PRODUCT MONOGRAPH

^{Pr}KEFUROX®
(cefuroxime for injection, USP)

IV
Antibiotic

Pharmaceutical Partners of Canada Inc.
45 Vogell Road, Suite 200
Richmond Hill, ON L4B 3P6

Date of Preparation:
January 14, 2008

Control No.: 119197

NAME OF DRUG

KEFUROX

(cefuroximefor injection, USP)

THERAPEUTIC CLASSIFICATION

IV

Antibiotic

ACTION

In vitro tests demonstrate that the bactericidal action of cefuroxime results from the inhibition of the transpeptidase and carboxypeptidase enzymes, thus inhibiting cell wall synthesis.

INDICATIONS

KEFUROX (cefuroxime) may be indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the following diseases:

Lower Respiratory Tract Infections: Pneumonia caused by *Streptococcus pneumoniae*. *Haemophilus influenzae* including ampicillin-resistant strains, *Klebsiella* species, *Staphylococcus aureus* (penicillinase- and non-penicillinase producing) including ampicillin-resistant (but not methicillin-resistant) strains. *Streptococcus pyogenes* and *Escherichia coli*.

Urinary Tract Infections: Caused by *Escherichia coli* and *Klebsiella* species.

Soft Tissue Infections: Caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase producing) including ampicillin-resistant (but not methicillin-resistant) strains. *Streptococcus pyogenes*, *Escherichia coli* and *Klebsiella* species.

Gonorrhea: Caused by *Neisseria gonorrhea* (penicillinase- and non-penicillinase producing strains) including ampicillin-resistant strains.

Meningitis: Caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase producing) including ampicillin-resistant (but not methicillin-resistant) strains,

Streptococcus pneumoniae, *Haemophilus influenzae*, including ampicillin-resistant strains, and *Neisseria meningitis*.

Bone and Joint Infections: Caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing strains).

Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibility to cefuroxime. Therapy may be instituted before results of susceptibility testing are known. However, modification of the treatment may be required once these results become available.

Prevention: The preoperative prophylactic administration of cefuroxime may prevent the growth of susceptible disease causing bacteria and thereby may reduce the incidence of certain post-operative infections: in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean contaminated or potentially contaminated: in patients undergoing open heart surgery in whom infections at the operative site would present a serious risk.

If signs of infection occur postoperatively, specimens for culture should be obtained for identification of causative organism and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS

KEFUROX (cefuroxime) is contraindicated in persons who have shown Type 1 hypersensitivity to cephalosporin antibiotics.

WARNINGS

BEFORE THERAPY WITH KEFUROX (CEFUROXIME) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFUROXIME, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. KEFUROX SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS ALLERGENICITY OF THE CEPHALOSPORINS AND PENICILLINS. **KEFUROX SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.** IF AN ALLERGIC REACTION TO KEFUROX OCCURS, DISCONTINUE TREATMENT WITH THE

DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported to be associated with treatment of cefuroxime (and other broad-spectrum antibiotics). Therefore, it is important to consider its diagnosis in patients administered KEFUROX who develop diarrhea. Treatment with broad-spectrum antibiotics including cefuroxime, alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *C. difficile* is one primary cause of antibiotic associated colitis.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases, should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis does not improve after administration of KEFUROX has been discontinued, or when it is severe, consideration should be given to the administration of oral vancomycin or other suitable therapy. Other possible cause of colitis should also be considered.

PRECAUTIONS

Cefuroxime should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Although KEFUROX (cefuroxime) rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

The total daily dose of KEFUROX should be reduced in patients with transient or persistent renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

Patients with altered renal or hepatic function should be carefully monitored during therapy with KEFUROX.

Prolonged use of KEFUROX may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy

Reproductive studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate well-controlled studies in pregnant women.. If the administration of KEFUROX to pregnant patients is considered necessary, its use requires that the potential benefits be weighed against the possible hazards to the fetus.

Nursing Mothers

Cefuroxime is excreted in human milk in low concentrations (0.5 mg/L). The clinical significance of this is unknown, therefore, caution should be exercised when KEFUROX is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in children below the age of 3 months have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

Geriatrics

The elimination of cefuroxime may be reduced due to impairment of renal function.

Laboratory Test Changes

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinitest® tablets, but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP). A false-negative reaction may occur in the ferricyanide test for blood glucose. KEFUROX does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

ADVERSE REACTIONS

The most common adverse effects observed during treatment with KEFUROX have been local reactions following intravenous administration.

Local Reactions

Thrombophlebitis, pain on intramuscular injection when using sterile water as the diluent, stiffness and inflammatory reaction within the injection site have all been reported.

Other adverse reactions observed include:

Hypersensitivity

Rash and eosinophilia, urticaria, pruritis and anaphylaxis. Drug fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have also been observed with cephalosporins.

Gastrointestinal Tract

Diarrhea, nausea, and vomiting. Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment.

Blood

Decreased hemoglobin and hematocrit have been observed as well as transient eosinophilia and positive Coombs' test. Neutropenia and leukopenia were less common. Hemolysis, aplastic anemia, agranulocytosis, pancytopenia, prolonged prothrombin time, and thrombocytopenia have been reported.

Hepatic

Transient rise in SGOT and SGPT, alkaline phosphatase, LDH, and serum bilirubin.

Renal

Increases in serum creatinine and/or BUN and a decreased creatinine clearance.

Other

Drowsiness, loose stools, faint feeling, sweating, palpitation and Candida intertrigo.

TREATMENT OF OVERDOSE

Other than general supportive treatment, no specific antidote is known.

The administration of inappropriately large doses of parenteral cephalosporins may cause seizures, particularly in patients with renal impairment. Dosage reduction is necessary when renal function is impaired (see **DOSAGE AND ADMINISTRATION**). If seizures occur, the drug should be promptly discontinued; anticonvulsant therapy may be administered if clinically indicated. Dialysis may be considered in cases of overwhelming overdosage.

DOSAGE AND ADMINISTRATION

KEFUROX (cefuroxime) may be administered intravenously after reconstitution. Dosage and route of administration should be determined by the severity of infection, susceptibility of the causative organisms, and condition of the patient. The intravenous route is preferable for patients with severe or life-threatening infections.

