- Oral cepham antibiotic -

**MEIACT MS®** Fine Granules


**STORAGE**
This product should be stored at room temperature protected from light.
(See “PRECAUTIONS FOR HANDLING” section.)

**Approval No.**
21600AMZ00136000

**Date of listing in the NHI reimbursement price**
July 2004

**Date of initial marketing in Japan**
August 2004

**Date of latest reevaluation**
September 2004

---

**CONTRAINDICATIONS** (MEIACT MS 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, MEIACT MS is contraindicated in the following patients. If the use of MEIACT MS 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 cepham antibiotics

**DESCRIPTION**

1. **Composition**
Each gram of MEIACT MS Fine Granules contains the following ingredients.

<table>
<thead>
<tr>
<th>Active ingredient</th>
<th>Cefditoren pivoxil</th>
<th>100 mg (potency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxypropylmethylcellulose 2910, hydroxypropylcellulose, croscarmellose sodium, sucrose, aspartame (L-phenylalanine compound), sodium chloride, Yellow No. 5 (FD&amp;C Yellow No. 6 [Sunset Yellow FCF]) and one other ingredient</td>
<td>Hydroxypropylmethylcellulose 2910, hydroxypropylcellulose, croscarmellose sodium, sucrose, aspartame (L-phenylalanine compound), sodium chloride, Yellow No. 5 (FD&amp;C Yellow No. 6 [Sunset Yellow FCF]) and one other ingredient</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactive ingredient</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavoring, dextrin, acacia, propylene glycol, vanillin, ethylvanillin</td>
<td>Flavoring, dextrin, acacia, propylene glycol, vanillin, ethylvanillin</td>
</tr>
</tbody>
</table>

2. **Product Description**

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Color</th>
<th>Taste</th>
<th>Odor</th>
<th>ID cord on sachet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine granules</td>
<td>Orange</td>
<td>Sweet and slightly bitter</td>
<td>Aromatic</td>
<td>M-23</td>
</tr>
</tbody>
</table>

This product has been verified to be bioequivalent to MEIACT Fine Granules (hereinafter “MF Granules”) which has been verified to be bioequivalent to MEIACT Granules (hereinafter “M Granules”).

**INDICATIONS**

*<Indicated bacteria>*
Cefditoren-susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, *Escherichia coli*, *Citrobacter* sp., *Klebsiella* sp., *Enterobacter* sp., *Serratia* sp., *Proteus* sp., *Morganella morganii*, *Providencia* sp., *Haemophilus influenzae*, *Bordetella pertussis*, *Peptostreptococcus* sp., *Bacteroides* sp., *Prevotella* sp. and *Propionibacterium acnes*

*<Indications>*
Superficial skin infections, deep skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infections in traumas, burns or surgical wounds, etc., perianal abscess, pharyngitis/laryngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, lung abscess, secondary infections in chronic respiratory lesion, cystitis, pyelonephritis, otitis media, sinusitis, periodontal tissue inflammation, gnathitis, scarlet fever, pertussis

**DOSAGE AND ADMINISTRATION**
For children, cefditoren pivoxil is usually administered in a single oral dose of 3 mg (potency)/kg 3 times a day, after meals.

The dosage may be adjusted according to the patient’s age and symptoms.

**Precautions**

(1) As a general rule, the duration of administration of this 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.
2. Important Precautions

(1) Since shock may occur, patients should be carefully interviewed.

(2) It has been reported that administration of antibiotics which have a pivoxil group (including this product, cefcapene pivoxil hydrochloride and cefteram pivoxil) cause serum carnitine decrease resulting from the metabolism/excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group)\(^1\).

In infants, it has been reported that long-term single or alternate administration of antibiotics with a pivoxil group causes hypoglycemia accompanying hypocalcemia and hypocalcemia. When an antibiotic with a pivoxil group is administered, patients should be carefully monitored, paying particular attention to carnitine decrease. (See “Adverse Reactions” section.)

3. Adverse Reactions

This product has been verified to be bioequivalent to MF Granules which has been verified to be bioequivalent to M Granules.

