:
Safety and effectiveness of SUPRAX in children less than six months old have not been established.

ADVERSE REACTIONS

Clinical Trials:
Five percent (5%) of patients in the clinical trials discontinued therapy because of drug-related adverse reactions. Thirty-six percent of the pediatric patient population experienced at least one adverse reaction (mild 25%, moderate 9%, severe 2%). Forty-seven percent of the adult patients experienced at least one adverse reaction (mild 24%, moderate 19%, severe 4%). The most commonly seen adverse reactions in the clinical trials of the tablet formulation were gastrointestinal events, which were reported in 37% of all adult patients treated (mild 21%, moderate 13%, severe 3%). The predominant adverse events seen in adults in clinical trials with SUPRAX (cefixime) were diarrhea 15%, (mild 7.2%, moderate 6.2%, severe 1.5%), headache 11%, stool changes 12%, nausea 9%, abdominal pain 5%, and dyspepsia 3%. The rates of the most prevalent adverse reactions were similar in the once a day and twice a day dosing regimens with the exception of headache, which appears slightly more frequently in adults, dosed once a day (12.9%) versus twice a day (8%). Other than for generally mild rashes or emesis, which

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were each observed in 5% of children treated, the incidence of adverse reactions in pediatric patients receiving the suspension was generally comparable to the incidence seen in adult patients receiving tablets.

These symptoms usually responded to symptomatic therapy or ceased when SUPRAX (cefixime) was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

When SUPRAX was used as single 400 mg dose therapy in clinical trials in the treatment of uncomplicated gonorrhoea, adverse reactions which were considered to be related to SUPRAX therapy, were reported for 5.9% (21/358) of patients. Clinically mild gastrointestinal side effects occurred in 3.7% of all patients, moderate events occurred in 0.9% of all patients and no adverse reactions were reported as severe. Individual event rates included diarrhea 1% and loose or frequent stools 1%. Incidence rates for all other adverse reactions reported for adults in these trials were less than 1%.

Other Adverse Events including Post-Marketing Surveillance Data:
The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as otherwise noted.

Central Nervous System:
Headaches (11%) and dizziness (3%).

Gastrointestinal:
Diarrhea (15%), stool changes (12%), nausea (9%), abdominal pain (5%), dyspepsia (3%), flatulence (3%), and vomiting (2%).
Pseudomembranous colitis has been reported rarely.

Hepatic:
Transient elevations of SGPT, SGOT and alkaline phosphatase.

Renal:
Transient elevations in Blood Urea Nitrogen (BUN) or creatinine.

Hemic and Lymphatic Systems:
Transient thrombocytopenia, thrombocytosis, leukopenia, eosinophilia, neutropenia and agranulocytosis. Prolongation in prothrombin time was seen rarely.

Hypersensitivity Reactions:
Skin rashes, drug fever and pruritus. Anaphylactic reactions (urticaria and angioedema) have been reported rarely.

Other:
Genital pruritus, vaginitis and candidiasis has been reported.

Skin:
Bullous skin reactions (erythema multiforme and Stevens-Johnson syndrome) have been reported very rarely.

In addition to the adverse reactions listed above which have been observed in patients treated with SUPRAX the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics. Allergic reactions were reported including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, and hemorrhage. Abnormal laboratory tests were reported including positive Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia and agranulocytosis.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE** sections). If seizures associated with SUPRAX occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Adults:
The recommended dose of SUPRAX (cefixime) is 400 mg once daily. When necessary, a dose of 200 mg (one-half of a 400 mg tablet) given twice daily may be considered except for urinary tract infections where once daily dosing must be used.

For treatment of uncomplicated gonococcal infections, a single oral dose of 400 mg is recommended.

Children*:*
The recommended dose of SUPRAX is 8 mg/kg/day once daily. When necessary, a dose of 4 mg/kg given twice daily may be considered except for urinary tract infections where once daily dosing must be used.

Table 1: Pediatric dosage chart

WEIGHT (Kg)	DOSE/DAY (mg)	DOSE/DAY (mL)
6	48	2.4
12.5	100	5.0
19	152	7.6
25	200	10.0
35	280	14.0

Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose. Safety and effectiveness in infants aged less than six months have not been established.

