Revised: May 2007 (12th version)

Standard Commodity Classification No. of Japan
876132

- Cephem antibiotic product for oral use -

TOMIRON® Tablets 50
TOMIRON® Tablets 100

< Cefteram pivoxil tablets >

Designated drug / Prescription drug[note)]

Storage
Store in a dry location at room temperature. Furthermore, caution should be exercised in storing the product after the aluminum pillow package is opened because exposure to light can lead to gradual loss of color.

Expiration date
Do not use after the expiration date indicated on the package.

	50 mg	100 mg
Approval No.	(62EM)1864	(62EM)1865
Date of listing in the NHI reimbursement price	August 1987	
Date of initial marketing in Japan	August 1987	
Date of latest reexamination	December 1994	
Date of latest reevaluation	September 2004	
Date of latest approval of indications	September 1991	

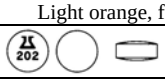
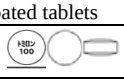
CONTRAINDICATIONS (TOMIRON® is contraindicated in the following patients.)

Patients with a history of shock due to any of the ingredients of the product

RELATIVE CONTRAINDICATIONS (As a general rule, TOMIRON® is contraindicated in the following patients. If the use of TOMIRON® is considered essential, it should be administered with care.)

Patients with a history of hypersensitivity to any of the ingredients of the product or other cephem antibiotics

DESCRIPTION

Brand name	TOMIRON® Tablets 50	TOMIRON® Tablets 100
Active ingredient	Cefteram pivoxil (JP)	
Content (per tablet)	50 mg (Potency)	100 mg (Potency)
Inactive ingredient	Lactose hydrate, Corn starch, Crystalline cellulose, Carmellose calcium, Hydroxypropyl cellulose, Magnesium stearate, Hypromellse, Polyoxyethylene (105) polyoxypropylene (5) glycol, Titanium oxide, Carnauba wax, FD&C Yellow No. 6 (Sunset Yellow FCF)	
Color/dosage form	Light orange, film-coated tablets	
Appearance		
Size (mm)	Diameter: 6.6, Thickness: 3.1	Diameter: 8.6, Thickness: 3.8
Identification code (PTP)		—

INDICATIONS

<Indicated bacteria>

Cefteram-susceptible bacteria; *Streptococcus* sp., *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Haemophilus influenzae*, and *Peptostreptococcus* sp.

<Indications>

- Pharyngitis/laryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, and secondary infections in chronic respiratory lesion
- Cystitis, pyelonephritis and urethritis
- Bartholinitis, intrauterine infection and uterine adnexitis
- Otitis media and sinusitis
- Periodontitis, pericoronitis and gnathitis

DOSAGE AND ADMINISTRATION

For pharyngitis/laryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, cystitis, pyelonephritis, bartholinitis, intrauterine infection and uterine adnexitis: The usual adult dosage for oral use is 150 – 300 mg (potency) of cefteram pivoxil daily in 3 divided doses after meals.

For pneumonia, secondary infections in chronic respiratory lesion, urethritis, otitis media, sinusitis, periodontitis, pericoronitis and gnathitis: The usual adult dosage for oral use is 300 – 600 mg (potency) of cefteram pivoxil daily in 3 divided doses after meals.

The dosage may be adjusted according to the patient's age and condition.

note) Prescription drug: Caution -- Use only as directed by a physician.

<Precautions>

1. The drug must be used with care, and the dose or dosing interval should be adjusted in **patients with severe renal dysfunction**. [See ″PHARMACOKINETICS″ section.]
2. As a general rule, the duration of administration of the drug should be limited to the minimum period required for the treatment of the patient's condition, after susceptibility of the microorganism to the drug has been confirmed, in order to prevent the emergence of drug-resistant microorganisms.

PRECAUTIONS

1. Careful Administration (TOMIRON® should be administered with care in the following patients.)

(1) Patients with a history of hypersensitivity to penicillin antibiotics
[Patients should be interviewed carefully because shock may develop.]

(2) Patients who or whose parents or siblings have a predisposition to develop allergic reactions such as bronchial asthma, rash and urticaria.
[The patient with allergic predisposition should be carefully interviewed because he/she is more likely to develop hypersensitivity.]

(3) Patients with severe renal dysfunction
[Persistently elevated blood concentrations may develop. (See ″PHARMACOKINETICS″ section.)]

