

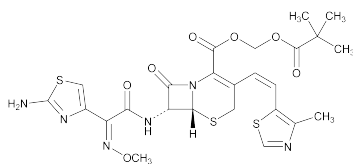
BRIEFING

Cefditoren Pivoxil. This monograph was posted on the USP Pending Monographs Web page on January 30, 2009, as a draft USP Pending Monograph for public comment. No comments were received. The MD-ANT Expert Committee reviewed the draft and approved the monograph as an Authorized USP Pending Monograph. The liquid chromatographic procedure in the Assay is based on analyses performed using a YMC-Pack ODS-AM brand of L1 column. The typical retention times for propylparaben and cefditoren pivoxil are about 11 and 15 min, respectively. The liquid chromatographic procedure in the test for *Organic Impurities* is based on analyses performed using a YMC-Pack ODS-AM brand of L1 column. The typical retention time for cefditoren pivoxil is about 26 min.

(MD-ANT: A. Wise.) RTS—C62509

Cefditoren Pivoxil

v. 1 Authorized July 1, 2009



$C_{25}H_{28}N_6O_7S_3$ 620.72
5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-, pivaloyloxymethyl, (6R,7R)-; (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate [117467-28-4].

DEFINITION

Cefditoren Pivoxil contains NLT 944 µg and NMT 1005 µg of $C_{25}H_{28}N_6O_7S_3$ per mg, calculated on the anhydrous basis.

IDENTIFICATION

- A. INFRARED ABSORPTION** (197K)
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Solution A: Transfer 1.6 g of ammonium formate to a 1-L volumetric flask, dissolve in 900 mL of water, adjust with a 0.4% aqueous solution of formic acid to a pH of 6.0, dilute with water to volume, and mix.

Mobile phase: Acetonitrile, methanol, and *Solution A* (27.5:27.5:45)

Standard solution: 0.4 mg/mL in acetonitrile

Sample solution: 0.4 mg/mL in acetonitrile

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm column; 5-µm packing L1

Flow rate: 0.9 mL/min

Injection size: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the quantity, in µg/mg, of $C_{25}H_{28}N_6O_7S_3$ in the portion of Cefditoren Pivoxil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times F$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Cefditoren Pivoxil RS in the *Standard solution* (mg/mL)

C_U = concentration of the *Sample solution* (mg/mL)

F = number of µg in 1 mg, 1000

Acceptance criteria: 944–1005 µg on the anhydrous basis

IMPURITIES

Inorganic Impurities

- RESIDUE ON IGNITION** (281): NMT 0.2%
- HEAVY METALS, Method II** (231): NMT 10 ppm

Organic Impurities

PROCEDURE

Solution A: 2.8 mg/mL solution of monobasic sodium phosphate in water adjusted with phosphoric acid to a pH of 3.0

Solution B: Acetonitrile and methanol (1:1)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
5	70	30
15	50	50
35	50	50
50	15	85
55	15	85
60	75	25
70	75	25

Diluent: *Solution A* and *Solution B* (1:1)

Blank: Acetonitrile and *Diluent* (1:4)

Resolution solution: 0.5 mg/mL of USP Cefditoren Pivoxil RS in *Diluent*. Heat the solution in a water bath at 95° for 30 min, then cool to room temperature.

Standard stock solution: Transfer USP Cefditoren Pivoxil RS to a suitable volumetric flask, dissolve first in acetonitrile, using 20% of the final volume, then dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of 0.1 mg/mL of USP Cefditoren Pivoxil RS.

Standard solution: 0.01 mg/mL of USP Cefditoren Pivoxil RS in *Diluent* from *Stock standard solution*

Sample solution: Transfer Cefditoren Pivoxil to a suitable volumetric flask, dissolve first in acetonitrile, using 20% of the final volume, then dilute with *Diluent* to volume, and mix to obtain a solution having a known concentration of about 1 mg/mL of Cefditoren Pivoxil.

Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm column; 5-µm packing L1

Flow rate: 1 mL/min

Injection size: 20 µL

System suitability

Sample: *Resolution solution*

Suitability requirements

Resolution: NLT 2.0 between cefditoren pivoxil and cefditoren Δ-3 isomer

2 / Cefditoren Pivoxil

Analysis

Samples: Blank, Standard solution, and Sample solution
Calculate the percentage of each impurity in the portion of Cefditoren Pivoxil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

- r_U = peak response of the impurity peak from the Sample solution
- r_S = peak response of the cefditoren pivoxil peak from the Standard solution
- C_S = concentration of USP Cefditoren Pivoxil RS in the Standard solution (mg/mL)
- C_U = concentration of Cefditoren Pivoxil in the Sample solution (mg/mL)
- F = relative response factor (see Impurity Table 1)

Acceptance criteria: [NOTE—Disregard peaks with a response less than 0.03 times the response of the principal

peak in the Standard solution (0.03%). Disregard any peaks in the chromatogram of the Sample solution that correspond to peaks in the chromatogram of the Blank.]

Individual impurities: See Impurity Table 1.

Total impurities: NMT 5.0%

SPECIFIC TESTS

- **OPTICAL ROTATION, Specific Rotation (7815):** -45° to -52° , measured at 20°
Sample solution: 0.5 mg/mL in methanol
- **WATER DETERMINATION, Method I (921):** NMT 1.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers. Store at controlled temperature between 2° and 8° .
- **USP REFERENCE STANDARDS (11)**
USP Cefditoren Pivoxil RS

Impurity Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Cefditoren ^a	0.32	1.0	0.20
Cefditoren, open ring ^b	0.82	0.76	1.0
Cefetamet pivoxil ^c	0.89	1.1	0.30
Cefditoren pivoxil	1.0	1.0	—
Cefditoren Δ -3 isomer ^d	1.08	0.95	1.5
Cefditoren, methoxymethyl ^e	1.24	1.0	0.20
Cefditoren E-isomer ^f	1.34	0.72	1.0
Cefditoren dipivoxil ^g	1.42	0.67	0.30
Cefditoren, pivaloyl ^h	1.78	1.0	0.20
Cefditoren dimer ⁱ	1.92	0.79	1.0
Cefditoren, open ring dimer ⁱ	1.96	0.76	1.0
Highest unknown impurity	—	1.0	0.10
Total impurities	—	—	5.0

^a Sodium (6R,7R)-7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

^b (R)-2-[(Z)-2-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2-[(R)-5-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-4-[(pivaloyloxymethoxy)carbonyl]-3,6-dihydro-2H-1,3-thiazin-2-yl]acetic acid.

^c (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

^d (2S,6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate.

^e (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(methoxyimino)-2-[2-(methoxymethylamino)thiazol-4-yl]acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylate.

^f (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(E)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

^g 2,2-Dimethylpropanoyloxymethyl (6R,7R)-7-[(2Z)-[2-[[[(2,2-dimethylpropanoyl)oxy]methyl]amino]-1,3-thiazol-4-yl]](methoxyimino)acetyl amino]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

^h (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-(methoxyimino)-2-(2-pivalamidothiazol-4-yl)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.

ⁱ 2,2'-[2,2'-Methylenebis(azanediyl)]bis(thiazole-4,2-diyl)]bis[N-[(6R,7R)-2-pivaloyloxymethoxycarbonyl-8-oxo-3-[(Z)-2-(thiazol-5-yl)vinyl]-5-thia-1-azabicyclo[4.2.0]oct-2-en-7-yl]-2-[(Z)-methoxyimino]acetamide}.

^j (6R,7R)-Pivaloyloxymethyl 7-[(Z)-2-[2-[(R)-2-[(Z)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetamido]-2-[(R)-5-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-4-[(pivaloyloxymethoxy)carbonyl]-3,6-dihydro-2H-1,3-thiazin-2-yl]acetamido]thiazol-4-yl]-2-(methoxyimino)acetamido]-3-[(Z)-2-(4-methylthiazol-5-yl)vinyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate.