PRODUCT MONOGRAPH

[Pr] AURO-CEPHALEXIN

Cefalexin Tablets, BP

250 mg and 500 mg

Antibiotic

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THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

Cefalexin is bactericidal against many gram-positive and gram-negative organisms. *In vitro* tests demonstrate that the cephalosporins are bactericidal through their inhibition of cell-wall synthesis [15].

INDICATIONS

AURO-CEPHALEXIN may be indicated for the treatment of bacterial infections of the respiratory tract [1,12][13,14], including otitis media [1,2], genitourinary tract [3] , bones and joints [4,5], skin and soft tissue [6,7] when the infection is caused by susceptible organisms. Culture and susceptibility studies should be performed.

CONTRAINDICATIONS

AURO-CEPHALEXIN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with AURO-CEPHALEXIN is instituted, careful inquiry should be made concerning previous hypersensitivity reactions to cephalosporins, penicillins or other drugs.

AURO-CEPHALEXIN should be given only with caution to penicillin-sensitive patients. There is some evidence of cross-allergenicity between the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both.

Antibiotics including AURO-CEPHALEXIN should be administered with caution, and then only when absolutely necessary, to any patient who has demonstrated some form of allergy, particularly to drugs. Of 12,917 clinical trial patients, 462 had histories of penicillin allergy [8].

Twenty-one of them (about 4.6 percent) were among those in whom possible allergic reactions to cefalexin were observed.
Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics including cefalexin; therefore, it is important to consider its diagnosis in patients administered AURO-CEPHALEXIN who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics including AURO-CEPHALEXIN may alter the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of antibiotic associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the administration of AURO-CEPHALEXIN has been discontinued, or when it is severe, consideration should be given to the administration of oral vancomycin. Other causes of colitis should be ruled out.

PRECAUTIONS

As is the case with all drugs, patients should be followed carefully so that adverse reactions or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to AURO-CEPHALEXIN occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

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

AURO-CEPHALEXIN should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

If AURO-CEPHALEXIN is to be used for long term therapy, periodic monitoring of hematology, renal and hepatic functions should be done.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy; e.g., the incision and drainage of abscesses.

Safety of this product for use during pregnancy has not been established.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

In patients being treated with AURO-CEPHALEXIN, a false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with Clinitest tablets, but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP).

ADVERSE REACTIONS

Of 12,917 patients treated with cefalexin in formal clinical trials, 771(6%) reported adverse events, of which 385 (3%) were judged to be drug related (8). Four hundred and sixty-two of these patients had known sensitivity to penicillin, 4.6% reacted. The incidence of reported side effects is shown in Table 1.

TABLE 1

Adverse Events Reported in 12,917 Patients Treated With cefalexin

	Relationship to Drug				
	Probable/definite	Uncertain	Discontinued Treatment	Total Reports	Percent
Gastrointestinal					
Diarrhea	87	77	31	164	1.3
Nausea	72	62	24	134	1.0
Vomiting	38	44	24	82	0.6
Dyspepsia/G.I. upset	24	7	5	31	0.2
Abdominal cramp/pain	9	8	5	17	0.1
Anorexia	11	6	2	17	0.1
Hypersensitivity					
Skin rash	52	42	42	94	0.7
Urticaria	22	12	19	34	0.3
Central Nervous System					
Headache	7	11	6	18	0.1
Genitourinary					
Genital Moniliasis	42	11	6	53	0.8
Vaginitis	15	11	4	26	0.4
Pruritus Vulvae	10	5	-	15	0.2

Other adverse reactions experienced less frequently include: glossitis/stomatitis, oral moniliasis, pruritus ani, gastroenteritis, fever, pruritus, a positive direct Coombs', allergy/anaphylaxis, intertrigo, angioedema, dizziness, paresthesia, somnolence, visual hallucination/diplopia, insomnia, tremor, leucorrhea, dysuria, malaise/fatigue, super infection, myalgia/back pain, nuchal swelling, dyspnea, cardiac arrhythmia and vasodilatation.

One hundred and seventy patients (1.3%) had abnormal laboratory values. There was no consistent pattern of abnormality and only 2 patients were withdrawn from studies as a result of these findings.

TABLE 2
Abnormal Laboratory Values

	Relationship to drug			
	Probable/Definite	Uncertain	Total Reports	Percent
Hematological				
Eosinophilia	27	18	45	0.4
Biochemical				
Elev. Alk Phosphatase.	9	15	24	0.2
Elev. SGOT	11	21	32	0.3
Elev. SGPT	6	16	22	0.2
Renal				
Elev. BUN	3	11	14	0.1

Other abnormal values reported less frequently included: elevated creatinine, bilirubin and cholesterol; decreased platelets, hemoglobin and/or hematocrit.

