Revised: June 2005 (10th version, Revisions associated with the amendment of the Pharmaceutical Affairs Law)

Standard Commodity Classification No. of Japan
876132

- Cephem antibiotic product for oral use -

TOMIRON® Fine granules 100 for pediatric

< Cefteram pivoxil granules >

Designated drug/prescription drug[note)]

Storage
Store in a dry location at room temperature. [See ″PRECAUTIONS FOR HANDLING″ section]

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

Approval No.	(02EM)0110
Date of listing in the NHI reimbursement price	Aug 1990
Date of initial marketing in Japan	Sep 1990
Date of latest reexamination	Dec 1996
Date of latest reevaluation	Sep 2004

CONTRAINDICATIONS (TOMIRON® is contraindicated in the following patients.)
Patients with a history of shock following exposure to any of the ingredients in 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 in the product or other cephem antibiotics.

DESCRIPTION

Brand name	TOMIRON® Fine granules 100 for pediatric	
Active ingredient	Cefteram pivoxil (JP)	
Content (per 1 g)	100 mg (Potency)	
Inactive ingredient	Refined sugar, Sucrose esters of fatty acids, Carmellose calcium, Crystalline cellulose/ Carmellose sodium, Aspartame (L-phenylalanine compound), Polydimethylsiloxane, Sorbitan fatty acid esters, Fatty acid esters of glycerol, Carmellose sodium, flavor, FD&C Yellow No. 6 (Sunset Yellow FCF)	
Color/dosage form	Light orange fine granules with a smell and sweet flavor	
Identification code (packets)	0.25g × 240 packets	0.5g × 240 packets
	大204	大205

• The drug may be seen as white granules on rare occasions because of unbalanced coloring.

INDICATIONS

<Indicated bacteria>
Cefteram -susceptible bacteria; *Streptococcus* spp., *Streptococcus pneumoniae*, Escherichia *coli*, *Klebsiella* spp., *Proteus* spp., *Morganella morganii*, *Providencia* spp. and *Haemophilus influenzae*

<Indications>

- Pharyngitis or laryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis and pneumonia
- Cystitis and pyelonephritis
- Otitis media and sinusitis
- Scarlet fever

DOSAGE AND ADMINISTRATION

For oral use, the usual pediatric dosage is 9 – 18 mg (potency) of cefteram pivoxil per kg daily in 3 divided doses.
The dosage may be adjusted according to the patient's age and symptoms.

<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.]

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

(2) Patients who or whose parents or siblings have a predisposition to develop allergic reactions such as bronchial asthema, 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 51 (7.20%) of 708 patients who had been observed at time of approval. And they were reported in 71 (1.29%) of 5,510 patients who had been observed during the 4 years after approval (June 1990 to June 1994).

Adverse reactions to the drug were reported in 122 (1.96%) of 6,218 patients at completion of reexamination. A total of 144 cases of adverse reactions were reported. The major adverse reactions were diarrhoea in 72 cases (1.16%), eosinophilia in 13 cases (0.21%), increased AST (GOT) in 13 cases (0.21%) and increased ALT (GPT) in 11 cases (0.18%).

For TOMIRON® tablet, which contain the same active ingredient as TOMIRON® fine granules 100 for pediatric, adverse reactions (including abnormal laboratory data) were reported in 317 (1.90%) of 16,703 patients at completion of reexamination. A total of 456 cases of adverse reactions were reported.

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 Muco-cutaneo-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, arthralgia[note1)]	Urticaria[note2)], erythema, pruritus, fever[note2)], edema, swollen lymph nodes[note2)]
Hematologic	Eosinophilia	Granulocytopenia, thrombocytopenia
Hepatic	Increased AST(GOT), increased ALT(GPT), Jaundice[note1)]	Increased Al-P, increased LDH

Type	2% > ≥ 0.1% or incidence unknown	< 0.1%
Gastrointestinal	Diarrhoea/ loose stools, stomach discomfort[note2)], anorexia[note2)]	Nausea/ vomiting, feeling of enlarged abdomen[note2)], heartburn[note2)], abdominal pain, epigastric pain[note2)]
Microbial substitution	-	Stomatitis[note2)], candidiasis
Vitamin deficiency	Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.)[note1)], vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)[note1)]	-
Others	increased CK(CPK)[note1)]	Headache[note2)], Dizziness[note2)], generalized fatigability[note2)]

(At completion of reexamination)

note1) : incidence unknown

note2) : The incidence with TOMIRON® fine granules 100 for pediatric was unknown, therefore, the one with TOMIRON® tablet, which has the same active ingredient, was used.

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.

The drug is intended for pediatric use.

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.

The drug is intended for pediatric use.

6. Pediatric Use

The safety of this drug in low birth weight infants and neonates has not been established.

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.

