



CEFIDEROCOL SULFATE TOSILATE

(CEFIDEROCOLI SULFAS TOSILATUM)

Draft proposal for inclusion in *The International Pharmacopoeia*

(30 June 2025)

DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidt@who.int), with a copy to **Ms Sinéad Jones** (jones@who.int, nsp@who.int).

Comments should be submitted through the online platform on or by **29 August 2025**. Please note that only comments received by this deadline will be considered for the preparation of this document.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/24.967

CEFIDEROCOL SULFATE TOSILATE

(CEFIDEROCOLI SULFAS TOSILATUM)

Description	Date
Drafting of the monograph by the Secretariat based on information received from manufacturers and found in the public domain.	July 2024
Draft monograph sent out for public consultation.	July to August 2025
Presentation to the 58 th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2025
Further follow-up action as required.	

[Note from the Secretariat. The monograph on Cefiderocol is proposed for inclusion in The International Pharmacopoeia.

Being one of the first public standards, the monographs on Cefiderocol and Cefiderocol powder for concentrate for solution for infusion are expected to play an important role in ensuring access to safe, effective and quality-assured essential medicines. Manufacturers, regulatory authorities, procurement agencies and other stakeholders are therefore invited to provide their feedback on the proposed specifications and analytical procedures.

The draft monograph is based on information and samples received from a manufacturer, found in the public domain and on laboratory investigations.

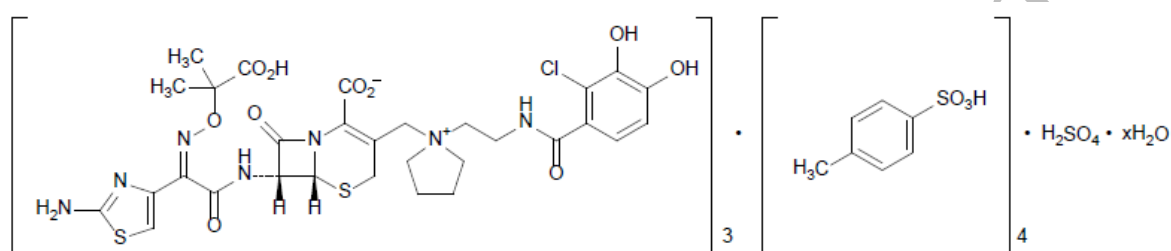
Draft monographs are subject to change.]

CEFIDEROCOL SULFATE TOSILATE

Molecular formula. $3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4 \cdot xH_2O$

Relative molecular mass. 3043.50 (anhydrous cefiderocol sulfate tosilate), 752.21 (cefiderocol base)

Graphic formula.



Chemical names. Tris[(6*R*,7*R*)-7-[(2*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-[(2-carboxypropan-2-yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate] tetrakis(4-methylbenzenesulfonate) monosulfate hydrate (*IUPAC*).

CAS Registry Number. 2009350-94-9

Description. A white to slightly yellow powder.

Solubility. It is freely soluble in methanol R, slightly soluble in water R and dehydrated ethanol R and practically insoluble in acetonitrile R.

Category. Antibacterial (reserve group antibiotic).

Storage. Cefiderocol should be kept in tightly closed containers and protected from light.

Additional information. Cefiderocol is hygroscopic and may show polymorphism.

Requirements

Definition. Cefiderocol sulfate tosilate contains not less than 95.0% and not more than 105.0% of $3\text{C}_{30}\text{H}_{34}\text{ClN}_7\text{O}_{10}\text{S}_2 \cdot 4\text{C}_7\text{H}_8\text{O}_3\text{S} \cdot \text{H}_2\text{SO}_4$, calculated with reference to the anhydrous substance.

Identity tests

- Either test A or test B or any two of tests E, C and D may be applied.
- A. Carry out the test as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from cefiderocol sulfate tosilate RS or with the reference spectrum of cefiderocol sulfate tosilate.

If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and cefiderocol sulfate tosilate RS in a small amount of methanol R. Evaporate to dryness and record new spectra using the residues. The infrared absorption spectrum is concordant with the spectrum obtained from cefiderocol sulfate tosilate RS.

- B. Carry out the test as described under *1.14.1 Chromatography, High-performance liquid chromatography*, using the conditions given under “Assay” but using, as the detector, a diode array detector to record the UV spectra of the peaks due to cefiderocol and 4-toluenesulfonic acid in each chromatogram in the range of 210 nm to 350 nm and injecting 10 µL of solutions (1) and (2). The retention times and the UV spectra of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (1) correspond to the retention times and the UV spectra of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (2).

- C. Carry out the test as described under *1.14.1 Chromatography, High-performance liquid chromatography*, using the conditions and solutions given under “Assay”.

