PRODUCT MONOGRAPH

Pr NU-CEFUROXIME

Cefuroxime Axetil Tablets

250 mg and 500 mg cefuroxime/tablet

Nu-Pharm Standard

ANTIBIOTIC

NU-PHARM INC.
50 Mural St., Units 1 & 2
Richmond Hill, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
<oral>	<tablets 250 mg, 500 mg>	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

NU-CEFUROXIME (cefuroxime axetil) is indicated for the treatment of patients with mild to moderately severe infections caused by susceptible strains of the designated organisms in the following diseases:

Upper Respiratory Tract Infections

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes*.

Otitis Media caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes* (group A beta-hemolytic streptococci), *Haemophilus influenzae* (beta-lactamase negative and beta-lactamase positive strains) or *Moraxella catarrhalis*. Sinusitis caused by *Moraxella catarrhalis*, *Streptococcus pneumoniae* or *Haemophilus influenzae* (including ampicillin-resistant strains).

Lower Respiratory Tract Infections

Pneumonia or bronchitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae*, *Klebsiella pneumoniae* or *Moraxella catarrhalis*.

Skin Structure Infections

Skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*.

Gonorrhea

Acute uncomplicated urethritis and cervicitis caused by *Neisseria gonorrheae*.

Bacteriologic studies to determine the causative organism and its susceptibility to cefuroxime should be performed. Once these results become available antibiotic treatment should be adjusted if required.

CONTRAINDICATIONS

NU-CEFUROXIME (cefuroxime axetil) is contraindicated for patients who have shown Type 1 hypersensitivity to cefuroxime, to any of its components, or to any of the cephalosporin group of antibiotics.

WARNINGS AND PRECAUTIONS

Before therapy with NU-CEFUROXIME (cefuroxime axetil) is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefuroxime, cephalosporins, penicillin, or other drugs. NU-CEFUROXIME should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. There is some clinical and laboratory evidence of partial cross-allergenicity of the cephalosporins and penicillin. Special care is indicated in patients who have experienced anaphylactic reaction to penicillins or other beta-lactams. If an allergic reaction to NU-CEFUROXIME occurs, treatment should be discontinued and standard agents (e.g. epinephrine, antihistamines, corticosteroids) administered as necessary.

Pseudomembranous colitis has been reported to be associated with the use of cefuroxime axetil and other broad-spectrum antibiotics. Therefore, it is important to consider its diagnosis in patients administered NU-CEFUROXIME who develop diarrhea. Treatment with broad spectrum antibiotics, including NU-CEFUROXIME, alters the normal flora of the colon and may permit overgrowth of Clostridia. Studies indicate that a toxin produced by Clo*stridium 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 is severe or not relieved by discontinuance of NU-CEFUROXIME administration, consideration should be given to the administration of oral vancomycin or other suitable therapy. Other possible causes of colitis should also be considered.

General

Broad-spectrum antibiotics including NU-CEFUROXIME (cefuroxime axetil) should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis. The concomitant administration of aminoglycosides and some cephalosporins has caused nephrotoxicity. There is no evidence that NU-CEFUROXIME, when administered alone, is nephrotoxic, although transient elevations of BUN and serum creatinine have been observed in clinical studies. However, the effect of administering NU-CEFUROXIME concomitantly with aminoglycosides is not known. Studies suggest that the concomitant use of potent diuretics, such as furosemide and ethacrynic acid, may increase the risk of renal toxicity with cephalosporins.

As with other antibiotics, use of NU-CEFUROXIME may result in the overgrowth of Candida. Prolonged use may also result in the overgrowth of other non-susceptible organisms (e.g. enterococci and *Clostridium difficile*), which may require interruption of treatment. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. Should an organism become resistant during antibiotic therapy, NU-CEFUROXIME should be discontinued and another appropriate antibiotic should be substituted.

Special Population

Pregnant Women

The safety of NU-CEFUROXIME in pregnancy has not been established. The use of NU-CEFUROXIME in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and fetus. Animal studies following parenteral administration have shown cefuroxime to affect bone calcification in the fetus and to cause maternal toxicity in the rabbit. Reproduction studies that have been performed in mice and rats at oral doses of up to 50 to 160 times the human dose have revealed

no evidence of impaired fertility or harm to the fetus due to cefuroxime axetil. There are, however, no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Women: Since cefuroxime is excreted in human milk, consideration should be given to discontinuing nursing temporarily during treatment with NU-CEFUROXIME.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following adverse reactions have been reported:

Gastrointestinal (approximately 8% of patients): Diarrhea (5.6%), nausea (2.4%), vomiting (2.0%), loose stools (1.3%). Reports of abdominal pain have occurred.

Hepatic (3% of patients): Transient increases of hepatic enzyme levels [ALT (SGPT), AST (SGOT), LDH].

Central Nervous System (2.2% of patients): Headache and dizziness.

