



World Health
Organization

CAPREOMYCIN FOR INJECTION
DRAFT PROPOSAL FOR
THE INTERNATIONAL PHARMACOPOEIA
(AUGUST 2010)

DRAFT FOR COMMENT

This document was provided by a quality control expert and was discussed at the recent WHO consultation on specifications for medicines and quality control laboratory issues. Previous comments received have been incorporated into this revised draft. Should you have any comments, please send these to Dr S. Kopp, Manager, Medicines Quality Assurance Programme, Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland; e-mail: kopps@who.int with a copy to Ms C. Mendy mendyc@who.int by 1 October 2010.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT
QAS/10.358
International Pharmacopoeia monograph on Capreomycin injection

	Date
Preparation of first draft by laboratory	February 2010
Discussion of first draft in telephone conference	25 March 2010
Discussion of the draft monograph in the consultation on specifications for medicines and quality control laboratory issues	10-12 May 2010
Mailing of draft monograph for comments	August 2010
Collation of comments received	September-October 2010
Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations	18-22 October 2010
Any further action as required	...

**Draft proposal for *The International Pharmacopoeia*
(August 2010)**

CAPREOMYCINI AD INJECTIONEM

CAPREOMYCIN FOR INJECTION

Description. A white or almost white powder.

Category. Antituberculosis drug.

Storage. Capreomycin for injection should be stored in a well-closed container.

Labelling. The designation on the container of capreomycin for injection should state that the active ingredient is in the sulfate form, and the quantity should be indicated in terms of the equivalent amount of capreomycin.

Additional information. Strength in the current WHO Model list of essential medicines: 1 g. Strength in the current WHO Model list of essential medicines for children: 1 g. The injection is reconstituted by dilution of Capreomycin powder for injections in Water for injections.

Requirements

The powder for injection and the reconstituted injection comply with the monograph for “Parenteral preparations”.

Definition. Capreomycin for injection is a sterile powder containing Capreomycin sulfate. It contains not less than 90.0% and not more than 115.0% of the amount of capreomycin stated on the label, taking into account the sum of capreomycins IA, IB, IIA and IIB.

Identity tests

- Either tests A and E or tests B, C, D and E may be applied.
- A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from capreomycin sulfate RS or with the *reference spectrum* of capreomycin sulfate.
- B. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 30 volumes of phenol R, 10 volumes of water R and 1 volume of ammonia (~260 g/l) TS as the mobile phase. Apply separately to the plate 4 µl of each of the following two solutions in water R. For solution (A), dissolve a quantity of the powder to obtain a solution containing 10 mg of the test substance per ml. For solution (B), use 10 mg of capreomycin sulfate RS

per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in air. Spray with triketohydrindene/methanol TS and heat the plate for 3 minutes at 120 °C. Examine the chromatogram in daylight.

The spots obtained with solution A correspond in position, appearance, and intensity with those obtained with solution B.

- C. Dissolve a quantity of the powder in hydrochloric acid (0.1 mol/l) VS to obtain a solution containing the equivalent of 20 µg of capreomycin per ml. The absorption spectrum of this solution, when observed between 230 nm and 350 nm, exhibits one maximum at about 268 nm.
- D. Dissolve a quantity of the powder in sodium hydroxide (0.1 mol/l) VS to obtain a solution containing the equivalent of 20 µg of capreomycin per ml. The absorption spectrum of this solution, when observed between 230 nm and 350 nm, exhibits a major maximum at about 287 nm.
- E. A solution of the powder containing the equivalent of 20 mg of capreomycin per ml yields reaction A described under 2.1 General identification tests as characteristic of sulfates.

Clarity of solution. A freshly prepared solution of the powder containing the equivalent of 1 g of capreomycin in 10 ml of carbon-dioxide-free water R is clear.

pH value (1.3). pH of a solution of the powder containing the equivalent of 0.3 g of capreomycin in 10 ml of carbon-dioxide-free water R, 4.5-7.5.

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 0.35 IU of endotoxin per mg of capreomycin.

Related substances. Carry out the test as described under 1.14.4 High performance liquid chromatography, using the conditions given under Assay.

Prepare the following solutions using water R as diluent. For solution (1) dissolve a quantity of the powder to obtain a solution containing the equivalent of 2.0 mg of capreomycin per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration of 10 µg of capreomycin per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 µl of solution (1). The test is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The test is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

Inject separately 20 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the four major peaks corresponding to capreomycins IA, IB, IIA and IIB, is not greater than 4 times the sum of the areas of the four major peaks obtained with solution (2) (2.0%). The area of not more than one such peak is greater than twice the sum of the areas of the four

major peaks obtained with solution (2) (1.0%). The sum of the areas of all peaks, other than the four major peaks, is not greater than 14 times the sum of the areas of the four major peaks obtained with solution (2) (7.0%). Disregard any peak with an area less than 0.1 times the sum of the areas of the four major peaks in the chromatogram obtained with solution (2) (0.05%).

Assay

Carry out the test as described under 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with base deactivated particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μm)¹.

The mobile phases for the gradient elution consist of a mixture of Mobile phase A and Mobile phase B, using the following conditions:

Mobile phase A: 5 volumes of acetonitrile R and 95 volumes of phosphate buffer pH 2.3.

Mobile phase B: 15 volumes of acetonitrile R and 85 volumes of phosphate buffer pH 2.3.

Prepare the phosphate buffer pH 2.3 by dissolving 54.4 g of potassium dihydrogen phosphate R in 1500 ml of water R, adjust the pH to 2.3 by adding phosphoric acid (~105 g/l) TS, add 9.4 g of sodium hexanesulfonate R and dilute to 2000 ml with water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-25	55 to 52	45 to 48	Linear gradient
25-40	52	48	Isocratic
40-60	30	70	Isocratic
60-70	55	45	Isocratic re-equilibration

Prepare the following solutions using water R as diluent. For solution (1) dissolve a quantity of the powder to obtain a solution containing the equivalent of 2.0 mg of capreomycin per ml. For solution (2) use an amount of capreomycin sulfate RS equivalent to 2.0 mg of capreomycin per ml.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 268 nm.

Inject 20 μl of solution (1). The assay is not valid unless the resolution between the two major peaks corresponding to capreomycin IA and capreomycin IB, with a relative retention of 0.89 and 1, respectively, is at least 2.0. The assay is also not valid unless the resolution between the peaks corresponding to capreomycin IIA and capreomycin IIB, with a relative retention of 0.53 and 0.63, respectively, is at least 3.5.

¹ Hypersil BDS column has been found suitable.

Inject separately 20 µl each of solutions (1) and (2).

Measure the areas of the peak responses obtained in the chromatograms from solutions (1) and (2) and calculate the content of capreomycin (sum of the four peaks corresponding to capreomycins IA, IB, IIA and IIB) from the declared content of capreomycin in capreomycin sulfate RS.

[Note from Secretariat: it is proposed that the ICRS will have its content expressed on the label in terms of capreomycin base and capreomycin sulfate]

Draft for comment