Otitis media should be treated with the suspension. Clinical studies of otitis media were conducted with the suspension only and the suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the suspension in the treatment of otitis media (see **PRECAUTIONS** section).

Duration of Therapy:
Duration of dosage in clinical trials was 10 to 14 days. The duration of treatment should be guided by the patient's clinical and bacteriological response.

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

Renal Impairment:
SUPRAX may be administered in the presence of impaired renal function. Normal dose and schedule may be employed in patients with creatinine clearances of 40 mL/min or greater. Patients whose clearance is between 20 and 40 mL/min should be given 75% of the standard daily dosage. Patients whose creatinine clearance is less than 20 mL/min should be given 50% of the standard daily dosage.

Experience in children with renal impairment is very limited.

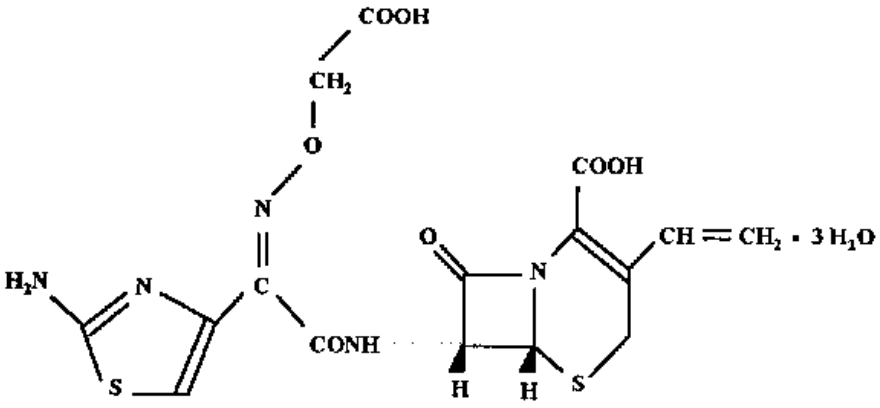
NOTE: Neither hemodialysis, nor peritoneal dialysis remove significant amounts of cefixime from the body.

PHARMACEUTICAL INFORMATION

Chemistry:

Trade Name: SUPRAX
Proper Name: Cefixime
Chemical Name: (6R, 7R)-7-[[(Z)-2-(2-aminothiazol-4-yl)-2-[(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid trihydrate.

Structural Formula:



Molecular Formula: $C_{16}H_{15}N_50_7S_2.3H_20$
Molecular Weight: 507.50
Description: Cefixime is a white to light yellow powder. Slightly soluble in water, soluble in methanol, sparingly soluble in ethanol, practically insoluble in ethyl acetate.

The pH of a 0.5 g in 10 mL suspension is between 2.6 and 4.1

Composition:

SUPRAX (cefixime) is available in scored 400 mg film coated tablets and in powder for oral suspension, which can be reconstituted to provide 100 mg/5 mL.

Inactive Ingredients:

Tablets:
The 400 mg tablets contain: Calcium phosphate dibasic dihydrate, hydroxypropyl methylcellulose, light mineral oil, magnesium stearate, microcrystalline cellulose, pregelatinized starch, sodium lauryl sulfate and titanium dioxide.

Powder for Oral Suspension:
The powder for oral suspension contains artificial strawberry flavour, sodium benzoate, sucrose and xanthan gum.

Reconstitution Directions for Oral Suspensions:

Bottle:

SIZE	RECONSTITUTION DIRECTIONS
50 mL	Suspend with 33 mL water.
Method:	Tap the bottle several times to loosen powder contents prior to reconstitution. Add 33 mL of water in TWO PORTIONS. Mix well after each addition. Provides 20 mg/mL.

After mixing, the suspension may be kept for 14 days at room temperature or under refrigeration without significant loss of potency. Keep container tightly closed. Shake well before using. Discard unused portion after 14 days.

AVAILABILITY

Tablets:

SUPRAX (cefixime) tablets 400 mg are biconvex, oblong, white film coated tablets, with rounded flattened corners, breaking scores on both sides and engraved EM 400 on one side. The 400 mg tablet can be split into two equal parts of 200 mg.

The 400 mg tablets are supplied as follows:
- Blister packs of 7 tablets;
- Blister packs of 10 tablets

Powder for Oral Suspension:

SUPRAX (cefixime) Powder for Oral Suspension is a white to cream-coloured-granulated powder which when reconstituted as directed contains 100 mg/5 mL cefixime.

