PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-CEFUROXIME

Cefuroxime Axetil Tablets, USP

Tablets, 250 mg and 500 mg, Oral

ANTIBIOTIC

APOTEX INC
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RECENT MAJOR LABEL CHANGES

3 Serious Warnings and Precautions Box	05/2023
4 Dosage and Administration, 4.1 Dosing Considerations	05/2023
7 Warnings and Precautions, 7.1.4 Geriatrics	05/2023
7 Warnings and Precautions, Neurologic	05/2023
7 Warnings and Precautions, Renal	05/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-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* (methicillin susceptible), *Streptococcus pyogenes* or *Streptococcus agalactiae*.

  Susceptibility to cefuroxime axetil will vary with geography and time. Local susceptibility data should be consulted where available. See 15 MICROBIOLOGY. 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.

  To reduce the development of drug-resistant bacteria and maintain the effectiveness of APO-CEFUROXIME and other antibacterial drugs, APO-CEFUROXIME should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

1.1 Pediatrics

Pediatrics (<12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APO-CEFUROXIME in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.3 Pediatrics.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from post-market experience suggests that use in the geriatric population is associated with differences in safety or effectiveness with renal impaired patients. See 4.2 Recommended Dose and Dosage Adjustment and 7.1.4 Geriatrics.

2 CONTRAINDICATIONS

APO-CEFUROXIME 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. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Hemolytic Anemia:** APO-CEFUROXIME should not be used in patients with a history of cephalosporin-associated hemolytic anemia since the recurrence of hemolysis is much more severe. See 7 WARNINGS AND PRECAUTIONS, Hemolytic Anemia, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests and 8.2 Clinical Trial Adverse Reactions, Blood and lymphatic system disorders.
- **Hypersensitivity:** Serious and occasionally fatal hypersensitivity (anaphylactic) and severe cutaneous adverse reactions (SCAR) have been reported in patients receiving therapy with beta-lactams, including cefuroxime. See 7 WARNINGS AND PRECAUTIONS, Hypersensitivity and 7 WARNINGS AND PRECAUTIONS, Skin.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The dose of cefuroxime that is selected to treat an individual infection should take into account:

- The expected pathogens and their likely susceptibility to cefuroxime axetil
- The site of the infection
- The age, weight and renal function of the patient.

The duration of therapy should be determined by the type of infection and the response of the patient and should generally not be longer than recommended.

4.2 Recommended Dose and Dosage Adjustment

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:

Table 1

TYPE OF INFECTION	DOSAGE
pharyngitis, tonsillitis, sinusitis, bronchitis, skin structure infections	250 mg twice daily
more severe infections eg. pneumonia	500 mg twice daily

Infants and Children less than 12 Years of Age

APO-CEFUROXIME tablets are not recommended for infants and children less than 12 years of age.

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

Renal Impairment

APO-CEFUROXIME is primarily excreted by the kidneys. In patients with markedly impaired renal function it is recommended that the dosage of APO-CEFUROXIME be reduced to compensate for its slower excretion (see the table 2 below).

Table 2

Creatinine Clearance	$T_{1/2}$ (hours)	Recommended Dosage
≥30 mL/min	1.4 to 2.4	No dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10 to 29 mL/min	4.6	Standard individual dose given every 24 hours
<10 mL/min	16.8	Standard individual dose given every 48 hours
During haemodialysis	2 to 4	A single additional standard individual dose should be given at the end of each dialysis

The safety and efficacy of the proposed dosing adjustment has not been established.

4.4 Administration

For optimal absorption, APO-CEFUROXIME should be taken with food.

4.5 Missed Dose

If the patient misses a dose, inform the patient to skip the missed dose and take the next dose at the regular dosing schedule.

5 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 7 WARNINGS AND PRECAUTIONS, Immune.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet / 250 mg, 500 mg of cefuroxime axetil	Colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, and titanium dioxide

250 mg tablets: each white to off-white, capsule shaped, biconvex, film-coated tablet, engraved "APO" on one side and "C250" on the other side, contains cefuroxime axetil equivalent to 250 mg of cefuroxime base. Available in bottles of 100.