The usual duration of treatment is 5 to 14 days. For β–hemolytic Streptococcal infections, therapy should be continued for at least 10 days.

DOSAGE IN PATIENTS WITH NORMAL RENAL FUNCTION:

Adults

The usual adult dosage range for KEFUROX is 750 mg every 8 hours.

In uncomplicated urinary tract infections, soft tissue infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750 mg dose every 8 hours is recommended.

For bone and joint disease, a dosage of 1.5 g intravenously every 8 hours (4.5 g/day) is recommended. Surgical intervention should be performed when indicated as an adjunct to cefuroxime therapy. Oral antibiotics should be administered when appropriate following the completion of parenteral administration of cefuroxime.

In bacterial meningitis the dose should not exceed 3.0 g every 8 hours.
In life-threatening or complicated infections or gram negative infections of the lower respiratory tract, 1.5 g three times daily may be required.

Infants, Children and Neonates

In bacterial meningitis, the usual dosage is 200-240 mg/kg/day IV in divided doses every 6-8 hours. Dosages may be reduced to 100 mg/kg/day after 3 days of clinical improvement (not to exceed the maximum adult dose).

Delayed sterilization of cerebrospinal fluid has been reported occasionally in children treated with cefuroxime for bacterial meningitis. Moderate to severe hearing impairment has occurred as a complication of meningitis on occasion in children treated with cefuroxime for bacterial meningitis.

The usual pediatric dosage for most other infections due to susceptible organisms is 30-100 mg/kg/day in 2-3 divided doses. For children > 3 months, the dosage is usually 60 mg/kg/day.

For bone and joint infections, a dosage between 70 to 150 mg/kg/day administered intravenously every 8 hours is recommended, to be followed by a course of oral antibiotics.

Neonates (Up To 1 Month)

In the first few weeks of life, the serum half-life of cefuroxime can be 3 to 5 times that in adults. Infections in neonates should be treated with dosages in the range 30 to 100 mg/kg/day in 2 or 3 equally divided doses.

For bacterial meningitis, a dosage of 100 mg/kg/day intravenously in 2 or 3 equally divided doses should be employed.

Note: As a general principle, antibiotic therapy should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of ten days of treatment is recommended in infections caused by group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infections and may be

required for several months after therapy has been completed; persistent infections may require longer treatment; doses smaller than those indicated above should not be used.

Prevention

Clean contaminated or potentially contaminated surgical procedures: The recommended dose is 1.5 g of cefuroxime administered IV just prior to surgery. This may be supplemented with 750 mg administered intravenously or intramuscularly at 8 and 16 hours when surgery is prolonged.

In general, prophylactic administration is usually not required after the end of surgical procedures, however, intraoperative administrations should be considered if the surgical procedure is lengthy.

In many surgical procedures, continuing prophylactic administration of any antibiotic does not appear to be associated with a reduced incidence of subsequent infection, but will increase the possibility of adverse reactions and the development of bacterial resistance.

Open Heart Surgery: The recommended dosage is 1.5 g of cefuroxime administered intravenously at the induction of anaesthesia and every 12 hours thereafter for 48 hours (for a total of 6.0 g is recommended).

DOSAGES IN PATIENTS WITH IMPAIRED RENAL FUNCTION:

When renal function is impaired, a reduced dosage must be employed. The dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1).

Table 1: Dosage of KEFUROX in Adults with Reduced Renal Function

Creatinine Clearance		Dose	Frequency
mL/min/1.73m^2	mL/s/1.73m^2		
>20	>0.33	750 mg - 1.5 g	Every 8 hours
10 - 20	0.17 - 0.33	750 mg	Every 12 hours
<10	<0.17	750 mg	Every 24 hours

For adults with severe infections who require doses higher than recommended in the table above, serum levels of cefuroxime should be monitored and dosage adjusted accordingly.

Insufficient information is available to recommend specific dosages for children with renal impairment. Consideration should be given to adjusting the frequency of administration consistent with the recommendations for renally impaired adults in the table above.

Since KEFUROX is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.9 x above value

ADMINISTRATION:

Intravenous Administration

KEFUROX should be given intravenously, especially for patients with bacterial septicemia or other severe or life-threatening infections or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.

Direct Intravenous (Bolus) Injection

Slowly inject the solution into a vein over a period of 3-5 minutes or give it through the tubing system by which the patient is also receiving other intravenous solutions.

Intravenous Infusion

IV infusion should be given over a period of 30 minutes.

For Intermittent Intravenous Infusion with a Y-Type Administration Set

Dosing can be accomplished through the tubing system by which the patient may be receiving other intravenous solutions. However, during infusion of the solution

containing KEFUROX it is advisable to temporarily discontinue administration of any other solutions at the same site.

For Continuous Intravenous Infusion

KEFUROX may also be administered over a longer period of time.

Note: If therapy with KEFUROX is carried out in combination with an aminoglycoside antibiotic, either, each of these antibiotics should be administered at different sites, or KEFUROX and aminoglycosides may be administered sequentially by intermittent intravenous infusion. After the administration of one of the two drugs, the tubing is carefully and thoroughly flushed with an approved solution for reconstitution and then the other drug solution is administered. An aminoglycoside should not be mixed with KEFUROX in the same container.

PHARMACEUTICAL INFORMATION

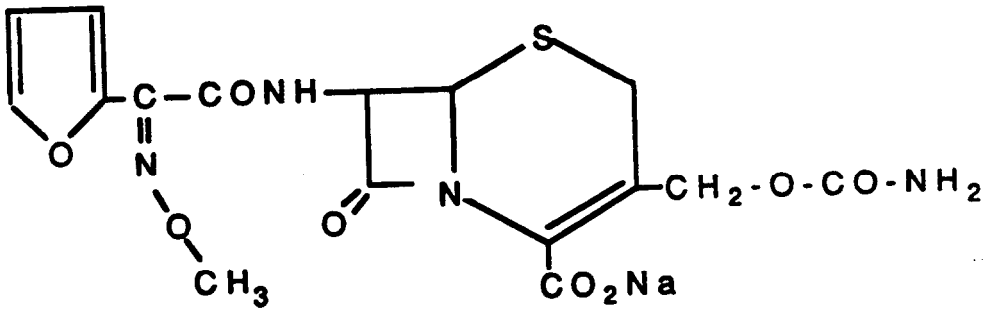
DRUG SUBSTANCE:

Trade Name: KEFUROX

Proper Name: Cefuroxime Sodium

Chemical Name(s): (1) 5-Thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid, 3[[(aminocarbonyl)oxy]methyl]-7-[[2-furanyl (methoxyimino)acetyl]amino]-8-oxo-, monosodium salt [6R-[6α,7ß(Z)]] -

(2) Sodium (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate, 7^2-(Z)-(O-methyloxime), carbamate(ester)



Molecular Formula: $C_{16}H_{15}N_4NaO_8S$

Molecular Weight: 446.37

Description:
KEFUROX (cefuroxime for injection, USP) contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity. The crystalline powder ranges in colour from white to faintly yellow and is insoluble in chloroform toluene, ether, ethyl acetate and acetone, sparingly soluble in ethanol and soluble in water. Solutions of KEFUROX range from light yellow to amber, depending upon the concentration and the diluent used. The pH of a freshly reconstituted solution usually ranges from 4.5 to 8.5.

RECONSTITUTION:
For Intravenous Use
Solutions for Reconstitution:
Sterile Water for Injection

Reconstitute as follows:

Reconstitution Table

Table 2: Method of Reconstitution for Intravenous Use

Vial Size	Diluent to be added to Vial	Volume to be Withdrawn	Approximate Average Concentration

750 mg VL7271	7.5 mL	Total (7.5 mL)	100 mg/mL
1.5 g VL7272	14 mL	Total (14 mL)	100 mg/mL

The prepared solution may be further diluted to the desired volume with any of the solutions for IV infusion listed below. Vials intended for further dilution should be reconstituted immediately prior to dilution.

Solutions for IV Infusion

0.9% Sodium Chloride Injection
5.0% Dextrose Injection
5.0% Dextrose and 0.9% NaCl Inj.
5.0% Dextrose and 0.45% NaCl Inj.
5.0% Dextrose and 0.225% NaCl Inj.
Ringer's Injection USP
Lactated Ringers Injection USP
10% Dextrose Injection
M/6 Sodium Lactate Injection

Pharmacy Bulk Vial

THE AVAILABILITY OF THE BULK PHARMACY VIAL IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM.

KEFUROX does not contain any preservatives. The Pharmacy Bulk Vial is intended for multiple dispensing for intravenous use only, employing a single puncture.

Reconstitution Table:

Table 3: Method of Reconstitution of Bulk Vial

Vial Size	Diluent to be added to Vial	Volume to be Withdrawn	Approximate Average Concentration
7.5 g VL7275	77 mL	Amount Needed*	99 mg/mL

* 8 mL of solution contains 750 mg of cefuroxime.

Reconstitute with Sterile Water for Injection.

Use reconstituted stock solution within 8 hours, and further diluted solutions within 8 hours if kept at 25°C and 48 hours if refrigerated from time of initial puncture.

STABILITY AND STORAGE RECOMMENDATIONS:

Dry Powder

The vials should be protected from light and stored at controlled room temperature, 15 - 30° C.

SOLUTIONS:

Intravenous

When the 750 mg and 1.5 g vials are reconstituted as directed with Sterile Water for Injection, the solutions of KEFUROX for intravenous administration maintain satisfactory potency for 8 hours at 25° C or for 48 hours under refrigeration (4°C).

Diluted solutions at concentrations of between 1 mg/mL and 30 mg/mL may be stored for up to 12 hours at 25° C or 48 hours under refrigeration.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
As with other cephalosporins, cefuroxime powder and solutions tend to darken, without adversely affecting potency.

AVAILABILITY OF DOSAGE FORMS

Vial # 7271 KEFUROX®, Cefuroxime for Injection, USP 750mg/10mL vial

Vial # 7272 KEFUROX®, Cefuroxime for Injection, USP 1.5g/25mL vial

Vial # 7275 KEFUROX®, Cefuroxime for Injection, USP 7.5 g/100mL vial

Vial # 7278 ADD-Vantage™ KEFUROX®, Cefuroxime for Injection, USP 750 mg

Vial # 7279 ADD-Vantage™ KEFUROX®, Cefuroxime for Injection, USP 1.5 g

The above ADD-Vantage™ Vials are to be used with Abbott Laboratories' "ADD-Vantage™ Diluent Container" containing:
0.9% Sodium Chloride Injection, USP, 50mL, 100mL or
5% Dextrose Injection, USP, 50mL, 100mL.

INSTRUCTIONS FOR USE – *ADD-Vantage*™ Vial

To Open:

Peel overwrap from the corner and remove container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container: USE ASEPTIC TECHNIQUE

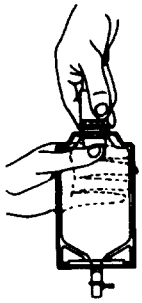
1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
   a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (SEE FIGURE 1.), then pull straight up to remove the cap. (SEE FIGURE 2.)
   NOTE: Once the breakaway cap has been removed, do not access vial with syringe.
   b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (SEE FIGURE 3.)
2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately ½ turn (180°) after the first audible click. (SEE FIGURE 4.) The clicking sound does not assure a seal; the vial must be turned as far as it will go.
   NOTE: Once vial is seated, do not attempt to remove. (SEE FIGURE 4.)
3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.
4. Label appropriately.

Fig. 1

Fig. 2

Fig. 3

Fig. 4



To Reconstitute the Drug:

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.
2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (SEE FIGURE 5.)
3. Pull the inner cap from the drug vial (SEE FIGURE 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.
4. Mix container contents thoroughly and use within the specified time.
5. Immediately prior to administration, confirm that the contents of the vial have been dissolved by observing the inner cap/stopper in the flexible container.

Fig. 5

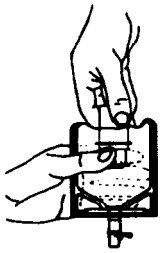
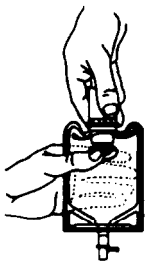


Fig. 6



™Licenced user of trademark owned by Abbott Laboratories.