Hypersensitivity (1.3% of patients): Rashes (0.6%), pruritus (0.3%), urticaria (0.2%), shortness of breath and rare reports of bronchospasm. Hypersensitivity reactions to NU-CEFUROXIME may occur in patients who report delayed hypersensitivity to penicillins (see WARNINGS). As with other cephalosporins, there have been rare reports of drug fever.

Hematologic: Increased erythrocyte sedimentation rate, eosinophilia, decreased hemoglobin and very rarely hemolytic anemia.

Miscellaneous: The following adverse reactions have been observed to occur, although infrequently, in association with parenteral cefuroxime sodium and may be potential adverse effects of oral cefuroxime axetil: drowsiness, vaginitis, positive direct Coombs test, and transient increases in serum bilirubin, creatinine, alkaline phosphatase, and urea nitrogen (BUN).

Postmarketing Experience With Cefuroxime Axetil

In addition to adverse events reported during clinical trials, the following events have been identified during clinical practice in patients treated with cefuroxime axetil and were reported spontaneously. Data are generally insufficient to allow an estimate of incidence or to establish causation.

General: The following hypersensitivity reactions have been reported: anaphylaxis, angioedema, pruritus, rash, serum sickness-like reaction, urticaria.

Gastrointestinal: Pseudomembranous colitis (see WARNINGS).

Hematologic: Thrombocytopenia, and leucopenia (sometimes profound).

Hepatic: Jaundice (predominantly cholestatic) and hepatitis have been reported very rarely.

Infections and Infestations: Candida overgrowth.

Neurologic: Seizure.

Skin: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Urologic: Renal dysfunction.

DRUG INTERACTIONS

Drug-Drug Interactions

Drugs which reduce gastric acidity may result in a lower bioavailability of NU-CEFUROXIME compared with that of the fasting state and tend to cancel the effect of enhanced post-prandial absorption.

In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

Drug-Laboratory Test Interactions

A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® Tablets) but not with enzyme-based tests for glycosuria (e.g. Clinistix®, Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving NU-CEFUROXIME.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Cephalosporins as a class tend to be absorbed onto the surface of red cell membranes and react with antibodies directed against the drug to produce a positive Coombs' test (which can interfere with cross-matching of blood) and very rarely hemolytic anemia.

Drug-Lifestyle Interactions

Ability to Perform Tasks That Require Judgment, Motor or Cognitive Skills: As this medicine may cause dizziness, patients should be warned to be cautious when driving or operating machinery.

DOSAGE AND ADMINISTRATION

NU-CEFUROXIME (cefuroxime axetil) may be given orally without regard to meals. Absorption is enhanced when NU-CEFUROXIME is administered with food.

Adults and Children 12 Years of Age and Older

The usual recommended dosage is 250 mg twice a day. However, dosage may be modified according to the type of infection present as indicated below:

TYPE OF INFECTION	DOSAGE
pharyngitis, tonsillitis, sinusitis, bronchitis, skin structure infections	250 mg twice daily

more severe infections eg. pneumonia	500 mg twice daily
uncomplicated gonorrhea	1000 mg single dose

There is presently no data available on the effects of NU-CEFUROXIME in patients with renal impairment. However, in patients where there is significant impairment, a reduction in NU-CEFUROXIME dosage may be required.

Infants and Children less than 12 Years of Age
NU-CEFUROXIME tablets are not recommended for infants and children less than 12 years of age.

The usual duration of treatment for NU-CEFUROXIME tablets is 7 - 10 days. For β-hemolytic streptococcal infections, therapy should be continued for at least 10 days.

OVERDOSAGE

Other than general supportive treatment, no specific antidote is known. Excessive serum levels of cefuroxime can be reduced by dialysis. For treatment of hypersensitive reactions, see WARNINGS AND PRECAUTIONS.

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

ACTION AND CLINICAL PHARMACOLOGY

Cefuroxime axetil is an orally active prodrug of cefuroxime. After oral administration, cefuroxime axetil, as cefuroxime axetil tablets, is absorbed from the gastrointestinal tract and rapidly hydrolyzed by nonspecific esterases in the intestinal mucosa and blood to release cefuroxime into the blood stream. Conversion to cefuroxime, the microbiologically active form, occurs rapidly. The inherent properties of cefuroxime are unaltered after its administration
as cefuroxime axetil. Cefuroxime exerts its bactericidal effect by binding to an enzyme or enzymes referred to as penicillin-binding proteins (PBPs) involved in bacterial cell wall synthesis.

This binding results in inhibition of bacterial cell wall synthesis and subsequent cell death. Specifically, cefuroxime shows high affinity for PBP 3, a primary target for cefuroxime in gram-negative organisms such as *E. coli*.

STORAGE AND STABILITY

Store tablets between 15°C and 30°C. Keep in tightly closed container.

DOSAGE FORMS, COMPOSITION AND PACKAGING

250 mg tablets: each white, capsule shaped, biconvex, film coated, tablet engraved “C250” on one side, contains cefuroxime axetil equivalent to 250mg of cefuroxime base. Available in bottles of 60, 100, and 250.