The following adverse reactions have been reported during postmarketing experience:

Gastrointestinal: Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported. The most frequent side effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Dyspepsia and abdominal pain have also occurred. As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported.

Hypersensitivity: Allergic reactions in the form of rash, urticaria, angioedema, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis have been observed. These reactions usually subsided upon discontinuation of the drug. In some of these reactions, supportive therapy may be necessary. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, headache, agitation, confusion, hallucinations, arthralgia, arthritis, and joint disorder. Reversible interstitial nephritis, eosinophilia, neutropenia, leukopenia, thrombocytopenia, and slight elevations in SGOT and SGPT have been reported.

Vertigo, tinnitus, hearing loss and behavioural changes in young children have been reported with cefalexin use.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and Symptoms: Symptoms of oral overdose may include nausea, vomiting, epigastric distress, diarrhea, and hematuria. If other symptoms are present, it is probably secondary to an underlying disease state, an allergic reaction, or toxicity due to ingestion of a second medication.

Treatment: Unless 5 to 10 times the normal dose of cefalexin has been ingested, gastrointestinal decontamination should not be necessary.

Protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of cefalexin; however, it would be extremely unlikely that one of these procedures would be indicated.

DOSAGE AND ADMINISTRATION

AURO-CEPHALEXIN is administered orally. The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 1 g/day in divided doses every 6 hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of AURO-CEPHALEXIN greater than 4 g are required, parenteral cephalosporins, in appropriate doses should be considered.

For the treatment of bacterial pharyngitis caused by Streptococcus pyogenes group A, and, acute cystitis, the daily dosage may be divided into two and given every 12 hours.

In severe infections, the dosage may be doubled.

In the treatment of beta hemolytic streptococcal infections, AURO-CEPHALEXIN therapy should be administered for at least ten days.

To obtain maximum peak levels, AURO-CEPHALEXIN should be administered on an empty stomach.

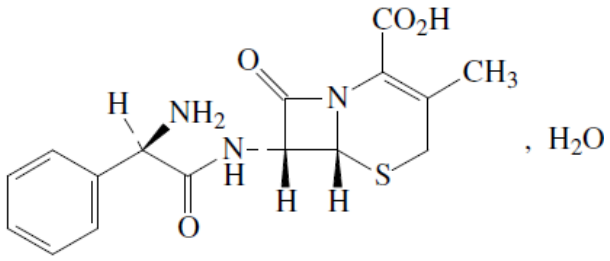
PHARMACEUTICAL INFORMATION

Drug Substance:

Trade Name: AURO-CEPHALEXIN

Proper Name: Cefalexin Monohydrate

Chemical Name: (6R, 7R)-7-[[(2R)-2-Amino-2-phenylacetyl] amino]-3-methyl-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid monohydrate



Molecular Formula: $C_{16}H_{17}N_3O_4S.\ H_2O$

Molecular Weight: 365.4 g/mol

Description: White or almost white, crystalline powder.
Sparingly soluble in water, practically insoluble in ethanol (96 percent).

STORAGE AND STABILITY:

Store at room temperature (15°C to 30°C).
Keep out of reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage form	**Tablets**	
Strength	**250 mg**	**500 mg**
Description	Orange coloured capsule shaped biconvex film coated tablets debossed with "L" on one side and "59" on the other side	Orange colored capsule shaped biconvex film coated tablets debossed with "L" on one side and with a score line in between "6" and "0" on the other side.
Composition	Medicinal ingredient: Cefalexin (as Cefalexin monohydrate). Non-medicinal ingredients: Sodium Starch Glycolate, Microcrystalline Cellulose, Magnesium Stearate, hypromellose, titanium dioxide, macrogol and FD&C Yellow #6 Sunset yellow FCF Aluminium Lake.	
Packaging	HDPE bottles of 100, 500 and 1000 tablets	

Comparative Bioavailability Studies

A double blind, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose oral bioequivalence study of 1 x 500 mg AURO-CEPHALEXIN Tablets [Aurobindo Pharma Limited, India manufactured for Auro Pharma Inc. (Canada)] versus 1 x 500 mg APO-CEPHALEX® (Cephalexin Tablets USP) 500 mg [Apotex Inc., Canada] was completed in 26 healthy, adult, male, human subjects under fasting conditions. A summary of the bioavailability data is presented in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Cefalexin (1 X 500 mg) From measured data **Geometric Mean Arithmetic Mean (CV %)**				
Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**90% Confidence Interval**
$AUC_{0\rightarrow t}$ (hr. ng/mL)	44.9 46.5 (25.2)	44.2 45.7 (25.3)	101.7	99.1-104.4
$AUC_{0\rightarrow\infty}$ (hr. ng/mL)	46.2 47.8 (25.6)	45.4 47.0 (25.5)	101.7	99.1-104.3
C_{max} (ng/mL)	19.8 20.6 (27.6)	20.6 21.6 (28.8)	95.7	85.9-106.7
T_{max}§ (h)	1.2 (0.7-3.0)	1.0 (0.33-2.50)		
$T_{½}$$ (h)	1.2 (13.3)	1.3 (17.0)		

*AURO-CEPHALEXIN (Cefalexin Tablets BP) 500 mg, by Auro Pharma Inc.
† APO-CEPHALEX® (Cephalexin Tablets USP) 500 mg, of APOTEX, INC., Canada were purchased from Canada.
§ Expressed as the median (range) only.
$ Expressed as arithmetic mean (% CV) only.
Cefalexin Tablets BP are "also known as Cephalexin".