The retention times of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (1) correspond to the retention times of the peaks due to cefiderocol and 4-toluenesulfonic acid in the chromatogram obtained with solution (2).

D. The absorption spectrum (1.6) of a 0.01 mg per mL solution of the test substance in methanol R, when observed between 210 nm and 350 nm, corresponds to the spectrum of cefiderocol sulfate tosylate RS, recorded using the same conditions.

E. Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R7 as the coating substance and a freshly prepared mixture of 1 volume of methanol R and 2 volumes of water R as the mobile phase.

Apply separately to the plate 10 µL of each of the following four solutions in methanol R. For solution (A), use a solution containing 1.0 mg of the test substance per mL. For solution (B), use a solution containing 20.0 mg of the test substance per mL. For solution (C), use a solution containing 1.0 mg of cefiderocol sulfate tosylate RS per mL. For solution (D), use a solution containing 3.4 mg of 4-toluenesulfonic acid RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air, and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with the spot due to cefiderocol in the chromatogram obtained with solution (C). The spot with an R_F value of about 0.83 obtained with solution (B) corresponds in position, appearance and intensity with the spot due to 4-toluenesulfonic acid in the chromatogram obtained with solution (D).

Water. Determine as described under *2.11 Micro determination of water by the Karl Fischer method*. Spread the test substance on a petri dish and let its water content equilibrate for 3 hours at room temperature and humidity. Then determine the water content using 60.0 mg of the equilibrated test substance: it is not less than 110 mg/g and not more than 150 mg/g.

Sulfated ash (2.3, Method B). Not more than 1.0 mg/g, determined on 1 to 2 g.

Heavy metals. Use 1.000 g for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3. Determine the heavy metals content according to Method B; not more than 20 µg/g.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (2.1 mm x 15 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (1.6 µm).¹

Prepare a 0.2% trifluoroacetic acid solution by diluting 2.0 mL of trifluoroacetic acid R to 1000.0 mL with water R.

Use the following conditions for gradient elution:

- mobile phase A: a mixture of 0.2% trifluoroacetic acid solution and acetonitrile (97:3 V/V);
- mobile phase B: acetonitrile R.

Time (minutes)	Mobile phase A (% V/V)	Mobile phase B (% V/V)	Comments
0–0.5	100	0	Isocratic
0.5–4.0	100 to 89	0 to 11	Linear gradient
4.0–9.0	89	11	Isocratic

¹ A CORTECS UPLC T3 or a CORTECS UPLC C18 column have been found suitable.

9.0–30.0	89 to 62	11 to 38	Linear gradient
30.0–31.0	62 to 100	38 to 0	Return to initial composition
31.0–40.0	100	0	Re-equilibration

142 Operate with a flow rate of 0.3 mL per minute. Maintain the column temperature
143 at 35°C and the autosampler at 5°C. Use an ultraviolet spectrophotometer set at a
144 wavelength of 261 nm.

145 Prepare the following solutions:

- 146 • Sodium dihydrogen phosphate solution (0.05 mol/L): dissolve 7.80 g of
147 sodium dihydrogen phosphate dihydrate R in water R to dilute to 1000 mL
148 with the same solvent.
- 149 • Disodium hydrogen phosphate solution (0.05 mol/L): dissolve 7.098 g of
150 disodium hydrogen phosphate R in water R and dilute to 1000 mL with the
151 same solvent.
- 152 • Phosphate buffer solution (5 mmol/L): prepare a mixture of water R,
153 sodium dihydrogen phosphate solution (0.05 mol/L), and disodium
154 hydrogen phosphate solution (0.05 mol/L) (18:1:1 V/V/V).

155 Use as a diluent a mixture of phosphate buffer solution (5 mmol/L) and
156 acetonitrile (9:1 V/V).

157 For solution (1), transfer 40 mg of the test substance into a 25 mL volumetric
158 flask, dissolve in diluent and dilute to volume with the same volume.

159 For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL with diluent.

160 For solution (3), dilute 3.0 mL of solution (2) to 100.0 mL with the diluent.

161 For solution (4), transfer 32 mg of cefiderocol sulfate tosilate RS into a 20 mL
162 volumetric flask, dissolve in diluent and dilute to volume with the same volume.

Heat the obtained solution at 50°C for 20 minutes and cool to room temperature.

Store the solution below -20°C prior to analysis.

Inject 2 µL each of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (4) to identify the peaks due to 4-toluenesulfonic acid, and the impurities A, B, C, E and G.

