Proposed revision of the monograph on

Capreomycin for injection (Capreomycini ad injectionem)

for The International Pharmacopoeia

(May 2017)

DRAFT FOR COMMENT

Should you have any comments on this draft, please send these to Dr Herbert Schmidt, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or email: schmidt@who.int by 31 July 2017.

In order to speed up the process for receiving draft monographs and for sending comments, please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list. Please specify if you wish to receive monographs.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/16.690:

Proposed revision of the monograph on

Capreomycin for injection

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<th>Date</th>
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<tr>
<td>Revision drafted taking into consideration decisions made at the meeting of WHO Expert Committee on Specifications for Pharmaceutical Preparations in October 2016</td>
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<tr>
<td>Discussion at consultation on new medicines, quality control and laboratory standards</td>
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<td>Draft revision sent out for public consultation</td>
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<tr>
<td>Presentation to WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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<td>Further follow-up action as required</td>
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[Note from the Secretariat. It is proposed to revise the monograph as follows:

- add a new reference substance - Capreomycin sulfate for identification RS - suitable for identity test A and B (identification by IR and TLC);
- add a note of the Secretariat with respect to ongoing discussions about the transition from microbiological to physicochemical assays for antibiotics;
- determine the percentage content of capreomycin per sealed container;
- update the style of the monograph.

Changes from the current monograph are indicated in the text by insert or delete.]
Proposed revision of the monograph on
Capreomycin for injection (Capreomycini ad injectionem)

[Note from the Secretariat. The user of the monograph should note that the monograph describes a chromatographic assay to determine if the concentrations of capreomycin IA, IB, IIA and IIB of a sample under investigation complies with the definition (see section definition). Other pharmacopoeias have the activity of the substance determined for assay by means of microbiological methods. A correlation between the concentration of IA, IB, IIA and IIB and the activity of the substance, determined with microbiological methods, has not been established yet.]

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 (EML): 1 g. Strength in the current EML for children: 1 g.

The injection is reconstituted by dilution of Capreomycin powder for injections in Water for injections.

The reconstituted injection should be used immediately after preparation.

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 capreomycin 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 for identification 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 powder for injection per mL. For solution (B) use 10 mg of capreomycin sulfate for identification 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 for injection 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 (1.6) of this solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 268 nm.

D. Dissolve a quantity of the powder for injection 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 (1.6) of this solution, when observed between 230 nm and 350 nm, exhibits a maximum at about 287 nm.

E. A solution of the powder for injection 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 for injection 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 for injection 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 Mobile phase A as diluent. For solution (1) dissolve a quantity of the powder for injection 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 (with a relative retention of about 0.89) and capreomycin IB (retention time about 38 minutes) with a relative retention of 0.89 and 1, respectively, is at least 2.0 and 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 capreomycin 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).

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.
Weigh and mix the contents of 5 containers. Prepare the following solutions using mobile phase A as diluent. For solution (1) dissolve a quantity of the mixed contents, containing the equivalent of about 100 mg of capreomycin, accurately weighed, and dilute to 50.0 mL. 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 solution containing 2.75 mg 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 (with a relative retention of 0.89) and capreomycin IB (retention time about 38 minutes), with a relative retention of 0.89 and 1, respectively, is at least 2.0. and 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.

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

Measure the areas of the peak responses for capreomycin IA, IB, IIA and IIB obtained in the chromatograms from solutions (1) and (2) and, using the sum of the areas, calculate the percentage content of capreomycin IA, IB, IIA and IIB per sealed container using from the declared content in capreomycin sulfate RS.

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