PRODUCT MONOGRAPH

[Pr]ratio-CEFUROXIME

cefuroxime axetil tablets USP

250 mg and 500 mg cefuroxime

Antibiotic

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Preparation:
September 19, 2017

Control: 208784

PRODUCT MONOGRAPH

[Pr]ratio-CEFUROXIME

cefuroxime axetil tablets USP

250 mg and 500 mg cefuroxime/tablet

Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

Cefuroxime axetil is an orally active prodrug of cefuroxime. After oral administration, cefuroxime axetil, as **ratio-CEFUROXIME***, 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.*

INDICATIONS AND CLINICAL USES

ratio-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

* All dosages are expressed in terms of cefuroxime (base).

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 **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 **ratio-CEFUROXIME** and other antibacterial drugs, **ratio-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.

CONTRAINDICATIONS

ratio-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

Before therapy with **ratio-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. **ratio-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 **ratio-CEFUROXIME** occurs, treatment should be discontinued and standard agents (e.g. epinephrine, antihistamines, corticosteroids) administered as necessary.

***Clostridium difficile*-Associated Disease**

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

months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *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.

Hemolytic Anemia

ratio-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 cephalosporin class antibacterials, including 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 2-3 weeks subsequent to the administration of **ratio-CEFUROXIME**, the diagnosis of a cephalosporin-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 **PRECAUTIONS** and **ADVERSE REACTIONS**).

Susceptibility/Resistance
Development of Drug Resistant Bacteria
Prescribing **ratio-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.

PRECAUTIONS

General
Broad-spectrum antibiotics including **ratio-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 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 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 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, **ratio-CEFUROXIME** should be discontinued and another appropriate antibiotic should be substituted.

Pregnancy

The safety of cefuroxime in pregnancy has not been established. The use of **ratio-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 Mothers

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

Drug Interactions

Drugs which reduce gastric acidity may result in a lower bioavailability of 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 **ratio-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 **WARNINGS** and **ADVERSE REACTIONS**).

Ability to Perform Tasks That Require Judgement, Motor or Cognitive Skills

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

ADVERSE REACTIONS

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, AST, 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 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, Positive Coomb's test and very rarely hemolytic anemia (see **WARNINGS** and **PRECAUTIONS**).

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

POSTMARKETING EXPERIENCE WITH CEFUROXIME PRODUCTS

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

Hypersensitivity Reactions: 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

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**.

DOSAGE AND ADMINISTRATION

For optimal absorption, **ratio-CEFUROXIME** (cefuroxime axetil) should be taken with food. In comparative bioavailability studies in healthy adults, cefuroxime axetil suspension was not bioequivalent to cefuroxime axetil tablets. The area under the curve for the suspension averaged 91% of that for the tablet, while the C_{max} for the suspension averaged 71% of the C_{max} of the tablets.

DOSAGE

ratio-CEFUROXIME TABLETS

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

Infants and Children less than 12 Years of Age:

ratio-CEFUROXIME tablets are not recommended for infants and children less than 12 years of

age.

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

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

Creatinine Clearance	**T1/2 (hours)**	**Recommended Dosage**
≥30 mL/min	1.4 - 2.4	No dose adjustment necessary (standard dose of 125 mg to 500 mg given twice daily)
10-29 mL/min	4.6	Standard individual dose given every 24 hours
<10 mL/min	16.8	Standard individual dose given every 48 hours
During hemodialysis	2 – 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.

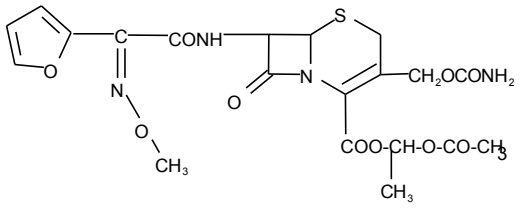
PHARMACEUTICAL INFORMATION

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, 72-(Z)-(0-methyl-oxime), 1-acetate 3-carbamate.

Structural Formula:



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

Molecular Weight: 510.5

Description: 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.

Composition:

TABLETS

Each **ratio-CEFUROXIME** tablet contains the following excipients: microcrystalline cellulose, croscarmellose sodium, hydrogenated vegetable oil, sodium lauryl sulphate, colloidal silicon dioxide, hydroxypropyl methylcellulose, propylene glycol, methylparaben and propylparaben, titanium dioxide and sodium benzoate.

ratio-CEFUROXIME Tablets are available in two strengths which contain 250 mg and 500 mg of cefuroxime (as cefuroxime axetil).

STORAGE

TABLETS

Store tablets between 15°C and 30°C.

