World Health Organization

CEFIDEROCOL POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

(CEFIDEROCOLI PULVIS PRO CONCENTRATO PRO SOLUTIONE PRO INFUSIONE)

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 (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@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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CEFIDEROCOL POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

(CEFIDEROCOLI PULVIS PRO CONCENTRATO PRO SOLUTIONE PRO INFUSIONE)

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 58th 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 powder for concentrate for solution for infusion 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.

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54 *Draft monographs are subject to change.]*

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CEFIDEROCOL POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

Category. Antibacterial (reserve group antibiotic).

Storage. Cefiderocol powder for concentrate for solution for infusion should be kept in a hermetically closed containers and protected from light.

Additional information. Strength in the current WHO Model List of Essential Medicines (EML): Powder for injection: 1 g (as sulfate toxilate) in vial.

Requirements

The powder for concentrate for solution for infusion and the reconstituted solution for infusion comply with the monograph for *Parenteral preparations*.

Definition. Cefiderocol powder for concentrate for solution for infusion is a sterile product consisting of Cefiderocol sulfate tosilate with excipients. It is supplied in a sealed container and contains not less than 90.0% and not more than 110.0% of the labelled amount of Cefiderocol sulfate tosylate ($3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S \cdot H_2SO_4$), per vial.

Identity tests

- Either test A, or tests B and C, may be applied.

A. 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

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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).

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions and solutions given under "Assay" but injection 10 µL of solutions (1) and (2).

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).

Carry out the test as described under *1.14.1 Chromatography*, Thin-layer chromatography, using silica gel R7 as the coating substance and a 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), shake a quantity of the powder, nominally containing 10 mg of cefiderocol sulfate tosilate, for 5 minutes with 10 mL, filter and use the clear filtrate. For solution (B), shake a quantity of the powder, nominally containing 200 mg of cefiderocol sulfate tosilate for 5 minutes with 10 mL, filter and use the clear filtrate. For solution (C), use a solution containing 1.0 mg of cefiderocol sulfate tosilate 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 sport with an R_F values of about 0.83 obtained with solution (B) corresponds in position, appearance and intensity with the

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sport due to 4-toluenesulfonic acid in the chromatogram obtained with solution (D).

pH value (1.13). Dissolve the content of 1 vial of the powder for concentrate for solution for infusion in 10 mL of carbon-dioxide water R. pH of the obtained solution, 5.0 to 6.0.

Clarity and colour of solution. Dissolve the content of 1 vial of the powder for concentrate for solution for infusion in 10 mL of water R. This solution is clear and not more intensely coloured than reference solution Y5, when compared as described under *1.11.2 Degree of coloration of liquids,* Method I.

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.

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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

Operate with a flow rate of 0.3 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.
- 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), gently remove the stoppers from 5 vials and retain the stoppers. Add 10 mL of diluent to each vial and re-insert the stoppers. Swirl the vial contents gently and then mix well by repeated inversions until the contents of the vials are fully dissolved. Transfer the solutions into a single 500 mL volumetric flask. Add again 10 mL of diluent to each vial, re-insert the stoppers, mix, and transfer the rinses also to the volumetric flask. Dilute to volume with diluent. Dilute 5.0 mL of this solution to 50.0 mL with the diluent.

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

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For solution (3), dilute 5.0 mL of solution (2) to 100.0 mL with the diluent.

For solution (4), transfer 32 mg of cefiderocol sulfate tosilate RS into a 20 mL 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-toluenesulonic 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 1.4 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (1.4 %);
- the area of any peak corresponding to impurity G, when multiplied with a correction factor of 1.6, is not greater than 0.7 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.7 %);
- the area of any peak corresponding to impurity E is not greater than 0.15 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (0.15 %);

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- 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 other impurity peak 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 sum of the areas of all impurity peaks is not greater than 2.6 times the area of the peak due to cefiderocol in the chromatogram obtained with solution (2) (2.6 %). Disregard all peaks with an area of less than the area of the peak due to cefiderocol in the chromatogram obtained with solution (3) (0.05 %) 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:

[2] Unison UK-C18 column has been found suitable.

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- 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.
- 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), gently remove the stoppers from 5 vials and retain the stoppers. Add 10 mL of diluent to each vial and re-insert the stoppers. Swirl the vial contents gently and then mix well by repeated inversions until the contents of the vials are fully dissolved. Transfer the solutions into a single 500 mL volumetric flask. Add again 10 mL of diluent to each vial, re-insert the stoppers, mix, and transfer the rinses also to the volumetric flask. Dilute to volume with diluent. Dilute 5.0 mL of this solution to 50.0 mL with the diluent. Dilute 5.0 mL of the resulting solution to 50.0 mL with the diluent.

For solution (2), transfer 50.0 mg of cefiderocol sulfate tosilate RS into a 50 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 tosilate ($3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S. \cdot H_2SO_4$) per vial using

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the declared contents of cefiderocol sulfate tosilate ($3C_{30}H_{34}ClN_7O_{10}S_2 \cdot 4C_7H_8O_3S. \cdot H_2SO_4$) in cefiderocol sulfate tosilate 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 0.101 IU of endotoxin per mg of the test substance.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Cefiderocol sulfate tosilate.

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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, $C_7H_8O_3S$, H_2O.

Content: minimum 87.0 % of $C_7H_8O_3S$.

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

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