CONTRAINDICATIONS (TOMIRON® is contraindi-
cated 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

<table>
<thead>
<tr>
<th>Brand name</th>
<th>TOMIRON® Fine granules 100 for pediatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient</td>
<td>Cefteram pivoxil (JP)</td>
</tr>
<tr>
<td>Content (per 1 g)</td>
<td>100 mg (Potency)</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>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&amp;C Yellow No. 6 (Sunset Yellow FCF)</td>
</tr>
<tr>
<td>Color/dosage form</td>
<td>Light orange fine granules with a smell and sweet flavor</td>
</tr>
<tr>
<td>Identification code (packets)</td>
<td>0.25g × 240 packets 0.5g × 240 packets</td>
</tr>
</tbody>
</table>

- 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.

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. 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%) 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-cutaneous-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.

2) 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.

3) 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.

4) Hemolytic anemia (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.

5) 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 cephalosporin (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 cephalosporin 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.

<table>
<thead>
<tr>
<th>Type</th>
<th>2% ≥ 0.1% or incidence unknown</th>
<th>&lt; 0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash, arthralgia (incidence unknown)</td>
<td>Urticaria (incidence unknown), urthema, pruritus, fever, edema, swollen lymph nodes</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Eosinophilia</td>
<td>Granulocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased AST(GOT), AL-P, LDH</td>
<td>Increased Al-P, LDH</td>
</tr>
<tr>
<td>Jaundice (incidence unknown)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>2% &gt; ≥ 0.1% or incidence unknown</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhoea/ loose stools, stomach discomfort&lt;sup&gt;2)&lt;/sup&gt;, anorexia&lt;sup&gt;2)&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Nausea/ vomiting, feeling of enlarged abdomen&lt;sup&gt;1)&lt;/sup&gt;, heartburn&lt;sup&gt;1)&lt;/sup&gt;, abdominal pain, epigastric pain&lt;sup&gt;1)&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Microbial substitution</td>
<td>-</td>
<td>Stomatitis&lt;sup&gt;1)&lt;/sup&gt;, candidiasis</td>
</tr>
<tr>
<td>Vitamin deficiency</td>
<td>Vitamin K deficiency symptoms (&lt;hypoprothrombinemia, bleeding tendency, etc.&gt;)&lt;sup&gt;1)&lt;/sup&gt;, vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>increased CK/CPK&lt;sup&gt;1)&lt;/sup&gt;</td>
<td>Headache&lt;sup&gt;1)&lt;/sup&gt;, Dizziness&lt;sup&gt;1)&lt;/sup&gt;, generalized fatigability&lt;sup&gt;1)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(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<sup>1)</sup>. 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.<sup>2)</sup>

2. Transfer to tissues (data for TOMIRON® tablet in adults)
Good transfer to sputum<sup>3)</sup>, tonsils<sup>4)</sup>, aural discharge<sup>5)</sup>, maxillary sinus mucosa<sup>6)</sup>, nasal polyps<sup>6)</sup>, and ethmoidal sinus mucosa<sup>6)</sup> 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<sup>7)</sup>. 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<sup>7)</sup>. 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%.<sup>2)</sup>

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).

<table>
<thead>
<tr>
<th>Severity of renal impairment (Ccr: mL/min)</th>
<th>Blood Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy (Ccr ≥ 100)</td>
<td>0.83</td>
</tr>
<tr>
<td>Mild (70 ≥ Ccr ≥ 40)</td>
<td>1.46</td>
</tr>
<tr>
<td>Moderate (30 ≥ Ccr ≥ 20)</td>
<td>4.36</td>
</tr>
</tbody>
</table>

**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.

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

**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 cephal 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 1Bα 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 (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetylamino]-3-(5-methyl-2H-tetrazol-2-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
Molecular formula: C₂₂H₂₇N₉O₇S₂
Molecular weight: 593.64
Structural formula:

![Structural formula image]

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**


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Customer Service Section,
Taisho Toyama Pharmaceutical Co., Ltd.
3-25-1 Takada, Toshima-ku, Tokyo 170-8635, Japan
Tel: 81-3-3985-5599

Distributed by:
Taisho Toyama Pharmaceutical Co., Ltd.
3-25-1 Takada, Toshima-ku, Tokyo 170-8635, Japan

Manufactured and Distributed by:
Toyama Chemical Co., Ltd.
3-2-5 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan