MEIACT® Tablets

DESCRIPTION

White film coated tablet.

MEIACT® 200 Tablets : Cefditoren pivoxil 200 mg (potency)

INDICATIONS

Cefditoren pivoxil is indicated for the treatment of following infections which are caused by susceptible strains.

- Community acquired pneumoniae
- Acute exacerbation of chronic bronchitis
- Pharyngotonsilitis
- Acute sinusitis
- Uncomplicated skin and soft structure infections

DOSAGE AND ADMINISTRATION

- Community acquired pneumoniae 400 mg BID for 14 days
- Acute exacerbation of chronic bronchitis 400 mg BID for 10 days
- Pharyngotonsilitis 200 mg BID for 10 days
- Acute sinusitis 200 mg BID for 10 days
- Uncomplicated skin and soft structure infections 200 mg BID for 10 days

Should be taken after meals

<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 severely impaired renal function, the administration interval should be prolonged. (See "Careful Administration" section and "PHARMACOKINETICS" section).

CONTRAINDICATIONS (MEIACT® Tablets is contraindicated in the following patients)

(1) Patients with a history of hypersensitivity to any of the ingredients contained in this product.

(2) Patients with cow's milk allergy
(This product contains sodium caseinate as an inactive ingredient).

RELATIVE CONTRAINDICATIONS (As a general rule, MEIACT® Tablets is contraindicated in the following patients. If the use of MEIACT® Tablets is considered essential, it should be administered with care).

Patients with a history of hypersensitivity to cephalosporin antibiotics.

PRECAUTIONS

1. Careful Administration (MEIACT® Tablets should be administered with care in the following patients)

(1) Patients with a history of hypersensitivity to penicillins.

(2) Patients with a personal or familial predisposition to allergic symptoms such as bronchial asthma, exanthema or urticaria.

(3) Patients with severely impaired renal function [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 may develop).

2. Important Precautions

The patients should be carefully interviewed to asses the risk of shock.

3. Adverse Reaction

Adverse reactions occurred in 127 (4.37%) of the 2,909 patients evaluated for the safety of the product. Digestive symptoms including diarrhea, loose stools, nausea and stomach discomfort accounted for 121 patients (4.16%), followed by 16 (0.55%) patients with allergic symptoms such as exanthema. Changes in laboratory test values were observed in 8.17% (187/2,289). They included abnormal hepatic function such as increased AST (GOT) in 3.37% (73/2,167) and increased ALT (GPT) in 4.21% (91/2,164); and abnormal hematology, such as eosinophilia, in 2.63% (47/1,790) (at the time of approval).

(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), mucocutaneo-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 per-formed. 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

	≥ 0.1% to < 0.5%	< 0.1%
Hypersensitivity Note1)	Exanthema, etc.	Urticaria, erythema, pruritus, fever, lymph node swelling, arthralgia, etc.
Hematologic Note2)	Granulocytopenia, eosinophilia, etc.	Thrombocytopenia, etc.
Hepatic Note2)	Increased AST (GOT), ALT (GPT) and Al-P, etc.	Jaundice, etc.
Renal	Increased BUN and serum creatinin, and proteinuria	
Gastrointestinal	Diarrhea, loose stools, nausea, stomach discomfort, abdominal pain	Abdomen enlarged feeling, nausea, vomiting, etc.
Microbial substitution		Stomatitis and candidiasis
Avitaminosis		Symptoms of vitamin K deficiency (hypoprothrombinemia, bleeding tendency, etc.), vitamin B complex deficiency symptoms (glossitis, stomatitis, anorexia, neuritis, etc.)
Others		Headache, dizziness, edema and numbness
	Abnormal laboratory test values (increased AST (GOT)/ALT (GPT), eosinophilia, etc.), tend to appear more frequently in patients under long-term treatment with this product.Note3)	

Note

1) If symptoms appear, administration should be discontinued and suitable measures should be taken.

2) The patients should be thoroughly monitored and if any abnormality appears, suitable measures including discontinuation of administration should be taken.

3) These patients should be monitored by performing periodical clinical 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 the physiological functions are generally reduced in the elderly, the product should be administered carefully, paying attention to the following two points: dose and dose intervals should be adjusted according to the patient's condition.