(4) Patients with poor oral food intake or who are receiving parenteral alimentation, and patients in poor general health.
[Patients who are unable to take vitamin K through food should be observed carefully because vitamin K deficiency may develop. (See ″(3) Other adverse reactions″ in ″3. Adverse Reactions″ section.)]

(5) Elderly patients
(See ″4. Use in the Elderly″ section.)

2. Important Precautions

The patients should be carefully interviewed because **shock** may develop.

3. Adverse Reactions

Adverse reactions (including abnormal laboratory data) to the drug were reported in 213 (6.57%) of 3,240 patients who had been observed at time of approval. And they were reported in 104 (0.77%) of 13,463 patients who had been observed during the 6 years after approval (June 1987 to June 1993).

Adverse reactions to the drug were reported in 317 (1.90%) of 16,703 patients at completion of reexamination. A total of 456 cases of adverse reactions were reported. The major adverse reactions were diarrhoea in 54 cases (0.32%), rash in 24 cases (0.14%), anorexia in 19 cases (0.11%), stomach discomfort in 19 cases (0.11%), increased ALT (GPT) in 81 cases (0.48%), increased AST (GOT) in 70 cases (0.42%), and eosinophilia in 29 cases (0.17%).

Adverse reactions with unknown incidence developed after approval are also included in the data presented in this section.

(1) Clinically significant adverse reactions

1) **Shock and anaphylactoid reactions (including dyspnoea, etc.)** (incidence unknown) may develop. The patients should be carefully monitored. If any signs of shock or anaphylactoid reactions are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

2) **Toxic epidermal necrolysis (Lyell syndrome) and Mucocutaneous ocular syndrome (Stevens-Johnson syndrome)** (incidence unknown) may develop. The patients should be carefully monitored. If any signs of these syndromes are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

3) **Serious nephropathy such as acute renal failure** (incidence unknown) may develop. The patients should be carefully monitored, and periodic renal function tests should be performed. If any abnormal findings are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

4) **Serious colitis with bloody stool such as pseudomembranous colitis** (incidence unknown) may develop. If abdominal pain or frequent diarrhoea is observed, appropriate therapeutic measures, such as immediate discontinuing administration, should be taken.

5) **Hepatic function disorder and jaundice** (incidence unknown) may develop. The patients should be carefully monitored. If any abnormal findings are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

6) **Agranulocytosis and thrombocytopenia** (incidence unknown) may develop. The patients should be carefully monitored. If any abnormal findings are observed, administration should be discontinued and appropriate therapeutic measures should be taken.

(2) Clinically significant adverse reactions (similar drugs)

1) **Hemolytic anemia** has been reported in patients treated with other cephem antibiotics (cefalotin sodium, cefaloridine, etc.). If any abnormal findings are observed, appropriate therapeutic measures, such as discontinuing administration, should be taken.

2) **Interstitial pneumonia and PIE syndrome with fever, cough, dyspnea, chest X-ray abnormalities, and eosinophilia** have been reported in patients treated with other cephem antibiotics. If such symptoms are observed, administration should be discontinued and appropriate therapeutic measures, such as administration of adrenocortical hormones, should be taken.

(3) Other adverse reactions

If the following adverse reactions are observed, appropriate therapeutic measures should be taken according to the patient′s condition.

Type	2 % > ≥ 0.1% or incidence unknown	< 0.1%
Hypersensitivity	Rash, erythema[note)], arthralgia[note)]	Urticaria, pruritus, fever, edema, swollen lymph nodes
Hematologic	Eosinophilia	Granulocytopenia, thrombocytopenia
Hepatic	Increased AST(GOT), increased ALT(GPT), jaundice[note)]	Increased Al-P, increased LDH
Gastrointestinal	Diarrhoea/loose stools, nausea/vomiting, anorexia, stomach discomfort	Feeling of enlarged abdomen, heartburn, abdominal pain, epigastric pain
Microbial substitution	Candidiasis[note)]	Stomatitis
Vitamin deficiency	Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.)[note)], vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)[note)]	-
Others	Increased CK (CPK)[note)] , decreased serum carnitine [note)]	Headache, dizziness, generalized fatigability

note) : incidence unknown (At completion of reexamination)

4. Use in the Elderly

Special attention should be paid to the following points when the drug is used in elderly patients. The drug should be used with caution and the dose and dosing interval must be adjusted based on careful clinical observation of the patient's condition.

(1) Elderly patients often have reduced physiological function, which may increase the risk of adverse reactions.