AVAILABILITY OF DOSAGE FORMS

TABLETS

ratio-CEFUROXIME tablets are available in two strengths which contain 250 mg and 500 mg cefuroxime (as cefuroxime axetil).

250 mg: The tablets are white to off-white, film coated, capsule-shaped, biconvex tablets, plain on one side and engraved GXES7 on the other side. Available in bottles of 60.

500 mg: The tablets are white to off-white, film coated, capsule-shaped, biconvex tablets, plain on one side and engraved GXEG2 on the other side. Available in bottles of 60.

MICROBIOLOGY

Cefuroxime has been demonstrated to be active against various susceptible strains of the following microorganisms both *in vitro* and in clinical infections (see **INDICATIONS AND CLINICAL USE**).

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
Neisseria gonorrhoeae
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 1. Quality control (QC) should be performed and evaluated according to CLSI published QC ranges as shown in Table 2.

Table 1: Disk and MIC breakpoints for cefuroxime susceptibility testing

Organism	Zone Diameter Interpretive Criteria* (mm) (30µg disk)			MIC Interpretive Criteria* (µg/mL)		
	Sensitive	**Intermediate**	**Resistant**	**Sensitive**	**Intermediate**	**Resistant**
Hemophils influenzae	≥20	17-19	≤16	≤4	8	≥16
Enterobacteriaceae	≥23	15-22	≤14	≤4	8-16	≥32
Staphylococcus spp.			Note 1			Note 1
Streptococcs pneumoniae	-	-	-	≤1	2	≥4
Streptococcs 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 2: Disk and MIC QC ranges for cefuroxime susceptibility testing

QC Strain	Disk Range* (mm)	MIC Range* (µg/ml
Escherichia coli ATCC 25922	20-26	2-8
Haemophilus influenzae 49766	28-36	0.25-1
Staphylococcus aureus ATCC 25923	27-35	-
Staphylococcus aureus ATCC 29213	-	0.5-2
Streptococcus pneumoniae ATCC 49619	-	0.25-1

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

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 3.

Table 3: Pharmacokinetics of cefuroxime axetil administered as Tablets to Adults

DOSE (mg)	ROUTE	FASTED /FED	PEAK SERUM CONCENTRA-TION (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 axetil 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.

Renal impairment:

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 **DOSAGE AND ADMINISTRATION**). In patients undergoing haemodialysis, 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.

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 4.

Table 4: 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 5.

Table 5: 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	-.0	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 (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 (1.0-2.5 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 6.

Table 6: 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 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 1 g/kg enhanced the severity of the furosemide-glycerol-induced necrosis in the outer cortex. Treatment with furosemide plus glycerol also lowered the dosage of cefuroxime to 2 g/kg required to produce necrosis of the inner cortex.

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 416 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 7.

Table 7: 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 F	0,125,250,500 0,125,250,500	10 30**	70 days prior to mating 21 days before mating to day 21 post partum	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)
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.

REFERENCES OR SELECTED BIBLIOGRAPHY

1. Adams DH, Wood MJ, Farrell ID, Fox C, Ball AP: Oral cefuroxime axetil: clinical pharmacology and comparative dose studies in urinary tract infections. J Antimicrob Chemother 1985; 16:359-366.
2. Bluestone CD: Otitis media and sinusitis in children. Role of Branhamella catarrhalis. Drugs 1986; 31(suppl 3):132-141.

3. Broekhuysen J, Deger F, Douchamps J, Freschi E, Mal N, Neve P, et al: Pharmacokinetic study of cefuroxime in the elderly. Br J Clin Pharmacol 1981; 12:801-805.

4. Brogden RN, Heel RC, Speight TM, Avery GS: Cefuroxime: a review of its antibacterial activity, pharmacological properties and therapeutic use.

5. Bundtzen RW, Toothaker RD, Nielson OS, Madsen PO, Welling PG, Craig WA: Pharmacokinetics of cefuroxime in normal and impaired renal function: comparison of high-pressure liquid chromatography and microbiology assays. Antimicrob Ag Chemother 1981; 19(3):443-449.

6. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. Twenty-Fourth Informational Supplement. CLSI document M100-S24. Wayne, PA; Clinical and Laboratory Standards Institute; 2014.

7. Finn AL, Straughn A, Meyer M, Chubb J: Effect of dose and food on the bioavailability of cefuroxime axetil. Biopharm Drug Dispos 1987; 8:519-526.