(1) Delay in excretion has been observed in patients with impaired renal function. Therefore, high serum levels of the product may persist for a longer period of time in the elderly.

(2) As for other analogous drugs, bleeding tendency due to vitamin K deficiency has been reported to occur in the elderly.

5. Use during Pregnancy, Delivery or Lactation

This product should be administered to 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 during pregnancy has not been established].

6. Pediatric Use

The safety of this product in low birth-weight infants, new borns, suckling infants, infants and children has not been established (few clinical experience).

7. Effects on Laboratory Test

(1) False-positive results may occur in urine glucose tests with Benedict's solution. Fehling's solution, and Clinitests, but not with Tes-Tape.

(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 severe complications such as mediastinitis.]

9. Other Precautions

It has been reported that this product reduces serum carnitine.

PHARMACOKINETICS

1. Absorption and distribution

(1) Blood concentration

The serum concentrations (Fig.1) and pharmacokinetics (Table 1) of cefditoren after oral administration of 100 or 200 mg to healthy adults after meals demonstrated dose dependency. Absorption was better when administered after meals than when given at fasting.

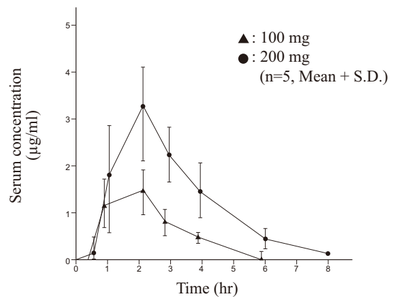


Fig. 1 Serum concentrations of Cefditoren after oral administration in healthy adults

Table1. Pharmacokinetic parameter in healthy adults

Dose (mg)	Tmax (hr)	Cmax (μg/mL)	$T_{1/2}$ (hr)	$AUC^{0\to\infty}$ (μg.hr/mL)
100	1.4	1.66	0.80	3.67
200	2.0	3.44	1.06	10.02

Nama Produk	Insertion Meiact Tablet (side 1)	**Tanggal Desain**	**Keterangan**
Ukuran	440 x 270 mm	23 Juni 2022 17 Januari 2023	-Revisi Clinically significant adverse reactions - Revisi penambahan informasi Zat Tambahan
Bahan	HVS 60 g		
Warna	Black		

(2) Body fluid and tissue concentrations
The drug transferred to the sputum, tonsillar tissue, mucous membrane of maxillary sinus, skin tissue, mammary gland tissue, gallbladder tissue, vagina, uterine neck, tarsal gland tissue and wound after tooth extraction. No transfer to the milk was noted.

(3) Protein binding
In vitro binding rate to human serum protein determined by ultrafiltration method was 91.5% at concentration of 25 µg/mL.

2. Metabolism and excretion
Cefditoren pivoxil is metabolized upon absorption and becomes cefditoren which has antibacterial activity, and pivalic acid. The latter is conjugated with carnitine and excreted into urine as pivaloil carnitine. Cefditoren is hardly metabolized and is excreted mainly into urine and bile. The urinary excretion rate (0-24 hours) of cefditoren upon oral administration after meals at doses of 100 mg and 200 mg to healthy adults was about 20%.
No accumulation of the drug was observed after continuous administration (200 mg x 3 times/day, for 8 days).

3. Serum concentration and urinary excretion in patients with renal function disorder
The serum concentrations (Fig. 2) and pharmacokinetics 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 delay in $T_{1/2}$ in parallel with degree of renal function disorder.

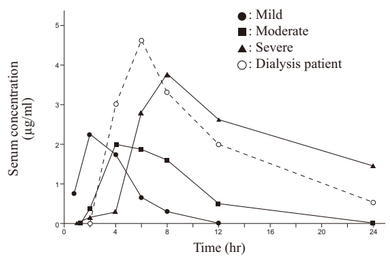


Fig. 2 Serum concentrations of cefditoren in patients with renal function disorder

Table 2 Pharmacokinetic parameter in patients with renal function disorder

Patient's condition [Ccr (mL/min)]	No. of patients	Tmax (hr)	Cmax (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 (Note 4)	1	6	4.60	5.37	50.2

Note

4) On day without dialysis
Urinary excretion rate lowered in parallel with degree of renal function disorder, showing delay in excretion.