500 mg tablets: each white, capsule-shaped, biconvex, film coated tablet, engraved “C500” on one side contains cefuroxime axetil equivalent to 500mg of cefuroxime base. Available in bottles of 60, 100, and 250.

In addition to cefuroxime axetil, NU-CEFUROXIME 250 mg and 500 mg tablets also contain the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, and titanium dioxide.

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PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

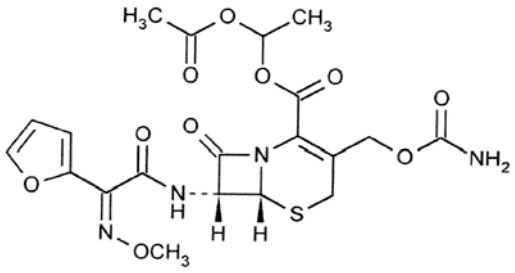
Proper Name: Cefuroxime axetil

Chemical Name: (RS)1-Hydroxyethyl(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)-(0-methyl-oxime), 1-acetate 3-carbamate.

Molecular formula: $C_{20}H_{22}N_4O_{10}S$

Molecular weight: 510.5

Structural Formula:



Physicochemical properties:

Cefuroxime axetil is an amorphous white to cream-colored powder. It is soluble in dimethyl sulfoxide, dimethylformamide, 1,4-dioxan, chloroform, acetone, glacial acetic acid, ethyl acetate, and methanol.

It is soluble with decomposition in 2N sodium hydroxide and slightly soluble in water, diethyl ether, 95% ethanol, and toluene, and insoluble in 2N hydrochloric acid. Cefuroxime axetil decomposes below its melting point.

CLINICAL TRIALS

A randomized, single oral-dose, two-way crossover comparative bioavailability study was performed on 18 healthy human volunteers (12 male, 6 female) under fasting conditions. The rate and extent of absorption of cefuroxime axetil was measured and compared following a single oral dose of Nu-cefuroxime (cefuroxime axetil) 500 mg and CEFTIN® 500 mg tablets. The results from measured data are summarized in the following table:

Cefuroxime Axetil (1 x 500 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Cefuroxime Axetil Tablets (Nu-Pharm Inc.) (Canada)	CEFTIN® Tablets (GlaxoSmithKline Inc.) (Canada)	% Ratio of Geometric Means#	90% Confidence Interval#
AUCt (mcg•h/mL)	20.577 21.512 (32)	19.381 20.287 (33)	106.2	99.0 – 113.9
AUCinf (mcg•h/mL)	21.145 22.090 (31)	19.943 20.844 (33)	106.0	98.9 – 113.7
Cmax (mcg/mL)	6.248 6.523 (31)	6.165 6.301 (22)	101.3	91.0 – 112.9
Tmax§ (h)	2.11 (54)	1.77 (38)		
Thalf§ (h)	1.26 (13)	1.29 (11)		

§ Expressed as the arithmetic mean (CV%) only

based on least squares estimate.

® CEFTIN® Tablets are manufactured by GlaxoSmithKline Inc., Canada, and were purchased in Canada.

MICROBIOLOGY

The minimum inhibitory concentrations (MIC_{50} and MIC_{90}) against various susceptible and non-susceptible organisms in vitro are shown in Table 1.

Table 1: Summary of *in vitro* activities against various organisms

Organism (No. of Strains)	Range	MIC (μg/mL)[a]		Reference
		50%	90%	
Haemophilus influenzae (97)*	0.25-4	0.5	1	Fass et al
Haemophilus parainfluenzae (2)	-	≤0.06	0.25	Knapp et al
Moraxella catarrhalis (53)	0.125-1.0	0.5	1	Alvarez et al
Neisseria meningitidis (40)	0.06-0.25	0.12	0.12	Perez Trallero et al
Escherichia coli (229)	0.5->64	1	4	Knapp et al
Klebsiella pneumoniae (20)	0.25->32	2	8	Neu et al
Klebsiella oxytoca (20)	2->64	2	16	Neu et al
Citrobacter diversus (15)	1->32	4	8	Neu et al
Salmonella sp (21)	0.5-4	1	4	Neu et al
Shigella sp (24)	0.25-32	1	4	Neu et al
Proteus mirabilis (53)	0.25->64	0.5	1	Knapp et al
Staphylococcus aureus				
Methicillin-susceptible (25)	1-4	N/A	4	Stratton et al
Methicillin resistant (25)	2-64	N/A	64	Stratton et al
Staphylococcus epidermidis				
Methicillin-susceptible (25)	0.5-2	N/A	2	Stratton et al
Methicillin resistant (25)	1-8	N/A	8	Stratton et al
Staphylococcus saprophyticus (20)	2-4	4	4	Fass et al
Streptococcus pyogenes (18)	≤0.015-0.06	≤0.015	0.06	Neu et al
Streptococcus pneumoniae (15)	0.015-0.12	0.015	0.12	Neu et al
Streptococcus viridans (27)	0.12-8	0.5	4	Neu et al
Streptococcus faecalis (21)	>32	>32	>32	Neu et al
Peptostreptococcus sp (10)	0.06-4	0.25	4	Goldstein et al
Fusobacterium sp (18)	≤0.03-0.5	0.25	0.5	Goldstein et al
Bacteroides sp (17)	0.06-32	0.25	32	Goldstein et al
Campylobacter pylori (30)	0.01-0.25	0.125	0.25	Garcia-Rodriguez et al

* 50 ß-lactamase positive, 47 ß -lactamase negative
NIA - Not Available

Stability to Beta-Lactamases

Although cefuroxime is resistant to hydrolysis by most beta-lactamases, these enzymes from certain species (*Bacteroides fragilis*, Enterobacter and indole-positive Proteus sp) have been shown to cause hydrolysis. Table 2 shows the degree of resistance of cefuroxime to beta-lactamase inactivation.

Table 2: Hydrolysis of cefuroxime by a range of beta-lactamases

Source of enzyme	ENZYME Class	μg of cefuroxime hydrolyzed/minute
Escherichia coli (R^+tem)	III	<1
E. coli (R^+GN238)	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 aeruginosa 1822	I	<1
Bacillus cereus 659/H9		72
Staphylococcus aureus PC 1*		<1

* Activity is expressed as micrograms hydrolyzed per hour.

Susceptibility Testing

The results of susceptibility testing, by either disk-diffusion or tube-dilution techniques, should be interpreted according to the criteria in Table 3.

Table 3: Susceptibility Testing:

	Zone diameter (30 μg cefuroxime disk)	Approximate MIC correlate
SUSCEPTIBLE (susceptible to the usual doses)	≥23 mm	≤4 μg/mL
MODERATELY SUSCEPTIBLE* (intermediate)	15-22 mm	8-16 μg/mL
RESISTANT	≤14 mm	≥32 μg/mL
CONTROL STRAINS		
S. aureus ATCC 25923	27-35 mm	0.5-2 μg/mL
E. coli ATCC 25922	20-26 mm	2-8 μg/mL

* Organisms that produce zones of 15 to 22 mm may be susceptible if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic concentrations are attained.

Only cefuroxime disks should be used, since cefuroxime has been shown by in vitro tests to be active against certain strains found resistant when other beta-lactamase disks are used.

DETAILED PHARMACOLOGY

Human

The bioavailability of cefuroxime tablets was investigated in a six-way crossover study with each of 12 male adult volunteers receiving a single intravenous dose of cefuroxime sodium and five oral doses of cefuroxime axetil. Blood samples were collected at specified intervals for 12h and urine for 24h following each dose. The results of this study are presented in Table 4.

Table 4: Pharmacokinetics of cefuroxime axetil tablets administered to adults

Dose (mg)	Route	Fasted / Fed	Peak Serum Concentration (μg/mL)	Time to Peak (h)	Area Under Serum Level-Time Curve (mg●h/L)	Urine Recovery 0-12 h (mg)	% Dose Recovered in Urine	% Dose Absorbed Relative to I.V.	Half-Life (h)
500	i.v.	fasted	53.2	0.1	52.8	415	83	100	1.3
500	po	fasted	4.9	2.3	18.9	161	32	36	1.6
125	po	fed	2.1	2.2	6.7	65	52	51	1.2
250	po	fed	4.1	2.5	12.9	127	51	49	1.2
500	po	fed	7.0	3.0	27.4	242	48	52	1.2
1000	po	fed	13.6	2.5	50.0	434	43	47	1.3

The mean values of pharmacokinetic parameters after 12 volunteers received a single i.v. dose of cefuroxime and 5 oral doses of cefuroxime axetil.

Increasing doses of cefuroxime produced linear increases in peak serum concentrations and AUC.

Bioavailability appears to be independent of dose but is increased by the presence of food. Absolute bioavailability of cefuroxime tablets (500 mg dose) increased from 36% in fasted subjects to 52% after food.

The amount of cefuroxime excreted in the urine over 24h averaged 83% following intravenous dosing and ranged from 43% to 52% following oral dosing when taken after food.

The half-life of cefuroxime following oral administration to healthy adult volunteers is 1.2 to 1.6 hours.

Animal Pharmacology

The secondary pharmacological effects of cefuroxime axetil have been investigated in mice, rats, and dogs following a single oral dose. Negative controls were administered a placebo suspension while positive controls received mecamylamine HCl (an inhibitor of gastrointestinal propulsion). The results are summarized in Table 5.

Table 5: Secondary pharmacological actions in animals after a single oral dose of cefuroxime axetil

Animal	Dose (mg/kg)	No. of Animals*	Pharmacological Actions	Observation Times	Effects
mice	0.5	10	Pupil diameter, body temperature, gross behaviour	0-1h, 24h intervals for 7d	Decreased body temperature in females
rat	0.5	10	Pupil diameter, body temperature, gross behaviour	0-1h, 24h intervals for 7d	Decreased body temperature in females
dog	0.5	2	BP, HR, ECG gross behaviour	2.25, 3, 6, 24h	none
rat	0.5	10	Gastrointestinal propulsion	0.75h	none

* Each group consisted of equal numbers of males and females

As can be seen, cefuroxime axetil had no effects on behaviour or pupil diameter in the mouse or the rat or on gastrointestinal propulsion in the rat. Cefuroxime axetil administered orally to dogs produced no acute effects on blood pressure, heart rate, or the electrocardiogram.

TOXICOLOGY

Acute Toxicity

The experimental details of single-dose toxicity studies are presented in Table 6.

Table 6: Acute Toxicity

Animal	Age	Route	Doses (g/kg)	Animals/Dose*	Length of Observation	LD_{50} (g/kg)
Mouse	Adult	p.o.	0, 6	20	3 days	>6
Mouse	Adult	p.o.	0, 6	20	14 days	>6
Mouse	Adult	p.o.	6	20	14 days	>6
Mouse	Adult	p.o.	1.5, 3	12	14 days	>6
Rat	Adult	p.o.	0, 6	12	3 days	>6
Rat	Adult	p.o.	0, 6	12	14 days	>6
Rat	Adult	p.o.	6	12	14 days	>6
Rat	10 days	p.o.	0, 3	20	3 days	>3
Rat	10 days	p.o.	0, 3	20	14 days	>3
Rat	Adult	s.c.	1.5, 3	12	14 days	>3
Dog	8-10 mo.	p.o.	1.5, 3	4	14 days	>3

* Each dosage group was composed of equal numbers of males and females.

All animals survived the experiments. The median lethal dose of cefuroxime axetil in these animals is, therefore, in excess of the test doses administered.

The only symptom of systemic toxicity observed was a temporary reduction in body weight in the juvenile (1 0-day-old) rats. All other animals remained apparently healthy during the observation period.

Mice and rats were sacrificed following the observation period. Histological examination of major organs and tissues revealed no evidence of systemic toxicity.

Subcutaneous injections in mice and rats caused local swelling due to the accumulation of large volumes of suspension. Small localized subcutaneous accumulations of test compound with slight peripheral tissue reaction were observed at autopsy. Compacted test material was still present in the stomachs of most mice and rats three days after oral dosing. Inflammatory changes observed in the stomach walls of several animals were considered to be due to the
mechanical irritation caused by these masses.

Long Term Toxicity

In subacute and chronic studies in rats receiving high oral doses of cefuroxime axetil (1.0-2.5 g/kg/day), accumulation of drug substance and the formation of concretions in the stomachs of many animals caused high rates of mortality. The concretions consisted of semicrystalline axetil, water, food, polymers and impurities comparable to that in the administered material. Concretions were not a problem in the dog studies, which all proceeded to completion. Experimental details of subacute and chronic toxicity studies are presented in Table 7.

Table 7: Subacute and Chronic Toxicity

Animal	Ages*	Route	Daily Doses (g/kg)	Animals/ Dose**	Intended duration of	
					Treatment	Recovery
Rat	7-9 wk	p.o..	0, 0.1, 0.4,	12	15 wk	-
Rat	7-9 wk	p.o.		12	15 wk	22 days
Rat	7-9 wk	p.o.	0.8, 1.7, 2.5	12	15 wk	-
Rat	8-10 wk	p.o.	0, 0.1, 0.4, 1.6	60	28 wk	-
Rat	9 wk	p.o.	0, 0.15, 0.4, 1.0	30	90 day	-
Rat	7 wk	p.o.		32	28 wk	-
Rat	7 wk	p.o.	0, 0.1, 0.4, 1.0	24	28 wk	5 wk
Rat	7 wk	p.o.		12	31 wk	-
Dog	12-16 wk	p.o.	0, 0.1, 0.2, 0.4, 0.8	6	5 wk	-
Dog	8 mo	p.o.	0, 0.15, 0.4, 1.0	8	90 days	-
Dog	4.5-6 mo	p.o.	0, 0.1, 0.4, 1.6	8	27 wk	-
Dog	4.5-6 mo	p.o.	0, 0.4	4	27 wk	3 wk

* Ages at commencement of treatment

** Each dosage group was composed of equal numbers of males and females.

Rat: 5-week study

There were no adverse effects related to treatment in the 0.1 and 0.4 g/kg groups.

By the end of the study, males in the 0.8 and 1.7 g/kg groups exhibited increased clotting times. An increase in serum alkaline phosphatase levels was seen in male rats in the 1.7 g/kg group. Histological changes in the stomach wall, similar to those seen in animals on 2.5 g/kg/day, were observed in males and females in the 1.7 g/kg group, and were considered to be primarily a consequence of the mechanical effects of drug accumulation.