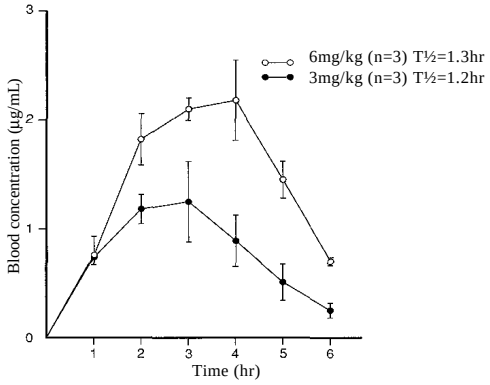
8. Other Precautions

The drug has been reported to decrease serum carnitine [1)]. Therefore, it is recommended that the drug not be used in children for periods longer than 2 weeks.

PHARMACOKINETICS

1. Blood concentration

When 3 mg and 6 mg per kg of TOMIRON® were orally administered to children after meals, mean peak blood concentrations of cefteram, the metabolite with antibacterial activity, were seen 3 to 4 hours after the medication was taken, and those peak concentrations were, respectively, 1.3 μg/mL and 2.2 μg/mL. The half-life was 1.2 to 1.3 hours [2)].



2. Transfer to tissues (data for TOMIRON® tablet in adults)

Good transfer to sputum [3)], tonsils [4)], aural discharge [5)], maxillary sinus mucosa [6)], nasal polyps [6)], and ethmoidal sinus mucosa [6)] was seen.

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 [7)].

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 [7)]. When 3 mg and 6 mg per kg of TOMIRON® were orally administered to children after meals, mean peak urine concentrations of cefteram were seen 2 to 4 hours after the medication was administered, and those peak concentrations were, respectively, 83 μg/mL and 156 μg/mL. The mean urinary recovery rate 8 hours after administration was 16% to 20% [2)].

4. Blood concentration in patients with renal impairment (data for TOMIRON® tablet in adults)

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 ta-

ble below, the blood half-life increased with decreasing renal function [8].

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 648 patients at medical institutions in Japan to investigate efficacy. The results of the studies are summarized in the table below.

Type of infection	Disease	Efficacy (%)
Respiratory infections	Pharyngitis or laryngitis,	97.0 (96/ 99)
	Tonsillitis (including peritonsillitis and peritonsillar abscess)	98.2 (164/167)
	Acute bronchitis	93.8 (60/ 64)
	Pneumonia	94.9 (93/ 98)
Urinary tract infections	Cystitis, pyelonephritis,	95.0 (76/ 80)
Otorhinological infections	Otitis media	90.9 (50/ 55)
	Sinusitis	100 (3/ 3)
Scarlet fever		98.8 (81/ 82)

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* spp. and *Streptococcus pneumoniae*, and against the Gram-negative organisms *Escherichia coli*, *Klebsiella* spp. and *Haemophilus influenzae*. Cefteram also showed excellent antibacterial activity against *Proteus* spp., *Morganella morganii*, *Providencia* spp., which have low sensitivity to conventional oral cephem antibiotics (cefalexin, cefaclor, etc.). Cefteram's action was bactericidal against these organisms [9),10),11)].

(3) Cefteram was stable against β-lactamase produced by different bacteria, and showed high antibacterial activity against β-lactamase-producing strains [9),10),11)].

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 [9)].

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 [9),10),11)].

PHYSICOCHEMISTRY

Nonproprietary name: Cefteram pivoxil (JAN), cefteram (INN)

Abbreviation: CFTM-PI

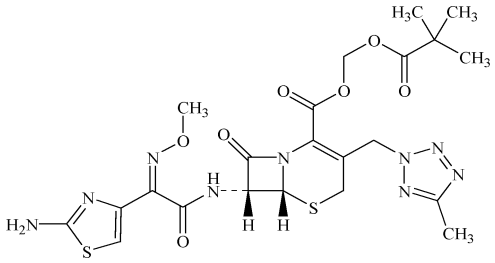
Chemical name:

2,2-Dimethylpropanoyloxymethyl (6*R*,7*R*)-7-[(Z)-2-(2-aminothizol-4-yl)-2-methoxyiminoacetylamino]-3-(5-methyl-2*H*-tetrzol-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 has a bitter taste. 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.

PRECAUTIONS FOR HANDLING

The drug easily absorbs vapor in air. So, put the stopper on the bottle not to moisten the drug. (Breakdown of the active ingredient may cause specific order)

Use packets as fast as possible after opening the aluminum pillow package.

In case of long preservation, store in a dry location.

PACKAGING

TOMIRON® fine granules 100 for pediatric:

100 g (0.25 g × 240 packets)
(0.5 g × 240 packets)

REFERENCES

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11) Nishino T. et al.: Chemotherapy, **34**(S-2), 44 – 60, 1986.

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