MICROBIOLOGY

Cefalexin is active against the following organisms *in vitro*:

Beta-hemolytic and other streptococci (many strains of enterococci; e.g., *Streptococcus faecalis*, are resistant).

Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains (a few strains of staphylococci are resistant to cefalexin).

Streptococcus pneumonia	*Proteus mirabilis*
Escherichia coli	*Klebsiella pneumonia*
Hemophilus influenzae	*Branhamella catarrhalis*

Cefalexin is not active against most strains of *Enterobacter sp., Pr. morganii*, and *Pr. vulgaris*. It has no activity against Pseudomonas or Herellea species. When tested by in vitro methods, staphylococci exhibit cross-resistance between Cefalexin and methicillin-type antibiotics.

Table 3 shows the tube dilution sensitivity data as supplied by several investigators.

TABLE 3 [11]

Susceptibility of Clinically Isolated Bacteria to Cefalexin Expressed as Cumulative Percent

MINIMUM INHIBITORY CONCENTRATION (μg/mL)							
ORGANISM	NO. OF ISOLATES	≤2	2.5 - 4	5-8	10-16	20-32	40-64
Staph. aureus (unspecified)	458	31	58	81	92	97	99
Staph. aureus (penicillin-resistant)	158	41	82	88	98	99	100
Staph. aureus (penicillin-sensitive)	171	68	84	98	100	100	100
Staph. epidermidis	42	29	62	83	91	95	95
Str. pneumoniae	259	57	94	100	100	100	100
Str. pyogenes (group A)	262	84	91	96	99	100	100
E. coli	1165	1	9	40	76	88	92
Klebsiella sp.	533	1	9	55	78	86	88
Pr. mirabilis	535	-	3	14	56	77	84
H. influenzae	258	18	33	62	88	99	100
B. catarrhalis	14	64	100	100	100	100	100

PHARMACOLOGY

Animal:

In the dog, there is evidence to show that cefalexin is absorbed primarily at the site of the duodenum. In dogs given 10 mg/kg of cefalexin intravenously, intramuscularly and orally, the blood serum level was approximately the same after 1 hour and 45 minutes [9]. Most of the drug is excreted in the urine. In rats, 5% of the administered dose was recovered in the bile. The

serum half-life in rats and mice is 1.5 hours and 45 minutes respectively. Insignificant amounts enter the cerebrospinal fluid of dogs and monkeys. Variable amounts can be recovered from the breast milk of rats. Cefalexin distributes well to various tissues of rats, particularly the liver and kidney. (See Table 4).

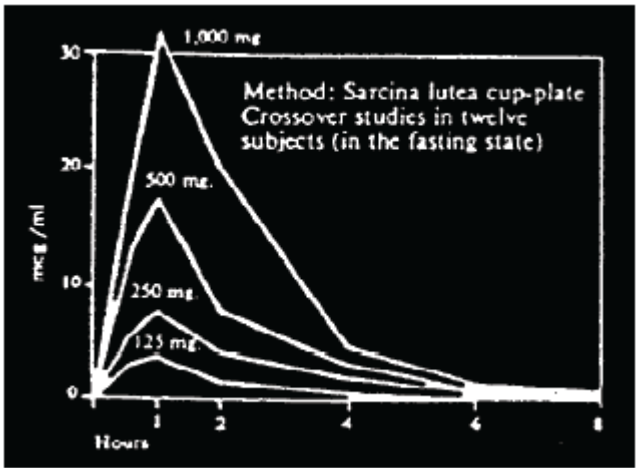
TABLE 4

Cefalexin-^{14}C tissue levels in rats and in mice after a single oral dose of cefalexin-^{14}C (46 μ moles/kg)

μg Cefalexin/g Tissue				
TISSUE	RAT	RAT	MOUSE	MOUSE
	1 Hour	4 Hours	1 Hour	4 Hours
Blood	3.71	2.09	3.59	0.53
Liver	17.11	7.25	12.96	1.93
Spleen	2.21	1.45	1.45	0.4
Kidney	39.93	23.69	27.23	3.53
Lung	3.38	2.58	1.63	0.30
Heart	1.52	1.09	3.31	1.07
Fat	1.54	0.80	1.41	0.34
Muscle	1.16	0.76	1.11	0.32
Brain	0.53	0.24	0.30	0.11

Human:
Cefalexin is well absorbed orally to produce effective peak blood levels within 1 hour. (Figure 1)

Figure 1 Cefalexin Blood Levels with Various Doses (Fasting Subjects)



Less than 10% of absorbed cefalexin is bound to serum protein in concentrations above 1g/mL [(10)]. More than 80% is excreted as cefalexin in the urine. Cefalexin is acid stable. Food in the stomach causes a delay in onset, a lower peak and a prolongation of blood levels. Approximately 10% less cefalexin is excreted in the urine of patients taking food than in that of fasting subjects.