The impurities are eluted, if present, at the following relative retentions with reference to cefiderocol (retention time about 10 minutes): 4-toluenesulfonic acid about 0.40; impurity A about 0.45; impurity B about 0.61; impurity C about 0.76; impurity F about 0.83, impurity D about 1.23, impurity E about 1.28 and impurity G about 1.83. The test is not valid unless, in this chromatogram obtained with solution (4), the resolution between the peaks due to 4-toluenesulfonic acid and impurity A is at least 1.5. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to cefiderocol is obtained with a signal-to-noise ratio of at least 20. In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A, when multiplied with a correction factor of 2.4, is not greater than 0.1 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peak corresponding to impurity B, when multiplied with a correction factor of 0.72, is not greater than 0.1 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.10 %);
- the area of any peak corresponding to impurity G, when multiplied with a correction factor of 1.6, is not greater than 0.1 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.10 %);
- the area of any other impurity peak is not greater than 0.05 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.05 %).

- The sum of the areas of all impurity peaks is not greater than the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (1.0 %). Disregard all peaks with an area of less than the area of the peak due to cefiderocol in the chromatogram obtained with solution (3) (0.03 %) and any peak due to 4-toluenesulfonic acid.

Assay. Carry out the test as described under *1.14.1 Chromatography, High-performance liquid chromatography*, using a stainless-steel column (4.6 mm x 10 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded octadecylsilyl groups (3 µm).²

Prepare a 0.1% trifluoroacetic acid solution by diluting 1.0 mL of trifluoroacetic acid R to 1000.0 mL with water R.

As the mobile phase, use a mixture of 0.1% trifluoroacetic acid solution and acetonitrile (86:14 V/V).

Operate with a flow rate of 1.0 mL per minute. Maintain the column temperature at 35°C and the autosampler at 5°C. Use an ultraviolet spectrophotometer set at a wavelength of 261 nm.

Prepare the following solutions:

- Sodium dihydrogen phosphate solution (0.05 mol/L): dissolve 7.80 g of sodium dihydrogen phosphate dihydrate R in water R and dilute to 1000 mL with the same solvent.
- Disodium hydrogen phosphate solution (0.05 mol/L): dissolve 7.098 g of disodium hydrogen phosphate R in water R and dilute to 1000 mL with the same solvent.

² Unison UK-C18 column has been found suitable.

- Phosphate buffer solution (5 mmol/L): prepare a mixture of water R, sodium dihydrogen phosphate solution (0.05 mol/L), and disodium hydrogen phosphate solution (0.05 mol/L) (18:1:1 V/V/V).

Use as a diluent a mixture of phosphate buffer solution (5 mmol/L) and acetonitrile (9:1 V/V).

For solution (1), spread the test substance on a petri dish and let its water content equilibrate for 3 hours at room temperature and humidity. Then transfer 40.0 mg of the equilibrated test substance into a 25 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent. Dilute 5.0 mL to 50.0 mL with the diluent.

For solution (2), transfer 40.0 mg of cefiderocol sulfate tosylate RS into a 25 mL volumetric flask, dissolve in diluent and dilute to volume with the same diluent. Dilute 5.0 mL to 50.0 mL with the diluent.

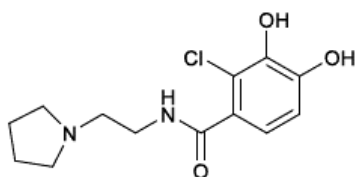
Inject 10 µL each of solutions (1) and (2) and record the chromatograms for 20 minutes.

Measure the areas of the peaks corresponding to cefiderocol obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of cefiderocol sulfate tosylate ($3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$) in the sample using the declared contents of cefiderocol sulfate tosylate ($3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$) in cefiderocol sulfate tosylate RS.

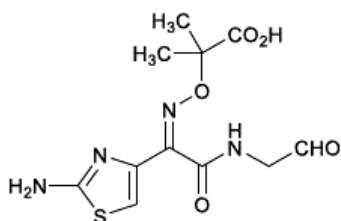
Bacterial endotoxins. If intended for use in the manufacture of a parenteral dosage form without a further appropriate procedure for the removal of bacterial endotoxins, carry out the test as described under *3.4 Test for bacterial endotoxins*; contains not more than 0.054 IU of endotoxin per mg of the test substance.

