MEIACT® MS FINE GRANULES 10 %
Cefditoren Pivoxil Fine Granules

DESCRIPTION

1. Composition
   Each sachet contains 100 mg of Cefditoren pivoxil in 1 g granule (10 %)

2. Product description

Dosage Form	Color	Taste	Odor
Fine granules	Orange	Sweet and slightly bitter	Aromatic

This product has been verified to be bioequivalent to MEIACT® MS FINE GRANULES 10% (hereinafter "MF Granules") which has been verified to be bioequivalent to MEIACT Granules (hereinafter "M Granules").

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.

INDICATIONS

<Indications>
Tonsilitis and Acute otitis media
<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*.

DOSAGE AND ADMINISTRATION

<In case of Acute otitis media>

For children, cefditoren pivoxil is usually administered in a single oral dose of 6 mg (potency)/kg 3 times a day, after meals. (The dosage may be decreased according to the patient's age and symptoms. Meanwhile, be sure not to exceed 600 mg a day (potency)).

<In case of tonsilitis>

For children, cefditoren pivoxil is usually administered in a single oral dose of 3 mg (potency)/kg 2 times a day, after meals. (The dosage may be increased according to the patient's age and symptoms as needed. However, be sure not to exceed 600 mg a day (potency)).

<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.

CONTRAINDICATIONS

MEIACT® MS FINE GRANULES 10 % is contraindicated in patients with a history of hypersensitivity to any of the ingredients contained in this product.

RELATIVE CONTRAINDICATIONS

As a general rule, MEIACT® MS FINE GRANULES 10 % is contraindicated in patients with a history of hypersensitivity to cephalosporin antibiotics. If the use of MEIACT® MS FINE GRANULES 10 % is considered essential, it should be administered with care.

PRECAUTIONS

1. **Careful Administration (MEIACT® MS FINE GRANULES 10 % 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) 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**
   (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 hydrate, cefteram pivoxil and tebipenem pivoxil) cause serum carnitine decrease resulting from the metabolism / excretion of pivalic acid (a metabolite of antibiotics with a pivoxil group)[1)].
   Administration of antibiotics with a pivoxil group may cause hypoglycemia accompanying hypocarnitinemia in children (in particular, infants and small children). Therefore when an antibiotic with a pivoxil group is administered, patients should be carefully monitored, paying particular attention to carnitine decrease. Do not administer this product if patients are found to have inborn errors of metabolism which may cause serum carnitine to decrease. (See "Adverse Reactions" section)
   (3) When this product is administered to children younger than 3 years in a single dose of 6 mg (potency)/kg 3 times a day, diarrhea/loose stool may occur with high frequency. If these symptoms are observed, approriate measures such as symptomatic treatment should be taken according to the symptoms. [See "Pediatric Use" section].

3. Undesirable effects

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

Incidences of adverse reactions by M Granules were as follows.

Adverse reactions occurred in 19 (4.17%) of 456 patients evaluated for the safety. Principal symptoms observed were diarrhea in 17 (3.73%) patients and allergic symptoms in 2 (0.44%) patients (1 patient each with rash and redness). Changes in laboratory test value were observed in 3.60% (10/278). They included abnormal hepatic function such as AST (GOT) increased in 0.45% (1/222) and ALT (GPT) increased in 0.90% (2/222), and abnormal hematology such as eosinophilia in 1.97% (5/254).

Data at the end of re-examination of MF Granules and M Granules

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.

Data for this product at the time of approval for a partial change in dosage and administration

As a result of a clinical study in which this product was administered to pediatric patients with pneumonia, otitis media or sinusitis in a single dose of 6 mg (potency)/kg 3 times a day, adverse reactions occured in 36 (31.3%) of 115 patients evaluated for safety. The main adverse reaction was diarrhea/loose stool in 28 (24.3%) patients. Abnormal changes in laboratory test values were observed in 7 (6.2%) of 113 patients who had a laboratory test and evaluated for safety. They included increased platelet count.