TOXICOLOGY

Acute Toxicity:

Table 5 summarizes the acute toxicity data [9], which indicate a low order of toxicity in mice, rats, cats, dogs, and monkeys when the drug is given orally. No toxicity was demonstrated until very high doses were reached. Only after single oral doses of 2 to 4.5 g/kg were employed in mice did lethargy or depression and anorexia persist for twenty-four hours. Diuresis was noted.

TABLE 5
Acute Toxicity of Cefalexin
LD_{50} (g/kg)

SPECIES	ORAL	INTRAPERITONEAL	INTRAVENOUS
Mouse	1.6-6.2	0.4-1.6	≥ 0.7
Rat	≥ 5.0 (LD_0)	≥ 3.65	≥ 0.7(LD_0)
(Weanling)	≥ 4.0		
(Newborn)	≥ 3.0		
Cat	≥ 1.0 (LD_0)	≥ 1.0	≥ 0.1(LD_0)
Dog	≥ 2.0 (LD_0)*	≥ 0.5 -≥ 1.0	≥ 0.1(LD_0)
Monkey	≥ 1.0 (LD_0)*		

* Emesis precluded a study of lethality in these species.

Although histological examination of the kidneys of animals that died revealed slight hydropic degeneration of the tubular epithelium, the cause or causes of death remain uncertain. Kidneys of some of the surviving animals showed regeneration in the tubular epithelium. Kidneys of the other mice surviving these high doses appeared normal. All blood chemistry parameters except BUN were unaffected by a 1000 mg/kg dose. The BUN concentrations increased to 200 mg in the mouse after 30 hours, but the concentrations at 72 hours were normal.

The rat was even less sensitive to cefalexin administered orally. All rats survived a 5 g/kg dose. Kidneys of these animals were found to be free of injury when examined microscopically.

In cats, dogs and monkeys, oral doses of 500 mg/kg produced salivation, emesis, and diarrhea; therefore a satisfactory study of the lethality in these species was precluded. Blood serum concentrations in the dogs and cats were as high as 200 g/mL after one and one-half hours. Twenty-four-hour trough levels were 4 g/mL or less.

A single oral dose of 400 mg/kg was well tolerated in the monkey.

From oral administration to animals, there was no indication that the pediatric formulation enhanced the toxicity of cefalexin. The largest practical dose, 40 mL/kg (1.0 g/kg), caused no deaths.

Intraperitoneal injections produced toxic effects similar to those seen after oral administration.

Subacute and Chronic Toxicity:

In animal toxicology studies, organic toxicity was not encountered at doses of 400 mg/kg administered over periods of one year.

The long-term safety of cefalexin was demonstrated in one-month studies in rats, dogs, and monkeys, and one-year studies in rats and dogs. The maximum daily doses of 1000 mg/kg for dogs and monkeys were well tolerated.

The only drug-related effects in the rats were transitory growth suppression, slight diarrhea of short duration, and enlargement of cecums and colons. The dogs developed transitory appetite suppression, salivation, occasional emesis, and occasional diarrhea. Histopathologic findings were normal, although blood concentrations were as high as 200 g/mL. Short-term studies showed that dogs can tolerate even larger doses (1000 to 2000 mg/kg) with salivation and emesis as the most serious side-effects. Salivation and moderate diarrhea were the only side-effects observed in monkeys.

Intravenous doses of 15 to 60 mg/kg/day of cefalexin were well tolerated for fourteen days by rats; dogs tolerated daily intravenous injections of 7.5 to 30 mg/kg. No apparent adverse effects were observed.

Reproduction and Teratology:
The fertility and reproduction of rats and mice were not affected by daily oral doses of cefalexin as great as 500 mg/kg. Skeletal abnormalities occurring in two out of twenty-two litters of mice included wavy ribs and varus limb conditions, but were not considered drug related[(9).] The survival of the rat progeny at twelve and twenty-one days of age was significantly less than that of the control animals in one study, but was similar to the control animals in another study.

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17. Product Monograph – APO-CEPHALEX (Cephalexin Tablets USP) Tablets 250 mg and 500 mg. APOTEX Inc., Date of Revision: November 9, 2000.