The powder for oral suspension is supplied in bottles of 50 mL.

Storage:

The tablets and powder for oral suspension should be stored at controlled room temperature 15 - 30°C.

MICROBIOLOGY

In vitro activity of SUPRAX (cefixime) against various gram-positive and gram-negative organisms is presented in Table 2.

Table 2: Activity of cefixime against clinical isolates of bacteria

Organism	Number of isolates	MIC_{50}[a] (µg/mL)	MIC_{90} (µg /mL)
GRAM-NEGATIVE			
Acinetobacter calcoaceticus	434	9.07	19.41
Moraxella catarrhalis *(formerly Branhamella catarrhalis)*	108	0.14	0.40
Campylobacter jejuni	10	1.60	1.60
Citrobacter amalonaticus	56	0.32	1.54
Citrobacter diversus	154	0.12	0.16
Citrobacter Freundii	766	2.01	57.40
Enterobacter aerogenes	644	0.85	38.30
Enterobacter agglomerans	63	0.40	25.70
Enterobacter cloacae	1532	2.48	48.40
Enterobacter species	442	3.27	20.00
Escherichia coli	6190	0.19	0.71
Haemophilus influenzae	751	0.04	0.13
H. influenzae, Ampicillin-susceptible	2236	0.03	0.12
H. influenzae, Ampicillin-resistant	30	0.08	0.08
H. influenzae, Beta-lactamase-negative	82	0.05	0.05
H. influenzae, Beta-lactamase-positive	188	0.03	0.06
H. parainfluenzae	2	0.05	0.05
Klebsiella oxytoca	490	0.04	0.06
Klebsiella pneumoniae	2760	0.06	0.10
Klebsiella species	128	0.08	0.34
Morganella morganii	741	0.74	17.00
Neisseria gonorrhoeae	325	0.15	0.15
Neisseria gonorrhoeae Beta-lactamase-negative	325	0.008	0.015
Neisseria gonorrhoeae Beta-lactamase-positive	195	0.008	0.03
Neisseria gonorrhoeae Tetracycline-resistant	99	0.008	0.015

Table 2: Activity of cefixime against clinical isolates of bacteria (cont'd)

Organism	Number of isolates	MIC_{50}[a] (µg/mL)	MIC_{90} (µg /mL)
GRAM-NEGATIVE			
Neisseria gonorrhoeae Chromasomally-resistant	173	0.015	0.06
Neisseria meningitis	19	0.06	0.06
Pasteurella multocida	1	0.06	0.06
Proteus mirabilis	1983	0.05	0.06
Proteus vulgaris	658	0.03	0.10
Proteus, indole-positive	118	0.06	5.91
Proteus species	4	0.25	0.25
Providencia rettgeri	346	0.05	0.37
Providencia stuartii	241	0.10	0.67
Providencia species	15	0.40	2.15
Pseudomonas aeruginosa	2003	47.00	53.10
Pseudomonas cepacia	132	2.42	6.87
Salmonella enteriditis	27	0.17	0.34
Salmonella species	337	0.09	0.21
Serratia marcescens	1552	0.71	12.90
Shigella species	327	0.12	0.48
Yersinia enterocolitica	62	0.37	1.62
GRAM-POSITIVE			
Enterococcus faecalis	161	65.60	100.00
Enterococcus species	988	33.00	33.00
Staphylococcus aureus	1949	17.50	36.50
Staphylococcus epidermidis	438	10.80	61.80
Streptococcus agalactiae	48	0.21	0.32
Streptococcus pyogenes	830	0.11	0.16
Streptococcus Group B	112	0.17	0.22
Streptococcus pneumoniae	547	0.13	0.29
Streptococcus viridans	42	0.84	26.70

[a] Geometric mean MIC for 50% and 90% of the isolates.
Abbreviation: MIC, minimal inhibitory concentration.

The following organisms are resistant to cefixime:

- *Pseudomonas* species
- strains of group D streptococci (including enterococci)
- *Listeria* monocytogenes
- most strains of staphylococci (including methicillin-resistant strains)
- most strains of *Enterobacter*
- most strains of *Bacteroides fragilis* and *Clostridia*.