500 mg tablets: each white to off-white, capsule shaped, biconvex, film-coated tablet, engraved "APO" on one side and "C500" on the other, contains cefuroxime axetil equivalent to 500 mg of cefuroxime base. Available in bottles of 100.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Driving and Operating Machinery

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

Gastrointestinal

Broad-spectrum antibiotics including APO-CEFUROXIME should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

***Clostridium difficile*-Associated Disease:** *Clostridium difficile*-associated disease (CDAD) has been reported with use of many antibacterial agents including APO-CEFUROXIME. See 8.5 Post-Market Adverse Reactions, Gastrointestinal disorders . CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of

colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

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

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases.

Hematologic

Hemolytic Anemia: APO-CEFUROXIME should not be used in patients with a history of cephalosporin-associated hemolytic anemia since the recurrence of hemolysis is much more severe.

An immune mediated hemolytic anemia has been observed in patients receiving cephalosphorin class antibacterials, including APO-CEFUROXIME. Severe cases of hemolytic anemia, including fatalities, have been reported in both adults and children. If a patient develops anemia anytime during, or within 2 to 3 weeks subsequent to the administration of APO-CEFUROXIME, the diagnosis of a cephalosphorin-associated anemia should be considered and the drug discontinued until the etiology is determined.

Patients may benefit from periodic monitoring for signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing, where appropriate. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 8.2 Clinical Trial Adverse Reactions, Blood and lymphatic system disorders.

Immune

Hypersensitivity: Before therapy with APO-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. APO-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 allergic reaction to penicillins or other beta-lactams. If an allergic reaction to APO-CEFUROXIME occurs, treatment should be discontinued and standard agents (e.g. epinephrine, antihistamines, corticosteroids) administered as necessary. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Monitoring and Laboratory Tests

Patients may benefit from periodic monitoring for:

- Signs and symptoms of hemolytic anemia, including measurement of hematological parameters or drug-induced antibody testing, where appropriate. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX, 7 WARNINGS AND PRECAUTIONS, Hemolytic Anemia and 8.2 Clinical Trial Adverse Reactions, Blood and lymphatic system disorders.
- Renal function in the elderly and renally impaired. See 4.2 Recommended dose and Dosage Adjustment, Renal impairment, 7 WARNINGS AND PRECAUTIONS, Renal, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency.

Neurologic

Cephalosporins have been associated with the occurrence of seizures. A known risk factor is renal impairment without dosage adjustment; however, seizures have also been described in individuals without a preceding history of renal impairment whose renal function deteriorates while taking the cephalosporin.

If seizures associated with APO-CEFUROXIME occur, APO-CEFUROXIME should be discontinued if clinically appropriate. Anticonvulsant therapy can be given if clinically indicated. See 8.5 Post-Market Adverse Reactions.

Renal

Cefuroxime is substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. It may be useful to monitor renal function in patients with renal impairment. See 4.2 Recommended dose and Dosage Adjustment, Renal impairment, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency.

Sensitivity/Resistance

Development of Drug Resistant Bacteria: Prescribing APO-CEFUROXIME in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

As with other antibiotics, use of APO-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, APO-CEFUROXIME should be discontinued and another appropriate antibiotic should be substituted.

Skin

Severe Cutaneous Adverse Reactions: Severe cutaneous adverse reactions (SCAR) such as acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) have been reported in association with beta-lactam treatment. When SCAR is suspected, APO-CEFUROXIME should be discontinued and appropriate therapy and/or measures should be taken. See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

7.1 Special Populations

7.1.1 Pregnant Women

The safety of APO-CEFUROXIME in pregnancy has not been established. The use of APO-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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<12 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of APO-CEFUROXIME in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥65 years of age): Evidence from post-market experience suggests that use in the geriatric population is associated with differences in safety or effectiveness with renal impaired patients. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See 4.2 Recommended dose and Dosage Adjustment, Renal impairment, 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, 7 WARNINGS AND PRECAUTIONS, Renal, and 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency.

Of the total number of subjects who received cefuroxime axetil in 20 clinical trials, 375 were aged 65 and older while 151 were aged 75 and older. No overall differences in safety or

effectiveness were observed between these subjects and younger adult subjects. Reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse reactions have been reported:

Blood and lymphatic system disorders: Eosinophilia, very rarely hemolytic anemia. See 7 WARNINGS and PRECAUTIONS, Hemolytic Anemia.

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

General disorders and administration site conditions (1.3% of patients): As with other cephalosporins, there have been rare reports of drug fever.