8. Foord RD: Cefuroxime Human Pharmacokinetics. Antimicrob Agents Chemother 1976; 9:741-747.

9. Ginsburg CM, McCracken GH, Petryka M, Olser K: Pharmacokinetics and bactericidal activity of cefuroxime axetil. Antimicrob Ag Chemother 1985; 28(4):504-507.

10. Gold B, Rodriguez J: Cefuroxime: mechanisms of action, antimicrobial activity, pharmacokinetics, clinical applications, adverse reactions and therapeutic indications. Pharmacother 1983; 3(2):82-100.

11. Harding SM, Williams PEO, Ayrton J: Pharmacology of cefuroxime as 1-acetoxyethyl ester in volunteers. Antimicrob Ag Chemother 1984; 25(1):78-82.

12. Kovatch AL, Wald ER, Michaels RH: Beta-lactamase-producing Branhamella catarrhalis causing otitis media in children. J Pediatr 1983; 102:261-264.

13. McCracken GH Jr, Ginsburg CM, Clahsen JC, Thomas ML: Pharmacologic evaluation of orally administered antibiotics and children: Effect of feeding on bioavailability. J Pediatr 1978; 62:738-743.

14. Philipson A, Stiernstedt G: Pharmacokinetics of cefuroxime in pregnancy. Am J Obstet

Gynecol 1982; 142(7):823-828.

15. Slevin NJ, Aitken J, Thornley PE: Clinical and microbiological features of Branhamella catarrhalis bronchopulmonary infections. Lancet 1984; 1:782-783.

16. Sommers DK, Van Wyk M, Moncrieff J: Influence of food and reduced gastric acidity on the bioavailability of bacampicillin and cefuroxime axetil. Br J Clin Pharmacol 1984; 18(4):535-539.

17. Sommers DK, Van Wyk M, Williams PEO, Harding SM: Pharmacokinetics and tolerance of cefuroxime axetil in volunteers during repeated dosing. Antimicrob Ag Chemother 1984; 25(3):344-347.

18. Tartaglione TA, Polk RE: Review of the new second-generation cephalosporins: cefonicid, ceforanide, and cefuroxime. Drug Intell Clin Pharm 1985; 19(3):188-198.

19. Williams PEO: Factors affecting the oral absorption of esterified antibiotics. Biochem Soc Trans 1985; 13:511-513.

20. Williams PEO, Harding SM: The absolute bioavailability of oral cefuroxime axetil in male and female volunteers after fasting and after food. J Antimicrob Chemother 1984; 13(2):191-196.

21. Wise R, Bennett SA, Dent J: The pharmacokinetics of orally absorbed cefuroxime compared with amoxycillin/clavulanic acid. J Antimicrob Chemother 1984; 13(6):603-610

22. Ceftin® Product Monograph Glaxo Smithkline Inc. Date of Revision June 14, 2017. Control Number: 203522.

CONSUMER INFORMATION

Pr ratio-CEFUROXIME

(cefuroxime axetil) tablets USP
250 mg and 500 mg cefuroxime/tablet

This leaflet is part of the ratio-CEFUROXIME Product Monograph and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ratio-CEFUROXIME. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ratio-CEFUROXIME is an antibiotic medicine. It is similar to other antibiotic medicines called cephalosporins. Your doctor has prescribed ratio-CEFUROXIME because you have an infection.

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

Antibacterial drugs like ratio-CEFUROXIME treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, ratio-CEFUROXIME should be used exactly as directed. Misuse or overuse of ratio-CEFUROXIME could lead to the growth of bacteria that will not be killed by ratio-CEFUROXIME (resistance). This means that ratio-CEFUROXIME may not work for you in the future. Do not share your medicine.

What it does:
ratio-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:
Do not use ratio-CEFUROXIME if you are allergic to cefuroxime or to cephalosporin antibiotics or to an of the other ingredients in ratio-CEFUROXIME (see What the important nonmedicinal ingredients are).

What the medicinal ingredient is:
Cefuroxime (as cefuroxime axetil)

What the important non-medicinal ingredients are:
Tablets: Non-medicinal ingredients include colloidal silicon dioxide, croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, methylparaben, microcrystalline cellulose, propylene glycol, propylparaben, sodium benzoate, sodium lauryl sulphate, and titanium dioxide.

What dosage forms it comes in:
Tablets: ratio-CEFUROXIME Tablets are supplied in two strengths, containing 250 mg or 500 mg of cefuroxime (as cefuroxime axetil). Your doctor will decide which strength you need.

WARNINGS AND PRECAUTIONS

BEFORE you use ratio-CEFUROXIME talk to your doctor or pharmacist if:
- you are allergic to or react badly to penicillins or other antibiotics.
- you have kidney problems, as your doctor may reduce your dose.
- you are having a urine test for sugar. False positive reactions may occur if using methods dependent on copper reduction such as Fehling's or Benedict's solution or with Clinitest® Tablets. For this reason, enzyme-based tests such as Tes-Tape® or Clinistix® should be used.
- you are pregnant or planning to become pregnant
- you are breastfeeding or planning to breastfeed. Cefuroxime is excreted in human breast milk. Discuss breastfeeding with your doctor.
- you are taking other medicines. Tell your doctor or pharmacist about all the medicines you are taking, including non-prescription drugs and natural health products.

As this medication may cause dizziness, do not drive or operate machinery if you are feeling dizzy.

Talk to your doctor if the following occurs while taking ratio-CEFUROXIME:
- you develop hemolytic anemia (breakdown of red blood cells) with symptoms such as pale skin, weakness, tiredness, shortness of breath, yellowing of your skin and/or the whites of your eyes.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with ratio-CEFUROXIME include:
- Medicines used to reduce the amount of acid in your stomach (e.g. antacids used to treat heartburn) can affect how ratio-CEFUROXIME works.
- Medicines that promote the production of urine (such as furosemide and ethacrynic acid) may increase the risk of kidney problems when taken while being treated with ratio-CEFUROXIME.
- ratio-CEFUROXIME may reduce how well the contraceptive pill works. If you are taking the contraceptive pill while you are being treated with

ratio-CEFUROXIME, you also need to use a barrier method of contraception (such as condoms). Ask your doctor for advice.

PROPER USE OF THIS MEDICATION

Usual Dose:
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. CONTINUE TAKING THE TABLETS UNTIL FINISHED, EVEN IF YOU BEGIN TO FEEL BETTER.

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

Take ratio-CEFUROXIME Tablets with food. This will help to make the treatment more effective.

Tablets:

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.

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

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

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

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. Your doctor may decide to stop your treatment.

You may experience diarrhea, nausea, vomiting, loose stools, abdominal pain, headache, dizziness, diaper rash, drowsiness, inflammation of the vagina 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.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, stop taking ratio-CEFUROXIME and contact your doctor immediately.

Other side effects include seizure and kidney problems. ratio-CEFUROXIME may also cause an increase in a type of white blood cell (*eosinophilia*), a decrease in the number of white blood cells (*leukopenia*), decrease in number of blood platelets (cells that help blood to clot) called thrombocytopenia or an increase in some substances (*enzymes*) produced by the liver. If you are taking a blood test, you should tell your doctor that you are taking ratio-CEFUROXIME, as it may affect your result.

On rare occasions, medicines like ratio-CEFUROXIME can cause an overgrowth of yeast (*Candida*) in the body which can lead to fungal infections (such as thrush). This side effect is more likely if you take ratio-CEFUROXIME for a long time. Tell your doctor as soon as possible if you think you have a fungal infection. Your doctor may need to stop your treatment.

Very rarely, ratio-CEFUROXIME may cause severe skin reactions, such as 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) known as erythema multiforme, and widespread rash with blisters and skin peeling on much of the body surface (*toxic epidermal necrolysis*), particularly around the mouth, nose, eyes and genitals (*Stevens-Johnson syndrome*). If these severe skin reactions occur, stop taking ratio-CEFUROXIME and contact your doctor immediately.

Very rarely, ratio-CEFUROXIME may cause effects such as:

- high temperature (*fever)*
- yellowing of the whites of the eyes or skin *(jaundice)*
- inflammation of the liver (hepatitis) with symptoms such as abdominal pain, vomiting, nausea and jaundice, and
- a faster breakdown of red blood cells leading to a form of anemia *(hemolytic anemia)* with symptoms such as fatigue, shortness of breath and looking pale

If these symptoms occur or persist, contact your doctor.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/Effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	**Overgrowth of Yeast (*Candida*):** fungal infections (such as thrush)		√	
Rare	**Bowel Inflammation:** severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			√
Very rare	**Allergic Reactions:** wheeziness and tightness of chest, swelling of eyelids, face or lips, or develop skin lumps or hives, or a skin rash (red spots)			√
	Skin Reactions: 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); widespread rash with blisters and skin peeling on much of the body surface, particularly around the mouth, nose, eyes and genitals			√

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

HOW TO STORE IT

Keep your tablets in a safe place where children cannot reach or see them.
Store ratio-CEFUROXIME Tablets at 15ºC to 30ºC.

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:

Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com ; or
Fax: 1-416-335-4472

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9
www.tevacanada.com

Last revised: September 19, 2017