Susceptibility testing:

Susceptibility Tests: Diffusion Techniques:
Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such procedure has been recommended for use with disks to test susceptibility to cefixime. Interpretation involves correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefixime.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 5 µg cefixime disk should be interpreted according to the following criteria:

Table 3: Recommended Susceptibility Ranges: Agar Disk Diffusion

Organisms	Resistant	Moderately Resistant	Susceptible
Neisseria gonorrhoeae[a]	-	-	≥ 31 mm
All other organisms	≤ 15 mm	16-18 mm	≥ 19 mm

[a] Using GC Agar Base with a defined 1% supplement with cysteine.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" indicates that inhibitory concentrations of the antibiotic may well be achieved if high dosage is used or if the infection is confined to tissues and fluids (e.g., urine) in which high antibiotic levels are attained. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 5 µg disk should give the following zone diameter:

Table 4: Control organisms: Agar Disk Diffusion

Organism	Zone Diameter (mm)
E. coli ATCC 25922	23-27
N. gonorrhoeae ATCC 49226[a]	37-45

[a] Using GC Agar Base with a defined 1% supplement with cysteine.

The class disk for cephalosporin susceptibility testing (the cephalothin disk) is not appropriate because of spectrum differences with cefixime. The 5 µg cefixime disk should be used for all *in vitro* testing of isolates.

Dilution Techniques:

Broth or agar dilution methods can be used to determine the minimum inhibitory concentration (MIC) value for susceptibility of bacterial isolates to cefixime. The recommended susceptibility breakpoints are as follows:

Table 5: MIC Interpretive Standards (µg /mL)

Organisms	Resistant	Moderately Resistant	Susceptible
Neisseria gonorrhoeae[a]	-	-	≤ 0.25
All other organisms	≥ 4	2	≤ 1

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Standard cefixime powder should give the following MIC ranges in daily testing of quality control organisms:

Table 6: Control organisms: Dilution technique

Organism	MIC Range (µg /mL)
E. coli ATCC 25922	0.25 - 1
S. aureus ATCC 29213	8 - 32
N. gonorrhoeae ATCC 49226[a]	0.004 - 0.03

[a] Using GC Agar Base with a defined 1% supplement with cysteine.

PHARMACOLOGY

Animal Pharmacology:

Tissue Distribution/Accumulation:
In rats, ^{14}C-labelled cefixime was distributed (in order of descending amounts) to the kidneys, lungs, liver, heart, spleen, and brain at 1 hour following a single oral dose of cefixime and to the kidneys, urinary bladder, blood, liver, and lungs at 5 minutes after a single intravenous dose. In dogs, tissue radioactivity was noted in bile, kidney, liver, lung, testes, heart, and brain after single or multiple intravenous dosing with ^{14}C-labelled cefixime.

After multiple oral dosing, accumulation of cefixime was negligible in the serum and urine of adult rats and dogs. The doses used in these studies were 100 and 1000 mg/kg/day administered for 1 month to rats and up to 400 mg/kg/day (100, 200 and 400 mg/kg/day) for 53 weeks to dogs. In addition, there was no evidence of drug accumulation in serum or urine after two weeks of intravenous dosing (320 and 1000 mg/kg/day) in adult dogs.

In animal studies, it was noted that cefixime is excreted in the bile in excess of 10% of the administered dose.

Human Pharmacokinetics:

Absorption:

SUPRAX (cefixime), given orally, is about 40% to 50% absorbed.

In adults a single 200 mg tablet of SUPRAX produces an average peak serum concentration of approximately 2 µg/mL (range 1 to 4 µg/mL); a single 400 mg tablet produces an average concentration of approximately 3.5 µg/mL (range 1.3 to 7.7 µg/mL). The oral suspension, in adults, following 200 mg and 400 mg doses produces average concentrations of 2.8 µg/mL (range 1 to 4.5 µg/mL) and 4.4 µg/mL (range 1.9 to 7.7 µg/mL), respectively. The area under the time versus concentration curve is greater by approximately 26.4% with the oral suspension than with the tablet after doses of 400 mg. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet.

Peak serum concentrations occur between 2 and 6 hours following oral administration of a single 200 mg tablet, a single 400 mg tablet or 400 mg suspension of SUPRAX. Peak serum concentrations occur between 2 and 5 hours following a single administration of 200 mg suspension. See Tables 7 and 8.