MICROBIOLOGY

Table 4:

Organism	No. of Strains	Cumulative % of strains inhibited at indicated concentrations (μg/mL)									
		0.06	0.13	0.25	0.5	1.0	2.0	4.0	8.0	16.0	62.0	>125
GRAM NEGATIVE												
Acinetobacter species	6				17			67		83		
Enterobacter spp	138							22	88	94	100	
Escherichia coli	129				5			89		98	100	
Haemophilus influenzae Ampicillin sensitive	16				100							
Haemophilus influenzae Ampicillin resistant	15				100							
Klebsiella species	73							51		81	99	100
Morganella morganii	9							11		44	78	100
Neisseria gonorrhea ß-lactamase producing	110	72		94			100					
Neisseria gonorrhea non ß-lactamase producing	75	2	60	92			97	100				
Proteus mirabilis	27							89		96	100	
Proteus rettgeri	4		25							50	75	100
Proteus vulgaris	21									29	86	100
Salmonella species	40							95		98	100	
Shigella species	10							90			100	
GRAM POSITIVE												
Staphylococcus aureus Penicillin sensitive	12				58	100						
Penicillin resistant	28				14	68	100					
Methicillin resistant	40				5	25	33					
Coagulase negative	39	3	10	28	54	79	85					
α and non-hemolytic Streptococci	40	70	75	85	100							
ß-hemolytic Streptococci	40	95	98	100								
Streptococcus pneumoniae	19	100										
Clostridium spp.	7	13		26			86		100			

Cefuroxime is ineffective against *Pseudomonas aeruginosa* and exhibits poor activity against *Proteus vulgaris*, *Bacteroides fragilis* and many *Serratia* species.

Penicillin-resistant *Streptococcus pneumoniae* is usually cross-resistant to beta-lactam antibiotics.

ß-Lactamase Stability

KEFUROX is resistant to hydrolysis by ß-lactamase from *Staphylococcus aureus* (penicillinase), and most species of Gram-negative aerobic bacteria. It is also stable to the type III ß-lactamases produced by *Haemophilus influenzae* and *Neisseria gonorrhea*.

KEFUROX is hydrolyzed by some type I ß-lactamases produced by various strains of *Serratia* and *Proteus rettgeri*, as well as the ß-lactamases produced by *B. fragilis* and *Pseudomonas aeruginosa*.

The following table shows the degree of hydrolysis of cefuroxime by ß-lactamases.

Table 5:

Source of Enzyme	**Enzyme Class**	**µg of antibiotic destroyed/min** _____ **Cefuroxime**
Escherichia coli (R+TEM)	III	< 1
E. coli (R GN23M)	V	4.5
E.coli D31	I	< 1
Proteus mirabilis	III	< 1
Klebsiella aerogenes K1	IV	54
Enterobacter cloacae P99	I	< 1
Proteus vulgaris	I	< 1
Bacteroides fragilis 1600	I	112
Pseudomonas aeroginosa 1822	I	< 1
Bacillus cereus 659/H9		72
Staphylococcus aureus PC1[b]		< 1

[b] Activity is expressed as micrograms destroyed per hour

Susceptibility testing continues to be the most effective method to determine the usefulness of a specific antibiotic in treating an infection.

Susceptibility Testing

The standard single-disc susceptibility test (using the 30µg Cefuroxime disc) and dilution susceptibility should be interpreted according to the criteria in Table 6.

Table 6:

	Zone Diameter (mm) (30µg Cefuroxime disc)	**Approximate MIC correlation (mg/L)**
Susceptible (susceptible to the usual doses)	≥ 18	< 8
Moderately Susceptible (intermediate)	15 – 17	16
Resistant	≤ 14	> 32

Organisms should be tested with cefuroxime discs, since cefuroxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam discs are used.

PHARMACOLOGY

Human

Cefuroxime is poorly absorbed when given orally; following a 1 g dose, serum levels of less than 1.2µg/mL were observed, and only between 1 and 1.3% of the administered dose was excreted in the urine. Cefuroxime, therefore, must be given via injection.

Intramuscular Administration

Deep intramuscular injection of 750 mg of cefuroxime sodium in the lateral side of the thigh, attained peak blood levels of 35 to 40 µg/mL, after thirty to forty minutes. (See Figure 1).

Serum cefuroxime concentrations greater than 12.5 µg/mL were maintained for approximately 3 1/2 hours, and 6.25 µg/mL for approximately 4 hours, after a 750 mg dose administered intramuscularly.

About 90% of the administered dose was recovered in the urine within 6 hours of injection, and over 96% after 24 hours. (See Table 7).

Figure 1: Cefuroxime blood levels following intramuscular injection of 750mg

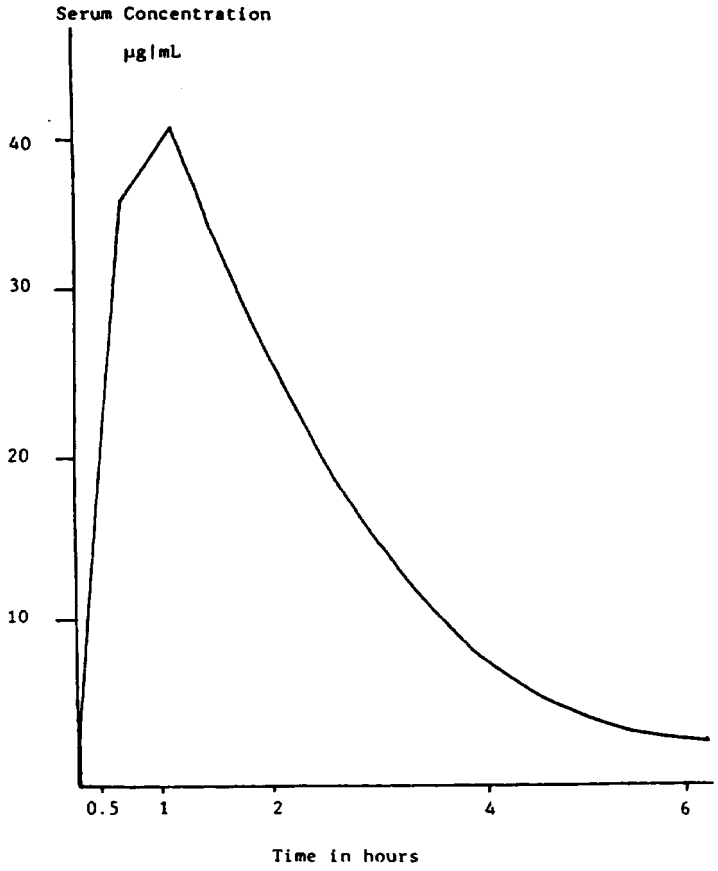

Serum Concentration
µg/mL
40
30
20
10
0.5
1
2
4
6
Time in hours

Table 7: Mean urinary recoveries after parenteral cefuroxime.