(1) Clinically significant adverse reactions

1) **Shock or anaphylaxis** (< 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) **Toxic Epidermal Necrolysis (TEN), Muco-cutaneo-ocular syndrome (Stevens-Johnson syndrome)** (< 0.1%) or erythema multiforme (incidence unknown) 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.

8) Administration of an antibiotic which has a pivoxil group may cause **hypoglycemia accompanying hypocarnitinemia** (incidence unknown) in children (in particular, infants and small children). 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 Note1)

	5 % > ≥ 0.1 %	< 0.1 %
Hypersensitivity Note2)	Rash	Urticaria, erythema, pruritus, fever, lymph node swelling, arthralgia
Hematologic Note3)	Eosinophilia	Granulocytopenia, thrombocytopenia
Hepatic Note3)	AST (GOT) increased, ALT (GPT) increased	Jaundice, Al-P increased
Renal		BUN increased, serum creatinine increased, proteinuria
Gastrointestinal	Diarrhea, loose stool, queasy, stomach discomfort, abdominal pain	Feeling of enlarged abdomen, nausea, vomiting
Microbial substitution		Stomatitis, candidiasis
Avitaminosis		Vitamin K deficiency symptoms (hypoprothrombinemia, bleeding tendency, etc.), vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)
Others		Headache, dizziness, edema, numbness
	Abnormal laboratory test values [AST (GOT) increased, ALT (GPT) increased, eosinophilia, etc.] tend to appear more frequently in patients under long-term treatment Note4)	

Note1) : Each adverse reaction is tabulated by the incidence obtained from data available at the time of approval and at the end of re- examination (for tablet, M Granules, and MF Granules).

Note2) : If any symptom occurs, administration should be discontinued and appropriate measures should be taken.

Note3) : The patients should be carefully monitored and if any abnormality is observed, appropriate measures such as discontinuation of administration should be taken.

Note4) : These patients should be monitored by performing periodic laboratory tests.

4. Pregnancy and breastfeeding use

The safety and efficacy in this population have not been established

5. Pediatric Use

(1) The safety of this product in low birth weight infants and newborns has ot been established.

(2) When this product is administered to children younger than 3 years in a single dose of 6 mg (potency)/kg 3 times a day, diarrhea/loose stool may occur with high frequency. Caution is required. [In a clinical study in which this product was administered to children with Community-aquired pneumoniae, Acute otitis media or Acute sinusitis in a single dose of 6 mg (potency)/kg 3 times a day, the incidence of the adverse reaction of diarrhea/loose stool was 36.2% (17/47) in children younger than 3 years and 16.2% (11/68) in children 3 years or older. (See “Important Precautions” section).

6. 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.

7. Effects on ability to drive and use machines

MEIACT® MS FINE GRANULES 10 % has no effects on the ability to drive and use machines.

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.

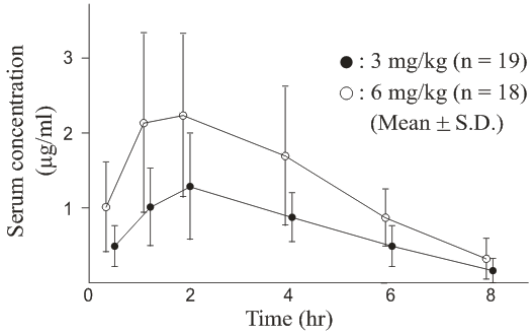

Fig. 1 Serum concentrations of cefditoren in pediatric patients with normal renal function

Table 1 Pharmacokinetic parameters in pediatric patients with normal renal function

Dose	C_{max} (μg/mL)	$T_{1/2}$ (hr)	$AUC^{0\rightarrow\infty}$ (μg.hr/mL)
3 mg/kg (n=19)	1.45	2.25	7.16
6 mg/kg (n=18)	2.85	1.68	11.90

[Reference]

(2) Body fluid and tissue concentrations (in the case of patients given MEIACT Tablets 100)

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.

