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 to other cepham antibiotics

DESCRIPTION
1. Composition
Each tablet of MEIACT MS Tablets 100mg 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>Inactive ingredient</td>
<td>Hydroxypropylmethylcellulose 2910, hydroxypropylcellulose, partly pregelatinized starch, croscarmellose sodium, D-mannitol, magnesium stearate, titanium oxide, macrocol 400, carnauba wax and one other ingredient</td>
<td></td>
</tr>
</tbody>
</table>

2. Product description

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Color</th>
<th>Appearance</th>
<th>Weight (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Film-coated tablets</td>
<td>White</td>
<td>(Surface)</td>
<td>197.0</td>
</tr>
</tbody>
</table>

This product has been verified to be bioequivalent to MEIACT Tablets 100.

INDICATIONS

<Indicated bacteria>

<Indications>
Superficial skin infections, deep skin infections, lymphangitis/lymphadenitis, chronic pyoderma, secondary infections in traumas, burns or surgical wounds, etc., mastitis, perianal abscess, pharyngitis/laryngitis, tonsillitis (including peritonsillar abscess), acute bronchitis, pneumonia, lung abscess, secondary infections in chronic respiratory lesion, cystitis, pyelonephritis, cholecystitis, cholangitis, bartholinitis, intrauterine infection, uterine adenitis, eyelid abscess, dacryocystitis, Hordeolum, tarsadenitis, otitis media, sinusitis, periodontal tissue inflammation, periocoronitis, gnathitis

DOSAGE AND ADMINISTRATION
For adults, cefditoren pivoxil is usually administered in a single oral dose of 100 mg (potency) 3 times a day, after meals. The dosage may be adjusted according to the patient’s age and symptoms. A single dose of 200 mg (potency) is orally administered 3 times a day after meals to patients with severe infections or to those for whom the usual dosage may be insufficient.

<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) In patients with severe renal disorder, the dosing interval should be prolonged. (See “Careful Administration” section and “PHARMACOKINETICS” section.)
PRECAUTIONS

1. Careful Administration (MEIACT MS should be administered with care in the following patients.)
   (1) Patients with a history of hypersensitivity to penicillin antibiotics
   (2) Patients with a personal or familial predisposition to allergic reactions such as bronchial asthma, rash or urticaria
   (3) Patients with severe renal disorder [Serum concentration persists. (See “PHARMACOKINETICS” section.)]
   (4) Elderly patients [See “Use in the Elderly” section.]
   (5) Patients with poor oral food intake or who are receiving parenteral alimentation, and patients in poor general health [Patients should be observed carefully because vitamin K deficiency symptoms may develop.]

2. Important Precautions
   Since shock may occur, patients should be carefully interviewed.

3. Adverse Reactions
   This product has been verified to be bioequivalent to MEIACT Tablets 100.

Data for MEIACT Tablets 100 at the time of approval
   Adverse reactions occurred in 127 (4.37%) of 2,909 patients evaluated for the safety of the product. The main adverse reactions were digestive symptoms (121 cases; 4.16%) such as diarrhea, loose stool, nausea and stomach discomfort and allergic symptoms (16 cases; 0.55%) such as rash. Changes in laboratory test values were observed in 8.17% (187/2,289). They included abnormal hepatic function such as AST (GOT) increased in 3.37% (73/2,167) and ALT (GPT) increased in 4.21% (91/2,164), and abnormal hematology such as eosinophilia in 2.63% (47/1,790).

Data for MEIACT Tablets 100 at the end of reexamination
   In post-marketing drug-use results surveys, a total of 4,907 clinical cases was reported from 792 medical institutions nationwide. Adverse reactions occurred in 35 (0.71%) patients with 39 episodes. The main adverse reactions were gastrointestinal system disorders (diarrhea, nausea, stomach discomfort, etc.) in 25 (0.51%) patients and liver and biliary system disorders [abnormal hepatic function, AST (GOT) increased, ALT (GPT) increased in 8.17% (187/2,289). They included abnormal hepatic function such as AST (GOT) increased in 3.37% (73/2,167) and ALT (GPT) increased in 4.21% (91/2,164), and abnormal hematology such as eosinophilia in 2.63% (47/1,790).

(1) Clinically significant adverse reactions
   1) Shock or anaphylactoid reaction (<0.1%) may occur. Patients should be carefully monitored and 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 if these symptoms occur, administration should be discontinued and appropriate measures such as administration of adrenocortical hormones 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 hemolytic 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.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Hypersensitivity</th>
<th>Rash</th>
<th>Urticaria, erythema, pruritus, fever, lymph node swelling, arthralgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash</td>
<td>Urticaria, erythema, pruritus, fever, lymph node swelling, arthralgia</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Eosinophilia</td>
<td>Granulocytopenia, thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>AST (GOT) increased, ALT (GPT) increased</td>
<td>Jaundice, Al-P increased</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>BUN increased, serum creatinine increased, proteinuria</td>
<td></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>
<td></td>
</tr>
</tbody>
</table>
Meiji Seika Kaisha, Ltd. 3

<table>
<thead>
<tr>
<th>Microbial substitution</th>
<th>Stomatitis, candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avitaminosis</td>
<td>Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.), vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)</td>
</tr>
<tr>
<td>Others</td>
<td>Headache, dizziness, edema, numbness</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 with this product.

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, granule, and fine granule products).
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. Use in the Elderly
The incidence of adverse reactions in the elderly does not differ from that in non-elderly adult patients. However, since elderly patients often have reduced physiological function, the product should be carefully administered, paying attention to the following two points, and dosage and dosing interval should be adjusted according to the patient’s condition.

(1) Delay in excretion of this product has been observed in patients with renal hypofunction. Therefore, blood concentrations may increase in the elderly.

(2) In the elderly, bleeding tendency due to vitamin K deficiency has been reported after the use of other similar drugs.

5. Use during Pregnancy, Delivery or Lactation
This product should be used in pregnant women or women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant women has not been established.]

6. Pediatric Use
(1) The safety of this product in low birth weight infants, newborns, suckling infants, infants and children has not been established (insufficient clinical experience).

(2) It has been reported that long-term administration of an antibiotic which has a pivoxil group (a preparation for children) causes hypoglycemia accompanying hypocarnitinemia in infants. (See “Other precautions” section.)

7. Effects on Laboratory Tests
(1) False-positive results may occur in urine glucose tests with Benedict’s solution, Fehling’s solution, and Clinitest, but not with Tes-Tape. Caution is required.

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

8. Precautions concerning Use

Precautions regarding dispensing
In the case of press-through packages, instruct the patient to remove the drug from the package prior to use. [If the PTP sheet is swallowed, its sharp corners may penetrate the esophageal mucosa, leading to serious complications such as mediastinitis.]

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

In infants, it has been reported that long-term single or alternate administration of antibiotics with a pivoxil group (preparations for children) causes hypoglycemia accompanying hypocarnitinemia. When an antibiotic with a pivoxil group is administered, patients should be carefully monitored, paying particular attention to carnitine decrease.

PHARMACOKINETICS
This product has been verified to be bioequivalent to MEIACT Tablets 100.

Data for MEIACT Tablets 100 at the time of approval

1. Absorption and distribution

(1) Blood concentration$^{1,2)}$

Fig. 1 and Table 1 show serum concentrations and pharmacokinetic parameters, respectively, of cefditoren obtained after single oral administration of 100 or 200 mg to healthy adults after meals. Dose dependency was observed. Absorption was better when administered after meals than when administered at fasting.
Table 1 Pharmacokinetic parameters in healthy adults

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Tmax (hr)</th>
<th>Cmax (μg/mL)</th>
<th>T1/2 (hr)</th>
<th>AUC0-→∞ (μg ⋅ hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1.4</td>
<td>1.66</td>
<td>0.80</td>
<td>3.67</td>
</tr>
<tr>
<td>200</td>
<td>2.0</td>
<td>3.44</td>
<td>1.06</td>
<td>10.02</td>
</tr>
</tbody>
</table>

(2) Body fluid and tissue concentrations

Transfer to sputum, tonsillar tissue, mucous membrane of maxillary sinus, cutaneous tissue, mammary gland tissue, gallbladder tissue, vagina, uterine neck, tarsal gland tissue, wound after tooth extraction, etc. was observed, but no transfer to the milk was noted. (Data of patients)

(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 - 24 hours) of cefditoren in healthy adults administered a single oral dose of 100 mg or 200 mg after meals was about 20%. No accumulation of the product was observed after repeated administration (200 mg × 3 times/day, for 8 days).

3. Serum concentration and urinary excretion in patients with renal function disorder

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 T1/2 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</th>
<th>No. of patients</th>
<th>Tmax (hr)</th>
<th>Cmax (μg/mL)</th>
<th>T1/2 (hr)</th>
<th>AUC0-→∞ (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*</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 MEIACT Tablets 100.

< Clinical results of MEIACT Tablets 100 at the time of approval >

Clinical trials were conducted in a total of 2,456 patients (1,965 in open clinical trials and 491 in comparative clinical trials) at medical institutions in Japan to investigate the efficacy of MEIACT Tablets 100. The results are summarized as follows.²,⁴,⁹,¹⁷-²⁷.

1. Infections in the field of dermatology

The efficacy rate of the product was 87.8% (288/328) in patients with superficial skin infections (impetigo contagiosa, folliculitis), deep skin infections [furuncle, furunculosis, carbuncle, erysipelas, phlegmon, suppurative paronychia (paronychia), felon], lymphangitis/lymphadenitis [lymphangitis (lymphadenitis)] and chronic pyoderma (subcutaneous abscess, hidradenitis, infectious atheroma, chronic pyoderma).

2. Infections in the field of surgery

The efficacy rate of the product was 78.9% (105/133) in patients with mastitis, perianal abscess and secondary infections in traumas, burns or surgical wounds, etc.

3. Respiratory tract infections

The efficacy rate of the product was 84.9% (666/784) in patients with pharyngitis/laryngitis [pharyngolaryngitis (throat abscess)], acute bronchitis, tonsillitis (including peritonsillitis and periortonsillar abscess), secondary infections in chronic respiratory lesion (chronic bronchitis, bronchiectasis with infection, secondary infections in chronic respiratory diseases), pneumonia and pulmonary suppuration.

4. Urinary tract infections

The efficacy rate of the product was 77.7% (453/583) in patients with pyelonephritis and cystitis.

5. Biliary tract infections

The efficacy rate of the product was 85.7% (30/35) in patients with cholecystitis and cholangitis.

6. Infections in the field of obstetrics and gynecology

The efficacy rate of the product was 92.9% (143/154) in patients with uterine adenexitis, intraterine infection and Bartholinitis.

7. Infections in the field of otorhinology

The efficacy rate of the product was 72.3% (141/195) in patients with otitis media and sinusitis.
8. Infections in the fields of ophthalmology

The efficacy rate of the product was 89.7% (78/87) in patients with hordeolum, eyelid abscess, dacryocystitis and tarsadenitis.

9. Infections in the fields of dentistry and oral surgery

The efficacy rate of the product was 85.4% (134/157) in patients with periodontal tissue inflammation, pericoronitis and gnathitis.

**PHARMACOLOGY**

1. Antibacterial activity

(1) Cefditoren pivoxil is metabolized into cefditoren on 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-lactamasen produced by various bacteria, and showed strong antibacterial activity against β-lactamase-producing strains.

2. Mechanism of action

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

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-Dimethylpropanoxyoxymethyl (6R, 7R)-7-[[Z]-2-(2-aminothiazol-4-yl)-2-(methoxylimino) 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

Structural formula:

![Structural formula]

Description:

Cefditoren Pivoxil occurs as a light yellowish white to light yellow crystalline powder.

It is sparingly soluble in methanol, slightly soluble in acetone 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 2.0</th>
<th>pH 4.0 - 6.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.92</td>
<td>&gt;3.0</td>
</tr>
</tbody>
</table>

**PRECAUTIONS FOR HANDLING**

This product should be stored in a dry place after opening.

**PACKAGING**

100 mg (potency)/tablet:

- 100 tablets (10 PTP sheets, each with 10 tablets)
- 500 tablets (10 PTP sheets, each with 10 tablets, in one bag; 5 bags)

**REFERENCES**


REQUEST FOR LITERATURE SHOULD BE MADE TO:
Drug Information Center
Meiji Seika Kaisha, Ltd.
4-16, Kyobashi 2-chome, Chuo-ku, Tokyo 104-8002, Japan

Manufactured and distributed by:
Meiji Seika Kaisha, Ltd.
4-16, Kyobashi 2-chome, Chuo-ku, Tokyo 104-8002, Japan