Route & Dose (g)	Mean % urinary recovery at hours after injection: 0 to 1	1 to 2	2 to 3	3 to 4	4 to 6	6 to 12	12 to 24	Total mean = SD	
I.M.									
0.25	26.4	31.6	17.7	9.3	6.4	4.0	0.4	95.8±	2.5
0.5	30.1	29.5	16.1	8.7	7.9	3.8	0.4	96.5±	7.9
0.75	35.6	29.3	17.3	9.0	6.9	3.6	0.2	101.9±	6.3
1.0	22.5	34.8	22.5	9.2	9.2	4.3	0.9	103.4±	15.6
I.V.									
0.25	60.2	23.2	14.2	6.1	6.3	3.6	0.5	114.1±	6.1
0.5	41.3	23.6	13.1	6.9	5.6	4.0	0.6	95.1±	4.4
1.0	53.6	21.5	12.0	5.2	4.1	2.5	0.2	99.1±	0.2

Volume of distribution after a 750 mg dose is approximately 15 L (12.5 to 18.3 L) which increases to about 23 L when the dose of cefuroxime is doubled.

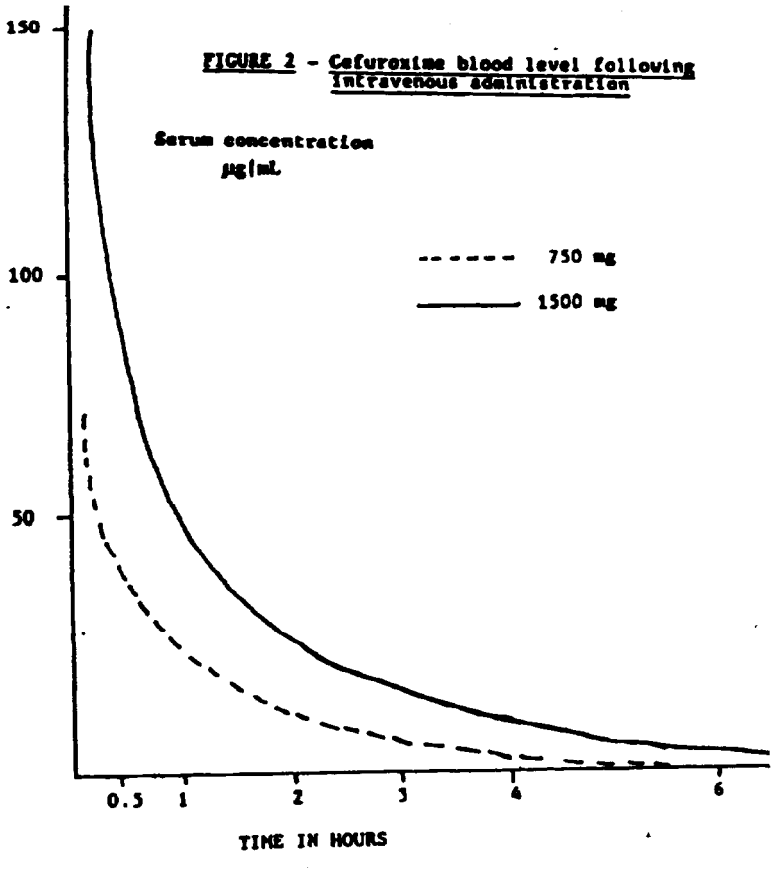
The mean half-life of a 750 mg intramuscular dose is about eighty minutes.

Intravenous Administration

Cefuroxime sodium 750 mg and 1.5 g resulted in blood levels of 73 µg/mL and 151µg/mL, respectively (See Figure 2), five minutes after the beginning of the injection.

Intravenous infusion of 750 mg over a thirty minute period, resulted in a serum level of 51 mg/mL at the end of the infusion. Intravenous administration of 1.5 g over a twenty minute period, resulted in a concentration of 146 µg/mL at the end of the infusion. Following intravenous administration, more than 95% of cefuroxime is excreted unmetabolized via the kidneys (See Table 7) with excretion evenly divided between glomerular filtration and tubular secretion. The half life of cefuroxime after intravenous injection is approximately eighty minutes.

Figure 2: Cefuroxime blood levels following Intravenous administration



Renal Impairment

The following table (Table 8) shows the effect of different degrees of renal impairment on the pharmacokinetics of cefuroxime (500 mg administered).

More than 95% of an intravenous dose of cefuroxime is excreted via the kidneys. Renal impairment alters the pharmacokinetics of the drug. Excretion occurs through glomerular filtration and tubular secretion.

Table 8: Pharmacokinetics of cefuroxime in renal impairment

EDTA clearance	Serum Concentration			Serum half-life		Urinary recovery	Urinary Concentration	
(mL/min)	Peak	6h	24h	(h)	(% of dose)	0.2h	4 - 5h	6 - 8h
20 - 50 (3pts.)	62	9.2	< 0.2	1.8	78.6	1263	264	242
< 20 (4pts.)	64	27.3	10.3	16.1	35.0	148	144	118
Anuria:	45	6.3[1]	-	3.3				
On Hemodialysis	51	26.8	-	15.2				
Between dialysis(5pts.)								

[1]Serum concentration at end of 8h dialysis.

Fluid and Tissue Concentrations

KEFUROX is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, CSF (in patients with meningitis), and aqueous humor.

Table 9: Concentration of cefuroxime in different tissues

Site	Dose Given (mg)	Route	Concentration (µg/mL)
Sputum	750 t.i.d. for 2 days	I.M.	2.0
	1500 t.i.d. for 4 days	I.M.	7.8
Bone	750 t.i.d. for 4 days	I.M.	3.9*
	1500 t.i.d. for 4 days	I.M.	13.5*
Skin Blister	750 single	I.M.	9.4
Bile	750 single	I.M.	8.6
	1500 single	I.M.	22.0
Aqueous humor	1500 single	I.M.	1.6

* µg/g

Biliary levels varied between 1.34 and 26 µg/mL, the lowest levels being in patients with non-functioning gall bladders.

After 750 mg intramuscular dose to 6 women in labor, average concentrations of cefuroxime in amniotic fluid (18.6 µg/mL) were similar to those in maternal serum; average peak maternal serum concentrations of 19.2 µg/mL were attained after 1.2 hours, while umbilical cord blood, the average peaks were one third of those in the mothers.

The extent of cefuroxime bound to protein in the serum is about 50%.

Probenecid Administration

The following table shows the effects of probenecid on the pharmacokinetics of cefuroxime.

Table 10: Effect of probenecid (0.5 g given orally two hours before and one hour after cefuroxime) on the pharmacokinetics of intramuscular cefuroxime 500 mg

Pharmacokinetic variable	With probenecid	Without probenecid	% change
Peak serum concentration (µg/mL)	29.4	22.7	+30
Ultimate serum half-life (min)	101	76.6	+32
Area under curve (µg/mL/h)	94.4	56.8	+56
Apparent volume of distribution (litres/1.73m^2)	11.7	14.8	-20
Urinary recovery: 0.2h (%)	47	60.4	-22
0.24h	95.6	100.2	-5
Renal clearance (mL/min/1.73m^2	79.6	133.8	-40
Cefuroxime/creatinine clearance ratio	0.74	1.25	-40

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases serum half-life by approximately 30%.

TOXICOLOGY

Acute Toxicity

Cefuroxime was administered to mice, rats, rabbits, cats, dogs, and monkeys. A low order of toxicity was observed with all species.

Table 11: LD_{50} Values of Cefuroxime

Species	No/Sex	Route(s)	Dose (g/kg)	Result
Mouse	5/sex	IV/SC		LD_{50} of about 10.4 g/kg
Rat	N/A N/A N/A	PO/SC/IP IV IM		LD_{50} of about 10 g/kg LD_{50} of about 8 g/kg LD_{50} greater than 2 g/kg
Cat	2/sex	IM	2 g/kg	transient pain on injection
Dog	2/sex	IM	2/g/kg	moderate pain on injection
Monkey	2/sex	IM	2/g/kg	diarrhea and weight loss
Rabbit	5/sex	IV	1.5 g/kg	3/10 deaths with marked distention of cecum

A study compared the acute toxicity of the Lilly cefuroxime with that of Glaxo in young of adult male and female Fischer 344 rats (10/sex/dose). A maximum dose of 1250 mg of cefuroxime/kg was administered intravenously and it was concluded that both products cause similar toxicity. Immediately following dosing, signs of toxicity included leg weakness in all animals and hypoactivity in one animal.

A similar study conducted in the ICR mouse with a dose of about 5000 mg/kg indicated comparable results.

Studies in beagle dogs at a test dose of 2000 mg/kg and the Rhesus monkey at doses of 250, 500, and 1000 mg/kg indicated that the drug was well tolerated with no ill effects except emesis in one dog.

Subacute Toxicity

Rats:

When rats were treated for a month with daily subcutaneous doses of 100 mg/kg of cefuroxime, the serum potassium was increased on day thirty-four. With doses of 200 mg/kg/day, peripheral erythrocyte values were somewhat reduced in males and with 400 mg/kg/day doses in females. Daily doses of 800 mg/kg caused moderate reactions at the injection site forming subcutaneous lumps and occasionally ulcers. The ulcerations usually resolved within ten days. There was also evidence of mild colitis. Rats were given doses of 1.25, 2.5 and 5.0 g/kg/day of cefuroxime subcutaneously for fourteen days. All the animals showed signs of extreme discomfort during and immediately after the injection. At autopsy, necrotic patches were observed at the injection sites of the rats given the highest dose. All rats had watery feces, increased leukocyte count, and dose-related decrease in hemoglobin concentration.

One month treatment of rats with cefuroxime 50, 100, 200 and 400 mg/kg/day intravenously, caused increased pack cell volume in all groups, increased urine output in the 200 mg/kg group and embolic reactions in many lungs, in both control and drug-treated animals. At doses of 100 and 400 mg/kg/day, a small but statistically significant decrease in spleen weights was observed.

Dogs:

Daily intramuscular administration of cefuroxime at doses of 60, 180 and 540 mg/kg for eleven days caused increased kidney and liver weights. In two male dogs, this was 1.5 times the weight of the controls.

Monkeys:

Cefuroxime administered intramuscularly for twenty-nine days at doses of 150 and 450 mg/kg/day, caused a moderate decrease of erythrocytes; leukocytosis with neutrophilia; eosinophilia and soft stools.

In all subacute tests, there was a slight-to-moderate dose-related inflammatory reaction around the subcutaneous and intramuscular injection sites. Hemorrhage at the injection sites was sometimes observed, occurring more frequently at higher doses.

Chronic Toxicity

Rats:

Three-month, subcutaneous study: Rats were dosed at 100, 300 and 900 mg/kg/day. A dose and duration-related, mild-to-marked subcutaneous reaction with hemorrhage at injection sites were observed at all three levels. Slight reduction of erythrocytes with mild reticulocytosis and a slight reduction of serum calcium were observed at both 300 mg and 900 mg/kg dose levels. Increased prothrombin time was observed in males dosed at 300 mg/kg/day, and in both sexes at 900 mg/kg/day.

At 900 mg/kg/day an increased total leukocyte count, decreased serum albumin and gamma-globulin, increased serum potassium (females on day fifty-six), marginally increased blood glucose (females on day fifty-six) and decreased alkaline phosphatase (males on day twenty-eight) were observed. There was an increased in relative weights of the liver, the kidney and the spleen in all females. Increased excretion of electrolytes and increased urinary volume in both sexes were observed at the high dose level after seventy-seven days.

Six month subcutaneous study: Rats were dosed at 0, 150 or 450 mg/kg/day. No mortality was observed. Dilatation of the lymphatics and enlargement of the spleen were observed at the higher doses. There was a statistically significant reduction of packed cell volume and hemoglobin, accompanied by reticulocytosis of a similar degree at 150 mg/kg/day. Reduction of serum alanine transaminase activity in both sexes as well as of pituitary weights in females were observed at the highest dose. Serum cholesterol was significantly increased in females at all dose levels while serum calcium levels were marginally reduced in males at high dose levels.

There was increased excretion of sodium and potassium, however statistically significant changes were seen in the excretion of potassium in the high dose male animals only. Other abnormalities included hyaline granular casts and erythrocytes in the urine as well as increased urinary protein content. The incidence and severity of these changes were greatest at the high dose levels. The mean kidney weights (absolute and relative) were increased 10 to 15% at high doses in both sexes.

Dogs:

Six-month toxicity study: Dogs received cefuroxime for six months at doses of 50 mg/kg/day intramuscularly, and doses of 150 and 450 mg/kg/day administered subcutaneously. There was a dose-related reaction at the injection site with subcutaneous hemorrhage occurring at the higher dose levels. In the group receiving the highest dose, hypochromia and increased serum iron binding capacity were observed. Serum triglyceride levels were increased after twenty weeks in animals receiving 150 and 450 mg/kg cefuroxime. Blood urea nitrogen was reduced and serum potassium was increased in the high dosage group. One dog in the 450 mg group developed Heinz body anemia after twelve weeks, but no causative agent was identified.

Nephrotoxicity

Mouse:

Mice received single subcutaneous doses of cefuroxime (10 g/kg) alone or in combination with furosemide (50 mg/kg) of furosemide plus glycerol (5.4 mL/kg). Cefuroxime alone caused no nephrotoxicity; together with furosemide there was proximal tubular necrosis in five of eight animals but this was not influenced by the addition of cefuroxime.

Rats:

Single-dose study: Cefuroxime at doses up to 10 g/kg were given either alone or together with furosemide (100 mg/kg) or furosemide plus glycerol (3.15 mL/kg). Three of six animals had proximal tubular necrosis in the inner cortex with 4 g of cefuroxime alone and the incidence and severity increased when furosemide or furosemide plus glycerol were given concomitantly. Cefuroxime at 1 g/kg enhanced the severity of the furosemide-glycerol-induced necrosis in the outer cortex. Treatment with furosemide plus glycerol also lowered the dosage of cefuroxime (to 2 g/kg) required to produce necrosis of the inner cortex.

Repeated dose study: Rats received cefuroxime at doses ranging from 1 to 5 g/kg/day subcutaneously for ten days. There was no histological evidence of tubular necrosis at 5 g/kg, but transient increases in urine volume, protein and enzymes, which peaked at day 2 - 3 were observed. The body weights of the animals were significantly reduced for the high dose group.

Combination with aminoglycosides: Rats were treated with gentamicin (35 mg/kg) for ten days. Cefuroxime was given either concomitantly during the ten days or as a single dose with ninth dose of gentamicin. Gentamicin-induced tubular necrosis was not potentiated by the administration of single doses of cefuroxime up to 6 mg/kg/day. Multiple doses of cefuroxime up to 4 g/kg protected rats against gentamicin-induced nephrotoxicity, but a doses of 6 g/kg/day of cefuroxime, severe tubular necrosis was observed after four days of treatment. Similar results were found with amikacin and tobramycin.

Teratogenicity

Mouse:

Cefuroxime was administered subcutaneously at doses of 800, 1600, 3200 and 6400 mg/kg/day from day six to day fifteen of pregnancy. At all doses, except at 3200 mg. there was a 15 to 21% incidence of bone immaturity as evidenced by a decrease in the calcification of various ossification centres, of the offspring. Based on historical controls the untreated animals had a 7% incidence of bone immaturity.

Rabbit:

Cefuroxime was administered intramuscularly at doses of 50, 100, 200 and 400 mg/kg/day from day six to day eighteen of pregnancy. Four rabbits given 400 mg/kg, one rabbit given 200 mg/kg and one rabbit given 100 mg/kg/day, died during the test. The offspring had an 8, 17, 25 and 10% incidence of bone immaturity and the incidence of bone abnormalities was 8, 21, 0 and 30% at the 50, 100, 200 and 400 mg/kg/day dose levels, respectively.

Fertility and Reproduction Studies

Male and female mice were given daily subcutaneous doses of 800, 1600 or 3200 mg/kg of cefuroxime prior to mating (males for sixty days and females for fourteen days). The pregnant females were continued on treatment until the seventeenth day of pregnancy. A few of their offspring were later mated to produce a second generation. Treatment had no apparent effect on gametogenisis. The fertility of the second generation was also unimpaired.

Perinatal and Postnatal Studies

Mouse:

Daily subcutaneous doses of 800, 1600, or 3200 mg of cefuroxime from day sixteen of pregnancy until the weaning of the litters, had no effect on gestation, parturition, lactation or the health of the dams or the pups.

Rabbit:

Daily administration of 50, 100 or 200 mg/kg of cefuroxime from day nineteen of pregnancy through lactation (at least fifty doses) had no effect on the litters or the development and health of the pups. Treatment caused the death of ten rabbits before parturition and one died after it had littered. Mortality was dose-related, and although believed to be caused by enteritis, a direct toxic effect could not be ruled out.

BIBLIOGRAPHY

1. Bullen BR, Ramsden CH, and Kester RC. Cefuroxime levels attained in tissues and wound exudates from severely ischemic limbs. J Antimicrob Chemother. 1981; 7: 163-170.

2. Brogden RN, Heel RC, Speight TM, and Avery GS. Cefuroxime: a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs 1979; 17: 233 - 66.

3. Corbeel L, Acker van G, Eekels R, Vandepitte J, and Verbist L. Cefuroxime plasma and CSF levels in children with meningitis. Archives of Diseases in Childhood. 1979; 54(9)729-730.

4. Craft I, et al.: Placental transfer of cefuroxime. Br J Obstet Gynaecol. Feb. 1981; 88(2): 141-145.

5. Eykyn S, Jenkins C, King A, and Phillips I. Antibacterial activity of cefuroxime, a new cephalosporin antibiotic compared with that of cephaloridine, cephalothin, and cefamandole. Antimicrob Agents and Chemotherapy 1976; 9: 690 - 695.

6. Foord RD. Cefuroxime: human pharmacokinetics. Antimicrobial Agents and Chemotherapy 1976; 9: 741 - 747.

7. Friedrich H, Haensel-Friedrich G, Langmaak H, and Daschner FD. Investigations of cefuroxime levels in the cerebrospinal fluid of patients with and without meningitis. Chemotherapy. 1980; 26: 91-97.