Table 7: Serum Levels of Cefixime in Adults after Administration of Tablets (µg/mL)

DOSE	1hr	2hr	4hr	6hr	8hr	12hr	24hr
100 mg*	0.3	0.8	1.0	0.7	0.4	0.2	0.2
200 mg	0.7	1.4	2.0	1.5	1.0	0.4	0.03
400 mg	1.2	2.5	3.5	2.7	1.7	0.6	0.04

* ½ x 200 mg tablets

Table 8: Serum Levels of Cefixime in Adults after Administration of Oral Suspension (µg/mL)

DOSE	1hr	2hr	4hr	6hr	8hr	12hr	24hr
100 mg	0.7	1.1	1.3	0.9	0.6	0.2	0.02
200 mg	1.2	2.1	2.8	2.0	1.3	0.5	0.07
400 mg	1.8	3.3	4.4	3.3	2.2	0.8	0.07

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

Metabolism:

There is no evidence of metabolism of cefixime *in vivo*.

Excretion:

Cefixime is excreted by renal and biliary mechanisms.

The urinary recoveries of orally administered 200 mg and 400 mg doses of cefixime in 12 healthy men are presented in Table 9. Over a 24 hour period, approximately 20% and 16% of a 200 mg and 400 mg dose of cefixime, respectively was excreted in the urine. An additional 10% or more was recovered from bile.

Table 9: Mean urinary excretion of cefixime after 200 and 400 mg dose in 12 healthy men

DOSE	24-h Urinary Recovery of Cefixime (% of administered dose)	Maximum Concentration of Cefixime in Urine (µg/mL)
200 mg	20.0	107
400 mg	16.1	164

Distribution and Accumulation:

Cefixime appears to be widely distributed, however, adequate tissue concentration data relating to tablet and suspension are not available.

Serum protein binding is concentration independent with a bound fraction of approximately 65%. Multiple dose studies conducted with 200 mg or 400 mg tablets in normal volunteers showed there was little or no accumulation of drug in serum or urine after dosing for 14 days.

Adequate data on CSF levels of cefixime are not available.

Factors Affecting Pharmacokinetics:

RENAL
In patients 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.

AGE (CHILDREN)

The dose proportionality of SUPRAX suspension was evaluated in 42 pediatric patients who were 6 months of age or older. With doses of 4, 6, and 8 mg/kg, serum concentrations at a single time point after administration (3.5 hours) increased with dose but not in a dose-proportional manner. In particular, the 8 mg/kg dose did not produce twice the serum level observed with the 4 mg/kg dose. The mean serum concentrations following the 4 mg/kg dose were 2.2 to 2.6 µg/mL. The serum concentrations after the 6 and 8 mg/kg doses were 2.5 to 4.8 µg/mL. (Table 10).

Table 10: Mean pharmacokinetic values in 42 pediatric patients following administration of a single dose of SUPRAX suspension

Mean Serum Concentration (µg/mL) at 3.5 h after administration at the following age ranges (yr)				
DOSE	**0.5 to 2**	**> 2 to < 6**	**≥ 6**	**All Patients**
4 mg/kg	2.56	2.51	2.22	2.44
6 mg/kg	4.48	2.51	4.82	4.07
8 mg/kg	3.40	3.55	4.79	3.91

AGE (ELDERLY PATIENTS)

All adults may be given the same dosage regimen of SUPRAX regardless of age. A comparative pharmacokinetic study in 12 healthy men over 64 years of age and in 12 men 18 to 35 years of age used a 400 mg dose of SUPRAX administered once daily for 5 days. Blood and urine samples were obtained at frequent intervals. Table 11 shows the mean serum concentration-time profiles of cefixime. C_{max} and AUC were greater in the elderly on the first (4.77 µg/mL and 41.0 µg.h/mL) and fifth (5.45 µg/mL and 49.5 µg.h/mL) days of dosing when compared with corresponding values in the young subjects on day 1 (3.64 µg/mL and 28.6 µg.h/mL) and day 5 (4.53 µg/mL and 34.9 µg.h/mL). These differences were statistically significant, but their magnitude was too small to be of clinical significance. $T_{1/2}$ values were not different between the two groups.