(2) In elderly patients, use of the drug may be associated with the development of a bleeding tendency due to vitamin K deficiency.

5. Use during Pregnancy, Delivery or Lactation

The safety of the drug in pregnant women has not been established. Therefore, the drug should be used in pregnant women and women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

6. Pediatric Use

(1)The safety of this drug in low birth weight infants, neonates, nursing infants and infants has not been established.

(2)The occurrence of hypoglycemia accompanying hypocarnitinemia has been reported due to long-term administration of antibiotics (pediatric preparations) having a pivoxyl group in infants [see "9. Other Precautions" section].

7. Effects on Laboratory Tests

(1) False-positive results may develop in urine glucose tests using reduction such as those with Clinitest and Benedict′s solution, etc., but not with Tes-Tape.

(2) Positive results may develop in the direct Coombs′ test. Therefore, caution is required.

8. Precautions concerning Use

Precaution regarding dispensing: Patients who are given the product supplied in a press-through package (PTP) must be instructed to remove the drug from the package before taking it. (It has been reported that, if the PTP is swallowed, the sharp edges of the package may perforate the esophagus, resulting in serious complications, such as mediastinitis.)

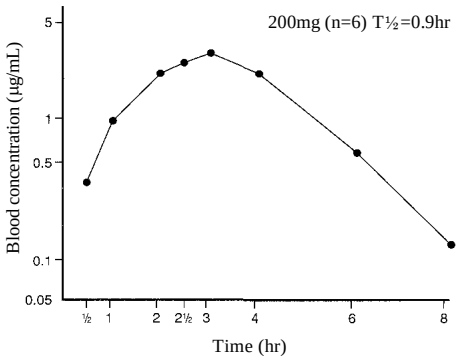
9. Other Precautions

Decreased serum carnitine levels have been reported accompanying metabolism and excretion of pivalic acid (metabolite of antibiotics having a pivoxyl group) due to administration of antibiotics having a pivoxyl group, including TOMIRON® (cefteram pivoxil, cefditoren pivoxil, cefcapene pivoxil hydrochloride hydrate). In addition, since the occurrence of hypoglycemia accompanying hypocarnitinemia has been reported due to single-agent doses or alternating long-term administration of antibiotics (pediatric preparations) having a pivoxyl group in infants, patients should be carefully monitored for decreases in serum carnitine levels during administration of antibiotics having a pivoxyl group.

PHARMACOKINETICS

1. Blood concentration

When 200 mg of TOMIRON® was orally administered to healthy adults after meals, high blood concentrations of cefteram, the metabolite with antibacterial activity, were seen. The peak concentration of 2.9 μg/mL was seen 3 hours after the medication was taken, and the half-life was 0.9 hours [2)].



2. Transfer to tissues

Good transfer to sputum [3], aural discharge [4], tonsils [5], maxillary sinus mucosa [6], nasal polyps [6], ethmoidal sinus mucosa [6], urethral discharge [7], and tooth extraction wounds [8] was seen. Transfer to the tissues of the uterus was also seen, but there was almost no transfer to milk [9),10)].

3. Metabolism/excretion

When it is absorbed, TOMIRON® is metabolized by esterases in the intestinal mucosa to form cefteram, the metabolite with antibacterial activity, and pivalic acid [11)]. Pivalic acid is conjugated with carnitine and excreted in the urine as pivaloylcarnitine. Some cefteram is excreted in bile while still active, but most cefteram is excreted in urine[11)]. When 200 mg of TOMIRON® was orally administered to healthy adults after meals, the urinary excretion rates 8 hours after administration was 32.8%[2)].

4. Blood concentration in patients with renal impairment

Prolongation of the blood half-life was observed in patients with renal impairment who were treated with single 100 mg doses of TOMIRON® after meals; as shown in the table below, the blood half-life increased with decreasing renal function [12)].

Severity of renal impairment (Ccr: mL/min)	Blood Half-life (hr)
Healthy (Ccr ≥ 100)	0.83
Mild (70 ≥ Ccr ≥ 40)	1.46
Moderate (30 ≥ Ccr ≥ 20)	4.36

CLINICAL STUDIES

The open clinical studies of TOMIRON® were conducted in a total of 2,243 patients at medical institutions in Japan to investigate efficacy. The results of the studies are summarized in the table below.

In addition, the usefulness of TOMIRON® was confirmed in double-blind comparative studies in patients with respiratory infections [13),14),15)], urinary tract infections [16)], gynecological infections [17)], otitis media [18)], and dental and oral surgical infections [19)].