Sterility. If intended for use in the manufacture of either a parenteral or other sterile dosage form without a further appropriate sterilization procedure, complies with 3.2 *Test for sterility.*

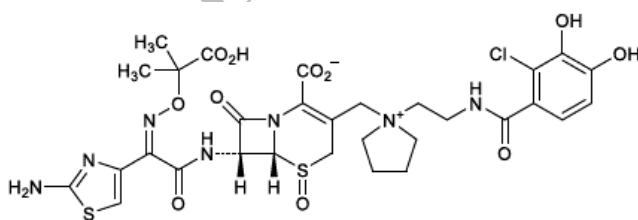
Impurities



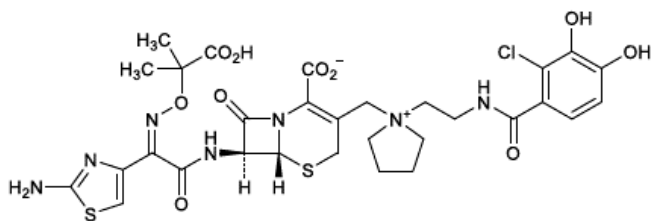
A. 2-Chloro-3,4-dihydroxy-N-[2-(pyrrolidin-1-yl)ethyl]benzamide (degradation product)



B. 2-[[Z]-{1-(2-Amino-1,3-thiazol-4-yl)-2-oxo-2-[(2-oxoethyl)amino]ethylidene}amino]oxy}-2-methylpropanoic acid (degradation product)

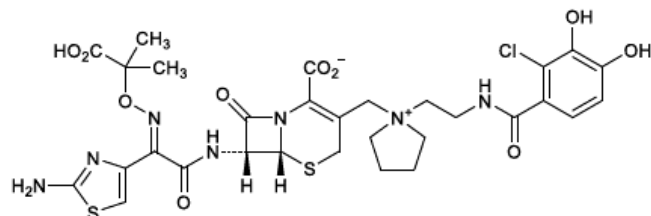


C. (6R,7R)-7-[(2Z)-2-(2-Amino-1,3-thiazol-4-yl)-2-[[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl]methyl]-5,8-dioxo-5λ4-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity and degradation product)



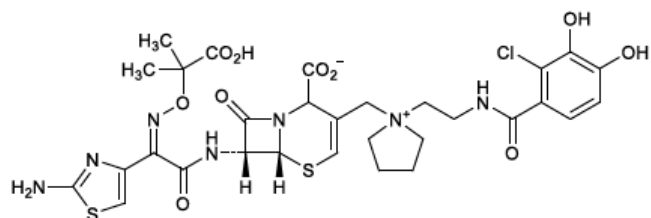
253

- 254 D. (6R,7S)-7-[(2Z)-2-(2-Amino-1,3-thiazol-4-yl)-2-[[2-(2-carboxypropan-2-
255 yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-
256 dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-
257 azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity, degradation
258 product)



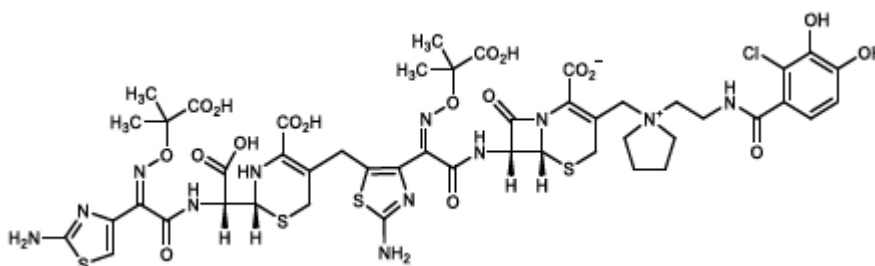
259

- 260 E. (6R,7R)-7-[(2E)-2-(2-Amino-1,3-thiazol-4-yl)-2-[[2-(2-carboxypropan-2-
261 yl)oxy]imino}acetamido]-3-({1-[2-(2-chloro-3,4-
262 dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-
263 azabicyclo[4.2.0]oct-2-ene-2-carboxylate (process related impurity, degradation
264 product)



265

- 266 F. [chemical name to be added at a later stage] (process related impurity and
267 degradation product)



- G. (6R,7R)-7-[(2Z)-2-(2-Amino-5-{[(2R)-2-{(R)-[(2Z)-2-(2-amino-1,3-thiazol-4-yl)-2-[[2-(2-carboxypropan-2-yl)oxy]imino}acetamido](carboxy)methyl}-4-carboxy-3,6-dihydro-2H-1,3-thiazin-5-yl)methyl}-1,3-thiazol-4-yl)-2-[[2-(2-carboxypropan-2-yl)oxy]imino}acetamido)-3-({1-[2-(2-chloro-3,4-dihydroxybenzamido)ethyl]pyrrolidin-1-ium-1-yl}methyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylat (degradation product)

Reference substances to be established.

Cefiderocol sulfate tosilate RS

- New International Chemical Reference Substance to be established.

Reagents to be established.

4-Toluenesulfonic acid R

4-Methylbenzenesulfonic acid, C₇H₈O₃S, H₂O.

Content: minimum 87.0 % of C₇H₈O₃S.

Description: White or almost white, crystalline powder or crystals, freely soluble in water, soluble in Ethanol (~750 g/L) TS.

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Draft for comments