3. Serum concentration and urinary excretion (in the case of patients with renal function disorder given MEIACT Tablets 100)

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 cases, showing a delay in T1/2 in pararrel with the degree of renal function disorder.

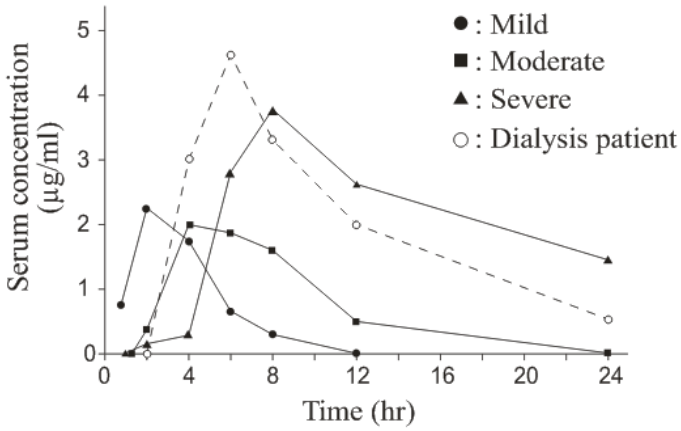

Fig. 2 Serum concentrations of cefditoren in patients with renal function disorder

Table 2 Pharmacokinetic parameters in patients with renal function disorder

Patient's condition [Ccr (mL/min)]	No. of patients	T_{max} (hr)	C_{max} (µg/mL)	$T_{1/2}$ (hr)	$AUC^{0\rightarrow\infty}$ (µg.hr/mL)
Mild [51 – 70]	3	2	2.32	1.13	10.2
Moderate [30 – 50]	4	4	2.17	2.06	16.4
Severe [< 30]	2	8	3.70	5.68	53.5
Dialysis patient (On day without dialysis)	1	6	4.60	5.37	50.2

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

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-lactamases 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 infection17,18,20)**
   Cefditoren pivoxil demonstrated excellent therapeutic effects on experimental infections in mice caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumonia* and *Proteus sp.* Its therapeutic effect on infections caused by β-lactamase-producing strains was equivalent or superior to similar drugs.

DRUG INTERACTION

The use of CDTR-PI with antacids or histamine H2 antagonists receptor will decrease the bioavailability of CDTR-PI. Besides the use together with probenecid will reduce the renal excretion of CDTR.

OVERDOSE

Information on cefditoren pivoxil overdosage in humans is not available. However, with other β-lactam antibiotics, adverse effects following overdosage have included nausea, vomiting, epigastric distress, diarrhea and convulsions. Hemodialysis may aid in the removal of cefditoren from the body, particularly if renal function is compromised (30% reduction of plasma concentrations following 4

hours of hemodialysis). Treat overdosage symptomatically and institute supportive measures as required.

INCOMPATIBILITIES
Not applicable

PRECAUTIONS FOR HANDLING
Sachets 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.

SHELF LIFE
3 years

STORAGE
Store below 30°C and protect from light

PACKAGING
100 mg (potency)/g :

MEIACT® MS FINE GRANULES 10 % of 30 mg :
Box, aluminium bag @ 15 sachet @ 0.3 g granules
Box, aluminium bag @ 60 sachet @ 0.3 g granules
Reg. No. DKI1963200622A1

MEIACT® MS FINE GRANULES 10 % of 50 mg :
Box, aluminium bag @ 15 sachet @ 0.5 g granules
Box, aluminium bag @ 60 sachet @ 0.5 g granules
Reg. No. DKI1963200622B1

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

Manufactured by
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Odawara Plant
1056, Kamonomiya, Odawara-shi, Kanagawa, Japan

Imported, secondary packaged and released by
meiji
PT MEIJI INDONESIAN
PHARMACEUTICAL INDUSTRIES
BANGIL - PASURUAN, JAWA TIMUR – INDONESIA

(CFPIFG 0622 J)

DISETUJUI OLEH BPOM : 22/02/2023

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