Data for MF Granules at the time of approval

In post-marketing drug-use results surveys for MF Granules and M Granules, a total of 5,821 clinical cases was reported from 875 medical institutions nationwide. Adverse reactions occurred in 136 (2.34%) patients with 146 episodes. The main adverse reactions were gastrointestinal system disorders (diarrhea, loose stool, etc.) in 121 (2.08%) patients and skin and appendages disorders (rash, urticaria) in 10 (0.17%) patients.

(1) Clinically significant adverse reactions

1) Shock or anaphylactoid reaction (<0.1%) may occur. Patients should be carefully monitored if any abnormalities such as feeling unwell, oral cavity discomfort, stridor, vertigo, defecation desire, tinnitus or diaphoresis are observed, administration should be discontinued and appropriate measures should be taken.

2) Serious colitis with bloody stool such as pseudomembranous colitis (<0.1%) may occur. Patients should be carefully monitored and if abdominal pain or frequent diarrhea occurs, administration should be discontinued immediately and appropriate measures should be taken.

3) Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome) or toxic epidermal necrolysis (Lyell syndrome) (<0.1%) may occur. Patients should be carefully monitored and if any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

4) Interstitial pneumonia, PIE syndrome (<0.1%), etc., with fever, cough, dyspnea, abnormal chest X-ray, eosinophilia, etc., may occur. Patients should be carefully monitored, and periodic laboratory tests should be performed. If any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

5) Hepatic function disorder (<0.1%) with jaundice or markedly increased AST (GOT), ALT (GPT) or Al-P may occur. Patients should be carefully monitored, and periodic laboratory tests should be performed. If any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

6) Serious renal disorder such as acute renal failure (<0.1%) may occur. Patients should be carefully monitored, and periodic laboratory tests should be performed. If any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

7) Agranulocytosis (<0.1%) or hemorrhagic anemia (<0.1%) may occur. Patients should be carefully monitored, and periodic laboratory tests should be performed. If any abnormality is observed, administration should be discontinued and appropriate measures should be taken.

8) It has been reported that long-term administration of an antibiotic which has a pivoxil group causes hypoglycemia.
glycemia accompanying hypocarnitinemia (incidence unknown) in infants. When symptoms of hypoglycemia such as convulsions or consciousness disorder are observed, administration should be discontinued and appropriate measures should be taken. (See “Important Precautions” section.)

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Note 1</th>
<th>5% &gt; 0.1%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity Note 2</td>
<td>Rash</td>
<td>Urticaria, erythema, pruritus, fever, lymph node swelling, arthralgia</td>
</tr>
<tr>
<td>Hematologic Note 3</td>
<td>Eosinophilia</td>
<td>Granulocytopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Hepatic Note 3</td>
<td>AST (GOT) increased, ALT (GPT) increased</td>
<td>Jaundice, Al-P increased</td>
</tr>
<tr>
<td>Renal</td>
<td>BUN increased, serum creatinine increased, proteinuria</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, loose stool, nausea, stomach discomfort, abdominal pain</td>
<td>Feeling of enlarged abdomen, nausea, vomiting</td>
</tr>
<tr>
<td>Microbial substitution</td>
<td>Stomatitis, candidiasis</td>
<td></td>
</tr>
<tr>
<td>Avitaminosis</td>
<td>Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.), vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Headache, dizziness, edema, numbness</td>
<td></td>
</tr>
</tbody>
</table>

Abnormal laboratory test values [AST(GOT) increased, ALT(GPT) increased, eosinophilia, etc.] tend to appear more frequently in patients under long-term treatment.

Note

1) Each adverse reaction is tabulated by the incidence obtained from data available at the time of approval and at the end of reexamination (for tablet, M Granules, and MF Granules).
2) If any symptom occurs, administration should be discontinued and appropriate measures should be taken.
3) The patients should be carefully monitored and if any abnormality is observed, appropriate measures such as discontinuation of administration should be taken.
4) These patients should be monitored by performing periodic laboratory tests.

4. Pediatric Use

The safety in low birth weight infants and newborns has not been established.

5. Effects on Laboratory Tests

(1) False-positive results may occur in urine glucose tests with Benedict’s solution, Fehling’s solution, and Clinistix, but not with Tes-Tape. Caution id required.

(2) Positive results may occur in the direct Coombs test. Caution is required.

PHARMACOKINETICS

This product has been verified to be bioequivalent to MF Granules which has been verified to be bioequivalent to M Granules.

Data for M Granules at the time of approval

1. Absorption and distribution

(1) Blood concentration

Fig. 1 and Table 1 show serum concentrations and pharmacokinetic parameters, respectively, of cefditoren obtained after single oral administration of 3 mg/kg or 6 mg/kg to pediatric patients with normal renal function after meals. Dose dependency was observed.

![Fig. 1 Serum concentrations of cefditoren in pediatric patients with normal renal function](image)

Table 1 Pharmacokinetic parameters in pediatric patients with normal renal function

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (μg/mL)</th>
<th>T1/2 (hr)</th>
<th>AUC0→∞ (μg · hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg (n=19)</td>
<td>1.45</td>
<td>2.25</td>
<td>7.16</td>
</tr>
<tr>
<td>6 mg/kg (n=18)</td>
<td>2.85</td>
<td>1.68</td>
<td>11.90</td>
</tr>
</tbody>
</table>

[Reference]

(2) Body fluid and tissue concentrations (In the case of patients given MELACT Tablets 100) 1-7

Transfer to sputum, tonsillar tissue, mucous membrane of maxillary sinus, cutaneous tissue, wound after tooth extraction, etc. was observed.

(3) Protein binding

Binding rate to human serum protein determined by the ultrafiltration method was 91.5% at a concentration of 25 μg/mL (in vitro).

2. Metabolism and excretion

Cefditoren pivoxil is metabolized on absorption and becomes cefditoren which has antibacterial activity, and pivalic acid. Pivalic acid forms a conjugate with carnitine and is excreted into urine as pivaloyl carnitine. Cefditoren is hardly metabolized and is excreted mainly into urine and bile. The urinary excretion rate (0 - 8 hours) of cefditoren on oral administration after meals at doses of 3
and 6 mg/kg to pediatric patients with normal renal function was about 20% and 17%, respectively.

[Reference]

3. Serum concentration and urinary excretion (In the case of patients with renal function disorder given MEIACT Tablets 100)\(^{(13)}\)

The serum concentrations (Fig. 2) and pharmacokinetic parameters (Table 2) of cefditoren are as follows. Oral administration of 200 mg to adult patients with renal function disorder or to those receiving artificial dialysis after meals demonstrated higher levels in all the cases, showing a delay in T\(_{1/2}\) in parallel with the degree of renal function disorder.

![Fig. 2 Serum concentrations of cefditoren in patients with renal function disorder](image)

Table 2 Pharmacokinetic parameters in patients with renal function disorder

<table>
<thead>
<tr>
<th>Patient’s condition [Ccr (mL/min)]</th>
<th>No. of patients</th>
<th>T(_{max}) (hr)</th>
<th>C(_{max}) (μg/mL)</th>
<th>T(_{1/2}) (hr)</th>
<th>AUC(_{0-\infty}) (μg ⋅ hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild [51 – 70]</td>
<td>3</td>
<td>2</td>
<td>2.32</td>
<td>1.13</td>
<td>10.2</td>
</tr>
<tr>
<td>Moderate [30 – 50]</td>
<td>4</td>
<td>4</td>
<td>2.17</td>
<td>2.06</td>
<td>16.4</td>
</tr>
<tr>
<td>Severe [&lt;30]</td>
<td>2</td>
<td>8</td>
<td>3.70</td>
<td>5.68</td>
<td>53.5</td>
</tr>
<tr>
<td>Dialysis patient(^{a})</td>
<td>1</td>
<td>6</td>
<td>4.60</td>
<td>5.37</td>
<td>50.2</td>
</tr>
</tbody>
</table>

* On day without dialysis

Urinary excretion rate lowered in parallel with the degree of renal function disorder, showing a delay in excretion.

CLINICAL STUDIES

This product has been verified to be bioequivalent to MF Granules which has been verified to be bioequivalent to M Granules.

<Clinical results of M Granules at the time of approval>\(^{(2)}\)

1. Infections in the field of dermatology

The efficacy rate was 93.1% (54/58) in patients with superficial skin infection (impetigo contagiosa), deep skin infections (phlegmon, suppurative paronychia (paronychia)), lymphangitis/lymphadenitis [lymphangitis (lymphadenitis)], and chronic pyoderma (subcutaneous abscess).

2. Infections in the field of surgery

The efficacy rate was 100% (1/1) in a patient with perianal abscess.

3. Respiratory tract infections

The efficacy rate was 97.9% (277/283) in patients with pharyngitis/laryngitis [pharyngolaryngitis (throat abscess)], acute bronchitis, tonsillitis (including peritonsillitis and peritonsillar abscess) and pneumonia.

4. Urinary tract infections

The efficacy rate was 94.6% (35/37) in patients with pyelonephritis and cystitis.

5. Scarlet fever

The efficacy rate was 100% (36/36) in patients with scarlet fever.

6. Pertussis

The efficacy rate was 100% (11/11) in patients with pertussis.

7. Infections in the field of otorhinology

The efficacy rate was 100% (18/18) in patients with otitis media and sinusitis.

<Clinical results of MF Granules at the time of approval of additional indications>\(^{(14)}\)

Infections in the fields of dentistry and oral surgery

The efficacy rate was 98.4% (62/63) in patients with periodontal tissue inflammation and gastritis.

PHARMACOLOGY

1. Antibacterial activity\(^{(15-21)}\)

(1) Cefditoren pivoxil is metabolized into cefditoren in absorption in the intestinal wall and shows its antibacterial activity.

(2) Cefditoren exerts broad spectrum antibacterial activity in vitro against gram-positive and gram-negative bacteria. Especially it showed strong antibacterial activity against gram-positive bacteria such as Staphylococcus sp., Streptococcus sp. and Streptococcus pneumoniae, and gram-negative bacteria such as Escherichia coli, Moraxella (Branhamella) catarrhalis, Klebsiella sp., Proteus sp. and Haemophilus influenzae, and against anaerobic bacteria such as Peptostreptococcus sp., Propionibacterium acnes, Bacteroides sp. and Prevotella sp. Cefditoren also showed antibacterial activity against β-lactamase-nonproducing ampicillin resistant Haemophilus influenzae (BLNAR).

(3) In vitro, cefditoren was stable against β-lactamases produced by various bacteria, and showed strong antibacterial activity against β-lactamase-producing strains.

2. Mechanism of action\(^{(15, 17, 19)}\)

Cefditoren inhibits the synthesis of bacterial cell walls. It has high affinity to penicillin binding proteins (PBPs) in various bacteria, showing a bactericidal effect.

3. Therapeutic effect on experimental infections\(^{(16, 17, 19)}\)

Cefditoren pivoxil demonstrated excellent therapeutic effects on experimental infections in mice caused by Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae and Proteus sp. Its therapeutic effect on infections caused by β-lactamase-producing strains was equivalent or superior to similar drugs.

PHYSICOCHEMISTRY

Nonproprietary name: Cefditoren Pivoxil

Chemical name:

2, 2-Dimethylpropanoyloxyethyl (6R, 7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)
acetylamino]-3-[(1Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

Abbreviation: CDTR-PI
Molecular formula: C$_{25}$H$_{28}$N$_{6}$O$_{7}$S$_{3}$
Molecular weight: 620.72

Description:
Cefditoren Pivoxil occurs as a light yellowish white to light yellow crystalline powder.
It is sparingly soluble in methanol, slightly soluble in acetonitrile and in ethanol (95), very slightly soluble in diethyl ether and practically insoluble in water.
It dissolves in dilute hydrochloric acid.
Melting point: 196-201°C (decomposition)

Partition coefficient:
<table>
<thead>
<tr>
<th>pH</th>
<th>Partition coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>0.92</td>
</tr>
<tr>
<td>4.0-6.0</td>
<td>&gt;3.0</td>
</tr>
</tbody>
</table>

PRECAUTIONS FOR HANDLING
Bottled preparations should be kept tightly sealed to keep contents dry. Sachets prepared from bottled preparations should be protected from light and moisture.
Furthermore, instructions should be given to keep divided preparations (prepackaged) dry and to only open them immediately before use.

PACKAGING
100 mg (potency)/g:
Bottles of 100 g each
240 sachets of 0.3 g each (20 sheets, each with 3 sachets, in one bag; 4 bags)
120 sachets of 0.5 g each (20 sheets, each with 3 sachets, in one bag; 2 bags)

REFERENCES
7) Sasaki J. et al.: Chemotherapy, 40(S-2), 664, 1992