Immune system disorders (1.3% of patients): Hypersensitivity reactions to APO-CEFUROXIME may occur in patients who report delayed hypersensitivity to penicillins. See 7 WARNINGS AND PRECAUTIONS, Immune.

Investigations: Increased erythrocyte sedimentation rate, decreased hemoglobin, Positive Coomb's test. Transient increases of hepatic enzyme levels [ALT, AST, LDH] (3% of patients).

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: Transient increases in serum bilirubin, creatinine, alkaline phosphatase, and urea nitrogen (BUN).

Nervous system disorders (2.2% of patients): Headache and dizziness.

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

Reproductive system and breast disorders: 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: Vaginitis.

Respiratory system and mediastinal disorders (1.3% of patients): Shortness of breath and rare reports of bronchospasm.

Skin and subcutaneous tissue disorders (1.3% of patients): Rashes (0.6%), pruritus (0.3%), urticaria (0.2%).

8.5 Post-Market Adverse Reactions

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.

Blood and lymphatic system disorders: Thrombocytopenia, and leucopenia (sometimes profound).

Gastrointestinal disorders: Pseudomembranous colitis. See 7 WARNINGS AND PRECAUTIONS, Gastrointestinal, *Clostridium difficile*-Associated Disease..

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

Immune system disorders: The following hypersensitivity reactions have been reported: Anaphylaxis, angioedema, serum sickness-like reaction.

Infections and Infestations: *Candida* overgrowth.

Nervous system disorders: Seizure. See 7 WARNINGS AND PRECAUTIONS, Neurologic.

Renal and urinary disorders: Renal dysfunction.

Skin and subcutaneous tissue disorders: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

The following hypersensitivity reactions have been reported: Pruritus, rash, urticaria.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 4 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect
Aminoglycosides	T	The concomitant administration of aminoglycosides and some cephalosporins has caused nephrotoxicity. There is no evidence that APO-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 APO-CEFUROXIME concomitantly with aminoglycosides is not known.
Diuretics	CT	Studies suggest that the concomitant use of potent diuretics, such as furosemide and ethacrynic acid, may increase the risk of renal toxicity with cephalosporins.
Drugs which reduce gastric acidity	T	Drugs which reduce gastric acidity may result in a lower bioavailability of APO-CEFUROXIME compared with that of the fasting state and tend to cancel the effect of enhanced post-prandial absorption.
Oral contraceptives	T	In common with other antibiotics, cefuroxime axetil may affect the gut flora, leading to lower estrogen reabsorption and reduced efficacy of combined oral contraceptives.

CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 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 APO-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. See 7 WARNINGS

AND PRECAUTIONS, Monitoring and Laboratory Tests and 8.2 Clinical trial Adverse Reactions, Investigations.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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*.

10.2 Pharmacodynamics

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 to 1h, 24h intervals for 7d	Decreased body temperature in females
rat	0.5	10	Pupil diameter, body temperature, gross behaviour	0 to 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.

10.3 Pharmacokinetics

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 6.

Table 6: Pharmacokinetics of cefuroxime axetil administered as cefuroxime axetil tablets to adults

DOSE (mg)	ROUTE	FASTED/ FED	PEAK SERUM CONCENTRATION (mcg/mL)	TIME TO PEAK (h)	AREA UNDER SERUM LEVEL-TIME CURVE (mg●h/L)	URINE RECOVERY 0 to 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 axetil tablets (500 mg dose) increased from 36% in fasted subjects to 52% after food.

Absorption

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

Elimination

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.

Special Populations and Conditions

- **Renal Insufficiency:** Cefuroxime pharmacokinetics have been investigated in patients

with various degrees of renal impairment. Cefuroxime elimination half-life increases with decrease in renal function which serves as the basis for dosage adjustment recommendations in this group of patients. See 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment. In patients undergoing hemodialysis, at least 60% of the total amount of cefuroxime present in the body at the start of dialysis will be removed during a 4-hour dialysis period. Therefore, an additional single dose of cefuroxime should be administered following the completion of haemodialysis.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature 15˚C to 30˚C. Keep in tightly closed container.

APO-CEFUROXIME should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended.

