Revision of the monograph on Ciclosporin

(August 2017)

DRAFT FOR COMMENT

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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 30 September 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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Please send any request for permission to:

Dr Sabine Kopp, Manager, Medicines Quality Assurance Programme, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; email: kopp@who.int.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.701:
Revision of the monograph on Ciclosporin

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[Note from the Secretariat. It is proposed to revise the monograph based on information found in the European Pharmacopoeia and the United States Pharmacopoeia. Changes from the current monograph are indicated in the text by insert or delete.]
Ciclosporin
(Ciclosporinum)

Molecular formula. $C_{62}H_{111}N_{11}O_{12}$

Relative molecular mass. 1203

Chemical name

Other name. Cyclosporin.

Description. A white or almost white powder.

Solubility. Practically insoluble in water; freely soluble in ethanol (~750 g/L) TS and dichloromethane R.

Category. Immunosuppressant drug.

Storage. Ciclosporin should be kept in a well-closed container, protected from light.

Additional information. Ciclosporin is a product derived from a fermentation process or obtained by other ways.

Requirements

Definition. Ciclosporin contains not less than 97.098.5% and not more than 102.0401.5% of $C_{62}H_{111}N_{11}O_{12}$, calculated with reference to the dried substance.

Identity tests

- Either test A alone or tests B and C 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 ciclosporin RS or with the reference spectrum of ciclosporin.
B. Carry out as described under 1.14.1 High-performance liquid chromatography using the conditions given under "Assay". The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to ciclosporin in the chromatogram obtained with solution (2).

C. Dissolve 5 mg in 5 mL of methanol R, and 1 drop of potassium permanganate (10 g/L) TS and allow to stand; the blue-red colour is gradually discharged.

Specific optical rotation. Use a 5.0 mg/mL solution in methanol R and calculate with reference to the dried substance; \([\alpha]_{D}^{20\degree} = -193\degree\) to \(-185\degree\).

Heavy metals. Use 1.0 g of the test substance 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 A; not more than 20 μg/g.

Clarity and colour of solution in ethanol. A solution of 4.015 g in 4015 mL of ethanol (~750 g/L) TS is clear and not more intensely coloured than standard colour solution Y₅, BY₃ or R₇ Yw3 or Rd1 when compared as described under 1.11.2 Colour of liquids. [Note from the Secretariat. The chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under the section 1.11.2 Degree of coloration of liquids.]

Sulfated ash (2.3). Not more than 1.0 mg/g.

Loss on drying. Dry 1.000 g of the test substance at 60 °C under reduced pressure (not exceeding 150.6 kPa or about 5 mm of mercury) for 3 hours; it loses not more than 20 mg/g.

Related substances. Carry out the test as described below under "Assay".

Prepare the following solutions in a mixture of equal volumes of acetonitrile R and water R. For solution (1) dissolve 30.0 mg of the test substance and dilute to 25.0 mL. For solution (2) dilute 2.0 mL of solution (1) to 200 mL. For solution (3) prepare a solution containing 1.0 mg of ciclosporin for system suitability RS (containing a 100:1 (w/w) mixture of ciclosporin and ciclosporin U) per mL.

Inject 20 μL of solution (3). The test is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 1.4, where Hp is the height above the baseline of the peak due to ciclosporin U and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin (retention time 25 to 30 minutes).

Inject alternately 20 μL each of solutions (1) and (2). Record the chromatograms for 1.7 times the retention time of the principal peak.

In the chromatogram obtained with solution (1):
• the area of any impurity peak, is not greater than 0.7 times the area of the peak due to ciclosporin in the chromatogram obtained with solution (2) (0.7%).

• the sum of the areas of all impurities is not greater than 1.5 times the area of the peak due to cyclosporine in the chromatogram obtained with solution (2) (1.5%).

Disregard any peak with an area less than 0.05 times the area of the peak due to ciclosporin in the chromatogram obtained with solution (2) (0.05%).

Measure the areas of the peak responses obtained in the chromatograms from solutions A and C, and calculate the content of the related substances as a percentage. In the chromatogram obtained with solution A, the area of any peak, other than the principal peak, is not greater than 0.7 times the area of the principal peak obtained with solution C (0.7%), and the sum of these areas is not greater than 1.5 times the area of the principal peak of the chromatogram obtained with solution C (1.5%).

Assay. Determine as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (25 cm × 4 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (3–5 μm). The column is connected to the injection port by a steel capillary tube about 1 m long with an internal diameter of 0.25 mm. Maintain the temperature of the column and of the steel capillary at 80 °C. As the mobile phase use a mixture of 52 volumes of water, 43 volumes of acetonitrile R, 5 volumes of tert-butyl methyl ether R and 0.1 volume of phosphoric acid (~1440 g/L) TS.

Prepare the following solutions in a mixture of equal volumes of acetonitrile R and water R. For solution (1) dissolve 30.0 mg of the test substance and dilute to 25.0 mL. 1.2 mg of Ciclosporin per mL. For solution (2) dissolve 30.0 mg of cyclosporine RS and dilute to 25.0 mL. 1.2 mg of ciclosporin RS per mL. For solution (3) dilute 2.0 mL of solution (2) to 200 mL. For solution (4) prepare a solution containing 1.0 mg of ciclosporin for system suitability RS (containing a 100:1 (w/w) mixture of ciclosporin and ciclosporin U) per mL. 3 mg of ciclosporin U RS in 2.5ml of the solvent mixture and add 2.5ml of solution B.

Operate with a flow rate of about 1.5 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of about 210 nm.

Inject 20 μL of solution (4). The assay is not valid unless the peak-to-valley ratio (Hp/Hv) is at least 1.4, where Hp is the height above the baseline of the peak due to ciclosporin U and Hv is the height above the baseline of the lowest point of the curve separating this peak from the peak due to ciclosporin (retention time 25 to 30 minutes). The assay is valid only if the relative standard deviation of the area of the principal peak is not more than 1.0%, unless the resolution between the two principal peaks is 1.0 and 1.8. The assay is not valid unless the retention time of the principal peak is between 25 and 30 minutes.

Inject alternately 20 μL each of solutions (1) and (2). Record the chromatograms for 1.7 times the retention time of the principal peak.
Measure the areas of the peaks corresponding to ciclosporin obtained in the chromatograms and calculate the percentage content of $C_{62}H_{111}N_{11}O_{12}$, using the declared content of $C_{62}H_{111}N_{11}O_{12}$ in ciclosporin RS.

**Impurities**

A. different ciclosporins [difference from ciclosporin (R = CH$_3$: ciclosporin A)]; ciclosporin B [7-l-Ala]; ciclosporin C [7-l-Thr]; ciclosporin D [7-l-Val]; ciclosporin E [5-l-Val]; ciclosporin G [7-(1-2-aminopentanoyl)]; ciclosporin H [5-d-MeVal]; ciclosporin L [R = H]; ciclosporin T [4-l-Leu]; ciclosporin U [11-l-Leu]; ciclosporin V [1-l-Abu]

B. [6-[(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)octanoic acid]]ciclosporin A.

C. isociclosporin A.

**Reference substances to be established**

Ciclosporine RS

Ciclosporine for system suitability RS

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