Table 11: Mean pharmacokinetic parameters for cefixime on day 5 in young and elderly subjects given 400 mg daily for 5 days

GROUP	**AGE (yrs)**	**C_{max} (µg/mL)**	**T_{max} (h)**	**$AUC_{0\text{-inf.}}$ (µg.h/mL**	**$T_{1/2}$ (h)**	**fe (% dose)**
Young	20-32	4.74	3.9	34.9	3.5	20.2
Elderly	65-74	5.68	4.3	49.5	4.2	24.6

Abbreviations: C_{max} = peak serum concentration;
T_{max} = time to reach maximum serum concentration;
AUC = area under the serum concentration versus time curve;
$T_{1/2}$ = serum half-life;
fe = urinary recovery of cefixime expressed as a fraction of the administered dose.

FOOD (EFFECT OF FOOD ON ABSORPTION)

There was no clinically significant effect of food on the absorption of cefixime. SUPRAX was administered as a single 400 mg dose with and without food in a crossover study in 20 healthy men. C_{max} values were 4.22 and 4.24 µg/mL in the fed and fasted states, respectively. Food slowed the time to reach C_{max} by about 1 hour (3.8 hours versus 4.8 hours). This effect is of no clinical significance and probably reflects a small delay in gastric emptying due to the presence

of food. Urinary recovery was unaffected by the presence of food: 18.4% (fed) and 17.7% (fasted) of the doses were recovered in 24 hours.

DRUG INTERACTION

A four-way crossover study in 12 healthy men evaluated the pharmacokinetics of SUPRAX when administered with, before, and after aluminum/magnesium containing antacids. The administration of antacid did not significantly alter the pharmacokinetic parameters of cefixime.

In a protein-binding interaction study using human serum, there was no statistically significant change in the fraction of unbound cefixime with the addition of acetaminophen, heparin, phenytoin, ibuprofen, furosemide or diazepam at their reported maximum therapeutic concentrations. With salicylic acid there was a significant, approximately two fold increase from 35% to 66% in the unbound fraction. When the interaction was studied in dogs, it was confirmed that ASA-related products (i.e. salicylic acid) caused an increase in the unbound fraction of cefixime, which ultimately resulted in an increase in the volume of distribution and the clearance of the drug. However, since the volume of distribution and clearance increased to the same extent, there was no net effect on the elimination half-life of cefixime.

An open-label, randomized, crossover study in 15 healthy men found that concomitant administration of ASA (650 mg) with SUPRAX 400 mg tablet had no effect on protein binding, half-life, or renal clearance of SUPRAX. ASA did, however, appear to decrease absorption of SUPRAX as evidenced by a 26% reduction in C_{max} and 19% reduction in AUC values.

TOXICOLOGY

Single-Dose Toxicity:
Oral LD_{50} values were > 10 g/kg for mice (5-10/sex/group), rats (5-10/sex/group) and rabbits (5/sex/group). In 13 dogs, lethal dose determination was limited by emesis occurring at a single oral dose of 0.32 g/kg or higher; there was no mortality among these dogs. After intravenous, intraperitoneal, or subcutaneous injection, LD_{50} values were greater than 3, 7, or 10 g/kg, respectively, for mice (5-10/sex/group), and 5, 8 or 10 g/kg, respectively for rats (5-10/sex/group). The tolerated intravenous dose in rabbits (3M/group) was 0.32 g/kg. In one male dog, a total intravenous infusion dose of 5.5 g/kg was not associated with lethality. Signs of toxicity in this dog were decreased blood pressure and respiratory rate, emesis, and electrocardiogram abnormalities.

Following oral dosing in young animals (10/sex/group), LD_{50} values were 3 g/kg in 4-day old mice, 7 g/kg in 4-day old rats, and > 10 g/kg in 20- and 34-day old rats. Oral doses of 3.2 g/kg in 2 week old dogs (2M/1F) and 8-week old dogs (1M/2F) were not lethal, did not affect body weight and were not associated with gross postmortem or histopathologic changes. Young dogs were able to tolerate higher doses of cefixime without emesis than were older dogs due to the incomplete maturation of the emetic centre in young dogs.