In the high-dose (2.5 g/kg) group, all of the males were killed on day 9 and three of the females were killed or died later during the study. The deaths followed clinical deterioration due to accumulation of drug ester in the stomach. In affected rats there was thrombocytopenia in most cases and a slightly prolonged plasma-activated partial thromboplastin time in one case.
Histological examination revealed mechanical damage to the stomach wall, and in one case there was scattered renal tubular eosinophilia and desquamation.

Rat: 90 day study

A number of rats died during the study; macroscopic and microscopic examination confirmed that these deaths were not related to cefuroxime axetil. The general condition of the surviving animals remained satisfactory throughout the study and the treatment did not affect the normal increase in body weight. There was a slight decrease in total leukocyte counts observed in all
dosage groups, resulting from a reduction in the number of neutrophils and lymphocytes and probably due to the protective effect of the test compound against those microbes that may influence leukocyte homeostasis. A reversible decrease in plasma coagulation activity occurred in males, predominantly in the high-dose (1.0 g/kg) group. This may have been due to a direct action of cefuroxime axetil on the coagulation system or to reduced synthesis of coagulation factors as a result of suppression of Vitamin K-producing organisms in the intestine.

Rat: 28-week study

Rats in the 0.1 and 0.4 g/kg groups showed no significant toxicity and were in good general condition when the study was terminated after 62 to 65 days of treatment. However, the animals given 1.6 g/kg/day suffered from gastrointestinal trauma resulting from the mechanical effects of firm agglomerates of cefuroxime ester. Despite reduction of their dose to 1.0 g/kg/day on Day 7, they continued to deteriorate and either died or were killed after 10 to 14 days treatment. In a further 28 week study in rats, there were no deaths attributable to any toxic effect of cefuroxime axetil.

Apart from loose faeces, seen mainly during the first six weeks of the study in animals receiving 0.4 and 1.0 g/kg/day, there were no significant effects on the general condition of rats surviving to the end of the study. Salivation, extension of the forearms, and walking on the toes was observed in treated animals at the time of dosing, but were considered to be primarily a response to the dosing procedures rather than a toxic effect of the drug.

A reduction in leukocyte counts was observed in all treatment groups, probably reflecting a protective action of the antibiotic against minor infections. Other laboratory abnormalities observed included lengthened clotting times in males, reduction in SGOT and SGPT, and increases in serum transaminases in a few individual females without histological evidence of hepatic damage.

At the end of the treatment period, 48% of the animals in the high-dose (1.0 g/kg) group had agglomerates of cefuroxime axetil in the stomach at autopsy, with one subject exhibiting an associated inflammation of the stomach wall.

Dog: 5-week study

Apart from a single case of vomiting shortly after dosing, the general condition of the dogs was not adversely affected by the treatment.

Laboratory abnormalities observed included transient decreases in total leukocyte and neutrophil counts, hyponatremia, and increased inorganic phosphorus and triglyceride levels. None of the individual results were sufficiently abnormal to be of clinical significance and there were no histological changes associated with treatment.

Dog: 90-day study

The general condition of the animals remained satisfactory throughout the study with normal increases in body weight attained. Isolated and occasional vomiting was the only apparent adverse effect, but this response can partly be attributed to the oral intubation.

Increases in erythrocyte sedimentation rate and in leukocyte and eosinophil counts were observed in animals with incidental helminthic infections. Females in the 0.4 and 1.0 g/kg groups exhibited increased total serum iron binding capacity. There is a statistically significant decrease in the absolute weights of livers in males and hearts in females in the 0.4 g/kg group, but this is insignificant when related to total body weights.

Dog: 27-week study

The general condition of the animals remained satisfactory throughout the study with the exception of 3 dogs, 2 of which were sacrificed suffering from illnesses unrelated to treatment.

In the high-dose (1.6 g/kg/day) group salivation and vomiting were noted, and in one dog there was a transient reduction in growth rate and a general loss of condition. Laboratory abnormalities included reduced erythrocyte counts, prolonged clotting times, reduction in plasma protein and cholesterol, and an increase in plasma triglyceride. Post mortem examinations revealed no signs of organ toxicity.

Nephrotoxicity Studies

Single Dose Administration

Mouse

Mice received single subcutaneous doses of cefuroxime sodium (1 0 g/kg) alone or in combination with furosemide (50 mg/kg) or furosemide plus glycerol 5.4 mL/kg. Cefuroxime alone caused no nephrotoxicity; when administered concomitantly with furosemide there was proximal tubular necrosis in 2 out of 9 animals. The combination of furosemide and glycerol caused tubular necrosis in 5 of 8 animals but this was not influenced by the
addition of cefuroxime.