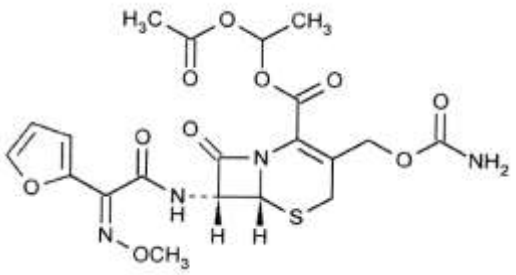
12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 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 and molecular mass:	$C_{20}H_{22}N_4O_{10}S$ and 510.5 g/mol.
Structural formula:	
Physicochemical properties	Cefuroxime axetil is an amorphous white to cream-coloured 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.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

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 APO-CEFUROXIME (cefuroxime axetil) 500 mg and CEFTIN® 500 mg tablets. The results from measured data are summarized in the following table 7:

Table 7

Cefuroxime Axetil (1 x 500 mg) From measured data Geometric Least Square Mean Arithmetic Mean (CV %)				
Parameter	Cefuroxime Axetil Tablets (Apotex Inc.) (Canada)	CEFTIN® Tablets (GlaxoSmithKline Inc.) (Canada)	% Ratio of Geometric Means#	90% Confidence Interval#
AUC_t (mcg•h/mL)	20.577 21.512 (32)	19.381 20.287 (33)	106.2	99.0 – 113.9
AUC_{inf} (mcg•h/mL)	21.145 22.090 (31)	19.943 20.844 (33)	106.0	98.9 – 113.7
C_{max} (mcg/mL)	6.248 6.523 (31)	6.165 6.301 (22)	101.3	91.0 – 112.9
T_{max}§ (h)	2.11 (54)	1.77 (38)		
T_{half}§ (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.

15 MICROBIOLOGY

Cefuroxime has been demonstrated to be active against various susceptible strains of the following microorganisms both in vitro and in clinical infections. See 1 INDICATIONS.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (methicillin susceptible)

Streptococcus pneumoniae

Streptococcus pyogenes (including group A beta-hemolytic streptococci)

Streptococcus agalactiae

Aerobic Gram-Negative Microorganisms:

Haemophilus influenzae (including beta-lactamase negative, beta-lactamase positive and ampicillin-resistant strains)

Haemophilus parainfluenzae

Klebsiella pneumoniae

Moraxella catarrhalis

In vitro susceptibility data is available for the following microorganisms.

Aerobic Gram-Positive Microorganisms:

Staphylococcus aureus (methicillin susceptible)

Coagulase negative Staphylococcus spp (methicillin susceptible)

Streptococcus agalactiae

Streptococcus pneumoniae (including penicillin-susceptible, -intermediate and –resistant strains)

Streptococci spp.-β-haemolytic

Streptococcus pyogenes

Aerobic Gram-Negative Microorganisms:

Citrobacter freundii

Enterobacteriaceae

Enterobacter spp.

Escherichia coli

Haemophilus influenza (including beta-lactamase negative and positive strains)

Haemophilus parainfluenzae

Klebsiella oxytoca

Klebsiella pneumoniae

Klebsiella spp.

Moraxella catarrhalis

Morganella morganii

Proteus mirabilis

Providencia spp

Anaerobes

Bacteroides spp.

Clostridium spp.

Fusobacterium nucleatum/necrophorum

Peptostreptococcus micros

Susceptibility Testing:

The results of susceptibility testing, by either disk-diffusion or broth microdilution techniques, should be interpreted according to the criteria established in CLSI M-100 S24 document as shown in Table 8. Quality control (QC) should be performed and evaluated according to CLSI published QC ranges as shown in Table 9.

Table 8: Disk and MIC breakpoints for cefuroxime susceptibility testing

Organism	Zone Diameter Interpretive Criteria* (mm) (30 mcg disk)			MIC Interpretive Criteria* (mcg/mL)		
	Sensitive	**Intermediate**	**Resistant**	**Sensitive**	**Intermediate**	**Resistant**
Hemophilus influenzae	≥20	17 to 19	≤16	≤4	8	≥16
Enterobacteriaceae	≥23	15 to 22	≤14	≤4	8 to 16	≥32
Staphylococcus spp.			Note 1			Note 1
Streptococcus pneumoniae	-	-	-	≤1	2	≥4
Streptococcus pyogenes	Note 2			Note 2		

*Interpretive criteria based on CLSI M100-S24 interpretive criteria

[1]Oxacillin-resistant S. aureus and coagulase-negative staphylococci are considered resistant to cefuroxime

[2]Penicillin-susceptible S. pyogenes can be considered susceptible to cefuroxime

Table 9: Disk and MIC QC ranges for cefuroxime susceptibility testing

QC Strain	**Disk Range* (mm)**	***MIC Range* (mcg/mL)***
Escherichia coli ATCC 25922	20 to 26	2 to 8
Haemophilus influenzae 49766	28 to 36	0.25 to 1
Staphylococcus aureus ATCC 25923	27 to 35	-
Staphylococcus aureus ATCC 29213	-	0.5 to 2

QC Strain	Disk Range* (mm)	*MIC Range* (mcg/mL)*
Streptococcus pneumoniae ATCC 49619	-	0.25 to 1

*Disk and MIC QC ranges published from CLSI M100-S24

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

The experimental details of single-dose toxicity studies are presented in Table 10 .

Table 10: Acute Toxicity

ANIMAL	AGE	ROUTE	DOSES (g/kg)	ANIMALS/ DOSE*	LENGTH OF OBSERVAT-ION	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 to 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 (10-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 to 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 11.

Table 11: 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 days	-
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 AST and ALT, 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 (10 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 to 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.

Genotoxicity

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 mcg/plate, 8.3 mcg/mL, and 833 mcg/mL respectively. The results of these tests were negative. Negative results were also obtained at high concentrations (833 mcg/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 416 mcg/mL, but this was not regarded as biologically significant since no effect was detected at 833 mcg/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.

Reproductive Developmental Toxicology

Rodents

The reproductive toxicity of oral cefuroxime axetil was investigated in rats and mice as summarized in Table 12.

Table 12: 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 liquified intestinal contents and distended, gas-filled caecums in many cases. Changes in intestinal microflora were thought to be the cause of the observed toxicity.

Special Toxicology

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. CEFTIN® cefuroxime axetil for oral suspension USP, 125 mg/5 mL, submission control 267904, Product Monograph. Sandoz Canada Inc. OCT 28, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-CEFUROXIME

Cefuroxime Axetil Tablets

Read this carefully before you start taking **APO-CEFUROXIME** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-CEFUROXIME**.

Serious Warnings and Precautions

Seek medical help if you think you are experiencing any of the following serious side effects – you may need urgent medical treatment:

- **Hemolytic anemia (breakdown of red blood cells):** If you have a history of cephalosporin-associated hemolytic anemia, you should not take APO-CEFUROXIME. If you develop hemolytic anemia, you may have symptoms such as pale skin, weakness, tiredness, shortness of breath, yellowing of your skin and/or the whites of your eyes, fever.
- **Allergic reactions:** signs may include difficulty breathing, swelling of the face or throat, severe skin rash, sudden swelling.
- **Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs)**: signs may include skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish); swelling and redness of eye or face; flu-like feeling, fever, chills, body aches, swollen glands, cough, shortness of breath, chest pain or discomfort.

What is APO-CEFUROXIME used for?

APO-CEFUROXIME is an antibiotic medicine. It is similar to other antibiotic medicines called cephalosporins. Your healthcare professional has prescribed APO-CEFUROXIME because you have an infection.

Your healthcare professional should test the type of bacteria causing your infection and monitor whether the bacteria are sensitive to APO-CEFUROXIME during your treatment.

Antibacterial drugs like APO-CEFUROXIME treat only bacterial infections. They do not treat viral infections such as the common cold.

How does APO-CEFUROXIME work?

APO-CEFUROXIME contains an antibiotic that reduces infections by:

- Stopping the growth of bacteria.
- Killing bacteria.

The infection can be cleared up if you take your medication in the proper way.

What are the ingredients in APO CEFUROXIME?

Medicinal ingredients: Cefuroxime (as cefuroxime axetil)

Non-Medicinal ingredients**:** colloidal silicon dioxide, crospovidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol and titanium dioxide**.**

APO-CEFUROXIME comes in the following dosage forms:

Tablets: 250 mg and 500 mg

Do not use APO-CEFUROXIME if:

- you are allergic to cefuroxime, to cephalosporin antibiotics or to any of the other ingredients in APO-CEFUROXIME (see What are the ingredients in APO CEFUROXIME?).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-CEFUROXIME. Talk about any health conditions or problems you may have, including if you:

- are allergic to or react badly to penicillins or other antibiotics.
- have any stomach or gut problems, such as colitis.
- have kidney problems.
- are pregnant or planning to become pregnant.
- are breastfeeding or planning to breastfeed. Cefuroxime is excreted in human breast milk. Discuss breastfeeding with your healthcare professional .