Multiple-Dose Toxicity:
Multiple-dose oral toxicity studies were conducted for periods of 4 weeks to 1 year in rats and dogs. Studies in rats utilized doses up to 3200 mg/kg administered once daily (15-20/sex/group) or up to 500 mg/kg given twice daily (12/sex/group). Studies in dogs (4-5/sex/group) employed doses up to 200 mg/kg administered twice daily. In addition, studies of 2 weeks duration were conducted in rats (10/sex/group) and dogs (2/sex/group) to assess the effects of daily intravenous administration of cefixime. An 8-day study in dogs (3/sex/group) utilizing ascending intravenous doses of 80 to 2500 mg/kg was conducted to assess the nephrotoxic potential of cefixime. The results of these studies follow.

Soft feces, enlargement of the cecum and increased cecal weights were seen across all rat studies. These are common findings in rats following treatment with antibiotics. Decreased urobilinogen was also observed and is considered to be related to changes in the intestinal flora resulting in reduced production of urobilinogen from bilirubin. The chronic nephropathy of aging rats was exacerbated following administration of high doses of cefixime (1000 mg/kg/day) for 53 weeks. In dog studies, emesis, which was related to treatment, was noted in some animals receiving cefixime orally; there were no other findings related to cefixime following oral administration. In an 8-day, ascending intravenous dose study in dogs, cefixime was not lethal at a cumulative dose of 7295 mg/kg. In this study, emesis and nephrotoxicity (i.e. elevated blood urea nitrogen and serum creatinine; protein, glucose, and ketones in the urine; tubular degeneration and necrosis of kidneys) were seen.

The multiple-dose oral toxicity of cefixime was also investigated in young rats (15/sex/group) and dogs (3/sex/group) at doses up to 3200 mg/kg and 400 mg/kg, respectively, administered once daily for 5 weeks. In addition, the oral toxicity of cefixime was investigated in young dogs (7/sex/group) at single daily doses of up to 180 mg/kg or 60 mg/kg administered twice daily for 5 weeks. The rat study showed cecal effects similar to those seen in the studies with adult animals. Soft feces were noted in all dose groups. Results of the dog studies showed no drug-related toxicity at doses up to 400 mg/kg/day in adult animals and up to 180 mg/kg/day in young animals.

Mutagenicity:

Cefixime did not exhibit mutagenic or clastogenic potential in a battery of genetic toxicology tests. Drug concentrations of 0.001 to 1.0 µg/plate were used in microbial mutagencity tests, 3200 µg/mL in a mammalian point mutation assay, 1 to 2500 µg/mL in an unscheduled DNA synthesis test, and 6000 to 10 000 µg/mL in an *in vitro* cytogenetics test. Two IP doses of 100 to 3200 mg/kg were given to mice in an *in vivo* micronucleus test.

Reproductive Toxicity:

Fertility and general reproductive performance, teratology, and perinatal/postnatal studies were conducted in animals. In the fertility and reproductive performance study in rats, no difference between control and drug-treated animals was detected in mating behavior, pregnancy rate, litter parameters (determined at sacrifice on day 13 of pregnancy), length of pregnancy or delivery at oral doses up to 1000 mg/kg/day administered to males (for 68 days prior to pairing and during

the cohabitation period) and females (for 14 days before pairing to weaning). The results of teratology studies in mice and rats show that cefixime, at doses up to 3200 mg/kg/day is not teratogenic. In these studies in mice and rats, cefixime did not affect postnatal development or reproductive capacity of the F_1 generation or fetal development of the F_2 generation. In studies designed to assess the teratogenic potential of cefixime in rabbits, cefixime at doses of 3.2, 10 or 32 mg/kg given daily on days 6 through 18 of pregnancy was not teratogenic in this species. Toxic responses (abortions and/or maternal deaths) typically associated with the administration of antibiotics in this species were elicited at $\geq$ 10 mg/kg. The results of studies in rats designed to assess the effect of cefixime administered to dams during the perinatal and postnatal periods, at oral doses up to 3200 mg/kg/day, show that cefixime does not affect the duration of pregnancy, process of parturition, or development and viability of offspring. In addition, reproductive capacity of the F_1 generation and development of their fetuses (F_2) were not affected.

Antigenicity:

Results of tests in mice, rats, rabbits, and guinea pigs show that cefixime alone has no antigenic potential when administered orally and only weak antigenic potential when administered parenterally with adjuvants or carrier proteins. There was no cross-reactivity detected between cefixime and several other cephalosporin antibiotics.

Carcinogenesis:

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted.

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