Rat

Cefuroxime sodium at doses up to 10 g/kg was administered either alone or in combination with furosemide (100 mg/kg) or furosemide plus glycerol (3.15 mL/kg). Three of 6 animals exhibited proximal tubular necrosis in the inner cortex following administration of 4 g of cefuroxime alone. The incidence and severity of necrosis increased with increasing doses of cefuroxime. The incidence of tubular necrosis also increased when furosemide or furosemide plus glycerol were given concomitantly. Cefuroxime at 1g/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.

Rat: Repeated dose study

Rats received cefuroxime at doses ranging from 1 to 5 g/kg/day subcutaneously for 10 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 10 days. Cefuroxime sodium was given either concomitantly during the 10 days or as a single dose with the ninth dose of gentamicin. Gentamicin-induced tubular necrosis was not potentiated by the administration of single doses of cefuroxime up to 6 g/kg/day. Multiple doses of cefuroxime up to 4 g/kg protected rats against gentamicin-induced nephrotoxicity, but at doses of 6 g/kg/day of cefuroxime, severe tubular necrosis was observed after 4 days of treatment. Similar results were found with amikacin and tobramycin.

Mutagenicity Studies

Several standard assays were done to assess the mutagenic properties of cefuroxime axetil. These included both *in vitro* (Ames test, fluctuation test, gene conversion assay) and *in vivo* (micronucleus tests) assays.

***In vitro* assays**

Cefuroxime axetil was subjected to standard Ames tests, fluctuation tests, and gene conversion tests in concentrations of up to 208 µg/plate, 8.3 µg/mL, and 833 µg/mL respectively. The results of these tests were negative. Negative results were also obtained at high concentrations (833 µg/mL) in a modified fluctuation test in which the test strains were rendered resistant to cefuroxime's antibacterial properties. A weak, but statistically significant response was observed at 41 6 µg/mL, but this was not regarded as biologically significant since no effect was detected at 833 µg/mL.

***In vivo* micronucleus test**

Groups of five male mice received oral doses of cefuroxime axetil equivalent to 1.486, 1.114, 0.743 and 0.372 g/kg cefuroxime. Negative control groups received vehicle only and positive controls were dosed with 100 mg/kg cyclophosphamide. At either 24 or 48h, groups of animals were killed and the bone marrow of both femurs collected.

Smears were prepared and examined for micronuclei.

There was no significant increase in the proportion of polychromatic erythrocytes with micronuclei in any of the groups treated with cefuroxime axetil when compared with their negative control at either expression time. The ratios of mature to immature erythrocytes observed in animals receiving cefuroxime axetil were not significantly different from the negative controls at either expression time.

Tolerance Studies

Cefuroxime axetil, applied as a 50% suspension in soft paraffin/liquid paraffin to intact and abraded guinea pig skin under occlusive dressing for 21 hours, produced negligible irritancy. Cefuroxime axetil was strongly sensitizing when applied to guinea pig skin. Sixteen days after application of sensitizing doses to 10 animals, challenge with the test material produced a positive erythematous response in 9 animals after 24 hours and in all 10 after 48 hours.

Reproduction and Teratology Studies

Rodents

The reproductive toxicity of oral cefuroxime axetil was investigated in rats and mice as summarized in Table 8.

Table 8: Reproduction and Teratology Studies

Animal	Sex	Doses (mg/kg/day)	Animals/ Dose	Duration of Treatment	Significant Observations*
Mouse	F	0, 150, 500, 1600	30**	Day 7 to day 16 of pregnancy	Decreased number of implants (F_0), increased F_1 male: female ratio
Rat	F	0, 125, 250, 500	20	Day 17 of pregnancy to day 21 post partum	Delayed pinna detachment (F_1 females)
Rat	M	0, 125, 250, 500	10	70 days prior to mating	Delayed F_1 mating, increased F_2 male: female ratio, delayed primary coat (F_2 females), delayed eye opening (F_2 males), delayed pinna detachment (F_2)
	F	0, 125, 250, 500	30**	21 days before mating to day 21 post partum	
Rat	F	0, 125, 250, 500	30***	Day 7 to day 16 of pregnancy	Decreased number of implants (F_0), decreased number of live F_1 fetuses.

* Apparent reproductive toxicity (i.e., other than F_0 organ toxicity) which was dose-related and not due to experimental artifacts or to the antimicrobial action of the drug (e.g., suppression of intestinal microflora).
** 20 animals were killed at term; 10 were allowed to litter and complete the treatment.
*** 15 animals were killed at term; 15 were allowed to litter and complete the treatment.

The most common gross abnormality observed in offspring of treated dams was hydronephrosis, seen in comparable numbers at all dose levels including controls. There was no evidence that cefuroxime axetil had adversely affected fertility or peri-/post-natal development or organogenesis in rats or mice.