The daily dosage in most cases was 150 – 600 mg.

Type of infection	Disease	Efficacy (%)
Respiratory infections	Pharyngitis or laryngitis	88.5 (23/ 26)
	Tonsillitis (including peritonsillitis and peritonsillar abscess)	93.9 (93/ 99)
	Acute bronchitis	85.3 (99/116)
	Pneumonia	85.6 (131/153)
	Secondary infections in chronic respiratory lesion	72.9 (258/354)
Urinary tract infections	Cystitis	79.5 (582/732)
	Pyelonephritis	74.3 (107/144)
	Urethritis	90.4 (122/135)
Gynecological infections	Bartholinitis	96.0 (24/ 25)
	Intrauterine infection	90.5 (57/ 63)
	Uterine adnexitis	84.6 (11/ 13)
Otorhinological infections	Otitis media	60.4 (81/134)
	Sinusitis	79.2 (38/ 48)
Dental and oral surgical infections	Periodontitis	90.2 (46/ 51)
	Pericoronitis	91.1 (51/ 56)
	Gnathitis	85.1 (80/ 94)

PHARMACOLOGY

1. Antibacterial activity

(1) Cefteram pivoxil is metabolized to cefteram in the body. Cefteram has antibacterial activity.

(2) Cefteram possesses a broad antibacterial spectrum against Gram-positive/negative organisms. Cefteram showed high activity against the Gram-positive organisms *Streptococcus* sp. and *Streptococcus pneumoniae*; and against the Gram-negative organisms *Neisseria gonorrhoeae*, *Escherichia coli*, *Klebsiella* sp., and *Haemophilus influenzae*; and the anaerobic *Peptostreptococcus* sp [20),21),22),23)].

Cefteram also showed excellent antibacterial activity against *Citrobacter* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, and *Providencia* sp., which have low sensitivity to conventional oral cephem antibiotics(cefalexin, cefaclor, etc.). Cefteram's action was bactericidal against these organisms [20),21),22)].

(3) Cefteram was stable against β-lactamase produced by different bacteria, and showed high antibacterial activity against β-lactamase-producing strains [20),21),22)].

2. Mechanism of action

The mechanism of action of cefteram is inhibition of bacterial cell wall synthesis. Cefteram exerts its bactericidal activity by strongly binding to penicillin-binding protein (PBP) 3, 1A, and 1Bs [20)].

3. Therapeutic effect in experimental infections

Cefteram had an excellent therapeutic effect in experimental infections in rats and mice caused by organisms such as *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Proteus vulgaris*. Furthermore, the therapeutic effect of cefteram in infections with β-lactamase-producing strains was superior to the effects of cefalexin and cefaclor [20),21),22)].

PHYSICOCHEMISTRY

Nonproprietary name:

Cefteram pivoxil (JAN), cefteram (INN)

Abbreviation: CFTM-PI

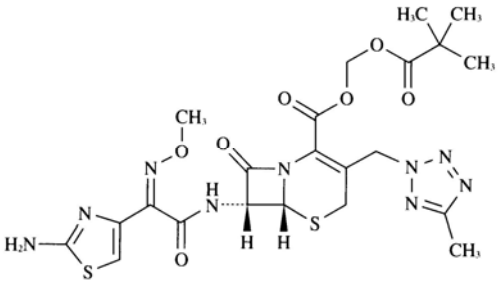
Chemical name:

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino) acetylamino]-3-(5-methyl-2*H*-tetrazol-2-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

Molecular formula: $C_{22}H_{27}N_9O_7S_2$

Molecular weight: 593.64

Structural formula:



Description:

Cefteram pivoxil occurs as a white to pale yellowish white powder. It is very soluble in acetonitrile; freely soluble in methanol, ethanol (95) and chloroform; and practically insoluble in water.

Melting point:

Cefteram pivoxil reaches a half-melted state at approximately 110°C. Subsequently, it gradually becomes colored and undergoes effervescent breakdown. An unambiguous melting point is not seen.

PACKAGING

TOMIRON® Tablets 50:

100 tablets in press-through packages
500 tablets in press-through packages

TOMIRON® Tablets 100:

100 tablets in press-through packages
500 tablets in press-through packages

REFERENCES

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23) Sawa K. et al.: Chemotherapy, **34**(S-2), 34 – 43, 1986.

REQUEST FOR LITERATURE SHOULD BE MADE TO:

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