Other warnings you should know about:

***Clostridium difficile*-Associated Disease (CDAD):** Some people who have taken this medication, or other medications like APO-CEFUROXIME have developed CDAD. CDAD is a gastrointestinal problem with symptoms such as diarrhea, abdominal cramping and/or colitis.

Driving and Operating Machinery: As this medication may cause dizziness, do not drive or operate machinery if you are feeling dizzy.

Monitoring and Tests: Your healthcare professional may perform blood tests during your treatment with APO-CEFUROXIME. If you are having a urine test for sugar, tell your healthcare professional that you are taking APO-CEFUROXIME. False positive reactions may occur when using certain test types. Your healthcare professional may have to use a different type of test.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-CEFUROXIME:

- Medicines used to treat bacterial infections such as aminoglycosides (such as gentamicin, amikacin, tobramycin).
- Medicines used to reduce the amount of acid in your stomach (such as antacids used to treat heartburn) can affect how APO-CEFUROXIME works.
- Medicines that promote the production of urine (such as furosemide and ethacrynic acid).
- APO-CEFUROXIME may reduce how well the contraceptive pill works. If you are taking the contraceptive pill while you are being treated with APO-CEFUROXIME, you also need to use a barrier method of contraception (such as condoms). Ask your healthcare professional for advice.

How to take APO-CEFUROXIME:

- Although you may feel better early in treatment, APO-CEFUROXIME should be used exactly as directed.
- Misuse or overuse of APO-CEFUROXIME could lead to the growth of bacteria that will not be killed by APO-CEFUROXIME (resistance). This means that APO-CEFUROXIME may not work for you in the future.
- Do not share your medicine.
- Take APO-CEFUROXIME Tablets with food. This will help to make the treatment more effective.

Usual dose:

The usual length of treatment is 7 to 10 days, although your healthcare professional 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. CONTINUE TAKING THE TABLETS UNTIL THEY ARE FINISHED, EVEN IF YOU BEGIN TO FEEL BETTER.

YOU SHOULD NOT INCREASE OR DECREASE THE PRESCRIBED DOSE UNLESS ADVISED BY YOUR HEALTHCARE PROFESSIONAL

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

The usual dose for adults is one 250 mg tablet twice a day. APO-CEFUROXIME has a bitter taste, therefore, do not chew or crush the tablets but swallow each one whole with a drink of water.

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 healthcare professional or nearest hospital emergency department immediately.

If you think you, or a person you are caring for, have taken too much APO-CEFUROXIME, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, skip the missed dose and take your next dose at the regularly scheduled time. Do not take two doses at once to make up for a missed dose.

What are possible side effects from using APO-CEFUROXIME?

These are not all the possible side effects you may have when taking APO-CEFUROXIME. If you experience any side effects not listed here, tell your healthcare professional.

- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Headache
- Dizziness
- Drowsiness
- Fever

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

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Increased levels of liver enzymes in the blood: dark urine, fatigue, loss of appetite, yellowing of the skin or eyes		√	
RARE			
Bowel Inflammation (*Clostridium difficile* colitis): severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			√
Overgrowth of Yeast (Candida): fungal infections (such as thrush, diaper rash, or inflammation of the vagina). This side effect is more likely to occur with		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
prolonged use.			
VERY RARE			
Allergic Reactions: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			√
Erythema multiforme (severe skin reaction): skin rash which may blister and looks like small targets (central dark spots surrounded by a paler area with a dark ring around the edge).			√
Hemolytic anemia (breakdown of red blood cells): pale skin, weakness, tiredness, shortness of breath, yellowing of your skin and/or the whites of your eyes, fever.			√
UNKNOWN			
Seizures (fits): uncontrollable shaking with or without loss of consciousness.			√
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): • Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish). • Swelling and redness of eyes or face • Flu-like feeling, fever, chills, body aches, swollen glands, cough • Shortness of breath, chest pain, or discomfort			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough

to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15˚C to 30˚C. Keep in tightly closed container.

Keep out of reach and sight of children.

If you want more information about APO-CEFUROXIME:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Revised MAY 11, 2023