Rabbit

Rabbits were found to be unsuitable for reproductive toxicity testing of cefuroxime axetil. Six unmated females were treated with daily doses of 0.1 to 0.5 g/kg while 6 mated females received 0.2 g/kg. All but one animal showed a chronic loss of body weight and deterioration in overall conditions (3 animals died). One of the mated animals maintained a viable pregnancy.
Two aborted and evidence of earlier resorption of implants was found in another two. Post mortem examination of rabbits in both groups revealed liquefied intestinal contents and distended, gas-filled caecums in many cases. Changes in intestinal microflora were thought to be the cause of the observed toxicity.

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PART III: CONSUMER INFORMATION

[Pr]Nu-cefuroxime
(Cefuroxime axetil tablets)

This leaflet is part III of a three-part "Product Monograph" published when NU-CEFUROXIME was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Nu-cefuroxime. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is NU-CEFUROXIME. It contains cefuroxime axetil. This medicine is similar to other medicines called cephalosporins, which are antibiotics.

What it does:

Your doctor has prescribed NU-CEFUROXIME because you have an infection. NU-CEFUROXIME is used to kill the bacteria or "germs" which cause infections. The infection can be cleared up if you take your medication in the proper way.

When it should not be used:

You should not use NU-CEFUROXIME if you are allergic to cephalosporins. Tell your doctor also if you are allergic to or react badly to penicillins or other antibiotics.

Tell your doctor if you are pregnant or breast feeding a baby. If you are pregnant or breast feeding, your doctor may decide not to prescribe this medicine, although, there may be circumstances when your doctor advises you differently.

What the medicinal ingredient is:

The active ingredient in NU-CEFUROXIME is cefuroxime axetil.

What the important nonmedicinal ingredients are:

In addition to cefuroxime axetil, NU-CEFUROXIME contains the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, and titanium dioxide.

What dosage forms it comes in:

NU-CEFUROXIME is available as tablets for oral use in two strengths, which contain 250mg and 500mg of cefuroxime (as cefuroxime axetil), supplied in packages of 60, 100 and 250.

WARNINGS AND PRECAUTIONS

Before starting NU-CEFUROXIME and to get the best possible treatment, be sure to tell your doctor if you:

- are allergic to cephalosporins.
- react badly to penicillins or other antibiotics.
- are pregnant or breast feeding a baby.

As this medicine may cause dizziness, you should be cautious when driving or operating machinery.

INTERACTIONS WITH THIS MEDICATION

Drugs which reduce gastric acidity may decrease the effectiveness of NU-CEFUROXIME.

Cefuroxime axetil may lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

PROPER USE OF THIS MEDICATION

Usual dose:

You must take the medicine as prescribed by your doctor. If you are not sure how many tablets to take, or how often to take them, consult your doctor or pharmacist.

YOU SHOULD NOT INCREASE OR DECREASE THE PRESCRIBED DOSE UNLESS ADVISED BY YOUR DOCTOR.

The usual dose for adults is one 250 mg tablet twice a day. NU-CEFUROXIME tablets are not recommended for infants and children less than 12 years of age.

NU-CEFUROXIME has a bitter taste, therefore, **do not chew or crush the tablets** but swallow each one whole with a drink of water.
NU-CEFUROXIME Tablets are more effective if taken after food.

The usual length of treatment is 7 - 10 days, although your doctor may adjust the prescription to suit your treatment. During the course of treatment, all the tablets must be taken to make sure that all germs have been killed. For β-hemolytic streptococcal infections, therapy should be continued for at least 10 days.

CONTINUE TAKING THE TABLETS UNTIL THEY ARE FINISHED, EVEN IF YOU BEGIN TO FEEL BETTER.

If your doctor decides to stop the treatment, do not keep any left over medicine unless your doctor tells you to. Please discard all unused NU-CEFUROXIME Tablets.

REMEMBER: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

Overdose:

It is important to follow the dosage instructions on the label of your medicine. Taking more than this dose is unlikely to be dangerous unless a large quantity of tablets is taken all at once. In this case, contact your doctor or nearest hospital emergency department immediately.

Missed Dose:

If you forget to take a dose, take another as soon as possible. Then continue with the normal dose. Do not double doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you experience wheeziness and tightness of chest, swelling of eyelids, face or lips, or develop skin lumps or hives, or a skin rash (red spots), tell your doctor immediately. Do not take any more medicine unless your doctor tells you to do so. He may decide to stop your treatment.

You may experience diarrhea, vomiting or symptoms that you do not understand. There is no need to stop taking your tablets, but you should tell your doctor of any of these symptoms as soon as possible. Other symptoms can include headache, nausea, dizziness, itching, shortness of breath, and fever.

If you feel worse or you have taken all the tablets and do not feel better TELL YOUR DOCTOR AS SOON AS POSSIBLE.

This is not a complete list of side effects. For any unexpected effects while taking NU-CEFUROXIME, contact your doctor or pharmacist.

HOW TO STORE IT

Store tablets between 15°C and 30°C. Keep in tightly closed container.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701C
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting the sponsor, Nu-Pharm, Inc. at:

1-800-267-1438

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