8. Gentry LO, Zeluff BJ, Cooley DA. Antibiotic prophylaxis in open-heart surgery: a comparison of cefamandole, cefuroxime, and cefazolin. Ann Thorac Surg 1988; 46:167-171.

9. Goodwin CS, Dash CH, Hill JP, and Goldberg AD. Comparative study of seven cephalosporins; susceptibility to beta-lactamases and ability to penetrate the surface layers of Escherichia coli. J Antimicrob Chemotherapy 1977; 3: 253.

10. Gotto S. The *in vitro* and *in vivo* antibacterial activity of cefuroxime. Proc Roy Soc Med 1977; 70: 56 (Suppl. 9).

11. Hedstrom SA, Lidgren L, & Nilsson-Ehle I. Cefuroxime in acute septic arthritis. Scand J Infect Dis 1984; 16:79-82.

12. Herold HZ, Shmueli G & Butler JK. Cefuroxime in the treatment of bone and joint infections. Curr Ther Res 1983; 33:892-897.

13. Hoffstedt B, Johansson O, Walder M, Cronberg S, and Price JD. Cerebrospinal fluid penetration of cefuroxime Current Chemotherapy and Infectious Disease, Proceedings of the 11th ICC and 19th ICAAC, 1980; 1: 634-635.

14. Hughes S, Robertson S, Want S, Darrell J, Kennedy M, and Dash CH. Cefuroxime in bone. In: Wood C, Rue Y, eds. Cefuroxime Update. International Congress and Symposium Series London: Proc Roy Soc Med, 1981; 38: 163-71.

15. Hughes SPF, Want S, Darrell JH, Dash CH, Kennedy M. Prophylactic cefuroxime in total joint replacement. Inter Ortho (SICOT) 1982; 6:155-161.

16. Hurlow RA, Strachan CJL, and Wise R. A comparative study of the efficacy of cefuroxime for preventing wound sepsis after cholecystectomy. In: Wood C, Rue Y, eds. Cefuroxime Update International Congress and Symposium Series,London: Pro Roy Soc Med 1981; 38: 1-8.

17. Jandial L, Reid TMS, Jandial V, Towler C, and MacGillivray L. Prophylactic use of cefuroxime in major gynaecological surgery. In: Wood C, Rue Y, eds. Cefuroxime Update International Congress and Symposium Series London: Royal Society of Medicine, 1981; 38: 41-49.

18. Johnson DP. Antibiotic prophylaxis with cefuroxime in arthroplasty of the knee. J Bone & Joint Surg 1987; 69B: 787-789.

19. Jones RN, Fuchs PC, Gavan TL, Gerlach H, Barry AL, and Thornsberry C. Cefuroxime, a new parenteral cephalosporin: collaborative in vitro susceptibility comparison with cephalothin against 5887 clinical bacterial isolates. Antimicrob Agents and Chemotherapy, 20. 12: 47 - 50.

20. Kuzemko JP, and Walker SR. Cefuroxime plasma and CSF levels in children with meningitis. Archives of Diseases in Childhood. 1979; 54(3): 235-236.

21. Ledbeater B, and Kingston J. Cefuroxime and metronidazole in gynaecological surgery. Br J Obstet. Gynaecol 1981; 88: 543-547.

22. Mitchell NJ, Evans DS, and Pollock D. Pre-operation single dose cefuroxime antimicrobial prophylaxis with and without metronidazole in elective gastrointestinal surgery. J Antimicrob Chemother. 1980; 6: 393-399.

23. Modai J, Pierre J, Bergogne-Berezin E, and Avril MF. Cerebrospinal fluid penetration of cefuroxime. Drugs under Experimental and Clinical Research, 1979; 5(2-3): 455-458.

24. Muller C, Netland A, Dawson AF, and Andrew E. The penetration of cefuroxime into the cerebrospinal fluid through inflamed and non-inflamed meninges. J Antimicrob Chemotherapy, 25. 6: 279-283.

25. Neu HC. The new beta-lactamase stable cephalosporins. Ann Intern Med Sept. 1982; 97(3): 408-419.

26. Neu HC, and Fu KP. Cefuroxime, a beta-lactamase-resistant cephalosporin with a broad spectrum of gram-positive and -negative activity. Antimicrob Agents and Chemotherapy 1978; 13: 657 - 64.

27. O'Callaghan CH, and Harding SM. The pharmacokinetics of cefuroxime in man in relation to its antibacterial activity. Proc Roy Soc Med 1977; (Suppl. 9) 70: 4 - 8 .

28. O'Callaghan CH, Sykes RB, Griffiths A, and Thornton JE. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. Antimicrob Agents and Chemotherapy 1976; 9,511-525.

29. O'Callaghan CH, Sykes RB, Ryan DM, Foord RD, and Muggleton PW. Cefuroxime, a new cephalosporin antibiotic: activity in vitro. J Antibiotics 1976; 29: 29.

30. Renlund M, and Pettay O. Pharmacokinetics and clinical efficacy of cefuroxime in the newborn period. Pro Soc Med 70 (suppl.(9), 1977; 179-182.

31. Richmond MH, and Wotton S. Comparative study of seven cephalosporins: susceptibility to beta-lactamases and ability to penetrate the surface layers of Escherichia coli. Antimicrob Agents and Chemotherapy 1976; 10: 219.

32. Sack K, Freisleben H, Schulz E, Marre R, and Henkel W. Experimental Investigations of Cefuroxime in renal tolerance and therapeutic efficacy in Pyelonephritis. Proc Roy Soc Med 1977; 70: 134 (Suppl. 9).

33. Slama TG, Sklar SJ, Misinski J, and Fess SW. Randomized comparison of cefamandole, cefazolin, and cefuroxime prophylaxis in open-heart surgery. Antimicrob. Agents Chemother.1986;29: 744-747.

34. Snell ES, Bax RP, Kennedy MRK, Mulhinger BM, and Walker SR. Abstract of paper presented at 18th Inter-science Conference on Antimicrobial Agents and Chemother., 36. October

35. Thornsberry C, Biddle JW, Perine PL, and Siegel M. In vitro susceptibility of beta-lactamase positive and beta-lactamase negative strains of neisseria gonorrhea to cefuroxime. Proc Roy Soc Med. 1977; 70: 122.