PHARMACOLOGY

1. Antibacterial activity

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

(2) Cefditoren exerts antibacterial activity in vitro against a wide spectrum of gram-positive and gram-negative bacteria. Its activity against gram-positive bacteria including *Staphylococcus sp.* and *Streptococcus sp.* such as *Streptococcus pneumoniae* as well as against gram negative bacteria including *E. coli, B. catarrhalis*, *Klebsiella sp.*, *Proteus sp.* and *H. influenzae* and anaerobic bacteria including *Peptostreptococcus sp.*, *P. acnes* and *Bacteroides sp.*, is particularly noteworthy.

(3) In vitro, cefditoren demonstrated stability against ß-lactamase produced by various bacteria. It also shows strong antibacterial activity against strains that produce β-lactamase.

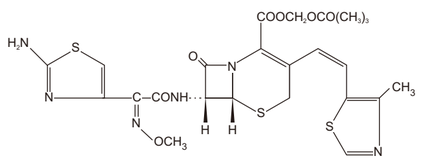
2. Mechanism of action
Cefditoren inhibits the synthesis of bacterial cell wall. It has high affinity to penicillin binding protein (PBPs) in various bacteria, showing a bactericidal effect.

3. Therapeutic efficacy on experimental infections
Cefditoren pivoxil demonstrated excellent therapeutic efficacy on experimental infections by *Staphylococcus aureus, S. pneumoniae, E. coli, Klebsiella pneumoniae* and *Proteus sp.*, in mice. Its therapeutic efficacy on the infections by β -lactamase-producing strains was equivalent or superior to similar drugs.

PHYSICOCHEMISTRY

Nonproprietary name :
Cefditoren pivoxil (JAN), Cefditoren (INN)
Chemical name :
(-)-(6R,7R)-2, 2-dimethylpropionyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(Z)-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 : $C_{25}H_{28}N_6O_7S_3$
Molecular weight : 620.72

Structural formula :



Description :
Cefditoren pivoxil, The Minimum Requirements for Antibiotic Products of Japan (MRAPJ) occurs as a light yellowish white to light yellow crystalline powder. It is freely soluble in diluted hydrochloric acid, sparingly soluble in methanol, slightly soluble in acetonitrile and in ethanol, very slightly soluble in ether and practically insoluble in water.

Melting point : 196-201ºC (decomposition)
Partition coefficient : -
(log_{10}1-octanol layer/water layer, 25 ± 2ºC)

pH 2.0	pH 4.0 - 6.0
0.92	> 3.0

Potency :
Indicated as the weight (potency) of cefditoren ($C_{19}H_{18}N_6O_5S_3$)
1.225 mg of Cefditoren pivoxil contains 1 mg (potency) of cefditoren.

List of Excipient
Tablet Core : Mannitol, Sodium caseinate, Croscarmellose sodium, Sodium tripoluphosphate, Magnesium stearate.
Tablet Coating : Opadry Y-1-7000 white combination, Carnauba wax, Opacode S-1-20986 blue combination.

STORAGE CONDITION

Store below 30°C, protect from light and moisture.

HOW SUPPLIED

MEIACT® 200 Tablets, Box 2 blisters @ 10 tablets,
Reg. No DKI0665600217A1

HARUS DENGAN RESEP DOKTER

Manufactured by
Meiji Pharma Spain, S.A., Madrid - Spain

Imported by
meiji
PT MEIJI INDONESIAN
PHARMACEUTICAL INDUSTRIES
BANGIL - PASURUAN, JAWA TIMUR - INDONESIA

(CFTMH 0123 J)

Nama Produk	Insertion Meiact Tablet (side 2)	Tanggal Desain	Keterangan
Ukuran	440 x 270 mm	23 Juni 2022 17 Januari 2023	-Revisi Clinically significant adverse reactions - Revisi penambahan informasi Zat Tambahan
Bahan	HVS 60 g		
Warna	Black		

DISETUJUI OLEH BPOM: 24/01/2023

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