Revision of the monograph on Atenolol
(May 2017)

DRAFT FOR COMMENT

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.700:
Revision of the monograph on Atenolol

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<td>Drafting of the revision by the Secretariat following a request from the WHO custodian centre for ICRS</td>
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<td>Discussion at the informal consultation on quality control laboratory tools and specifications for medicines</td>
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[Note from the Secretariat. It is proposed to revise the monograph based on information found in the European Pharmacopoeia and in the scientific literature. Changes from the current monograph are indicated in the text by insert or delete.]
Atenolol  
(Atenololum)

\[
\begin{align*}
C_{14}H_{22}N_{2}O_{3}
\end{align*}
\]

Relative molecular mass. 266.3

Chemical name. 2-\[p-\{2-Hydroxy-3-(isopropylamino)propoxy\}phenyl\]acetamide (racemate); CAS Reg. No. 29122-68-7.

Description. A white or almost white powder.

Solubility. Sparingly soluble in water; soluble in ethanol (~750 g/L) TS; slightly soluble in dichloromethane R.

Category. Cardiovascular agent; β-adrenoreceptor blocking agent.

Storage. Atenolol should be kept in a tightly closed container.

Requirements

Atenolol contains not less than 99.0% and not more than 101.0% of \(C_{14}H_{22}N_{2}O_{3}\), calculated with reference to the dried substance.

Identity tests

• Either tests A and D or tests B and C, and D 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 atenolol RS or with the reference spectrum of atenolol.

B. The absorption spectrum of a 0.10 mg/mL solution in methanol R, when observed between 230 nm and 350 nm, exhibits 2 maxima at about 275 nm and 282 nm. The ratio of the absorbance at 275 nm to that at 282 nm is between 1.15 and 1.20.

C. Carry out the test as described under 1.14.1 Thin-layer chromatography using silica gel R4 as the coating substance and a mixture of 99 volumes of methanol R and 1 volume of ammonia (~260 g/L) TS as the mobile phase. Apply separately to the plate 10 μL of each of 2 solutions in methanol R containing (A) 10 mg of the test substance Atenolol per mL and (B) 10 mg of atenolol RS per mL. After removing the
plate from the chromatographic chamber and examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution (A) corresponds in position, appearance and intensity with that obtained with solution (B).

D. Melting temperature. About 154 °C.

Solution S. Dissolve 0.10 g of the test substance in carbon-dioxide-free water R and dilute to 10.0 mL with the same solvent.

Specific optical rotation (1.4). Use solution S: $[\alpha]_{D}^{20} = +0.10^\circ$ to $-0.10^\circ$.

Clarity and colour of solution. Solution (S) is clear and not more intensely coloured than degree 6 of the range of reference solutions of the most appropriate colour, when compared as described under 1.11.2 Degree of coloration of liquids, Method II.

[Note from the Secretariat. Chapter 1.11 Colour of liquids is currently under revision. Reference is already made to a new test procedure to be added under section 1.11.2 Degree of coloration of liquids.]

Chlorides. Dissolve 0.25 g in a mixture of 2 mL of nitric acid (~130 g/L) TS and 20 mL of water and proceed as described under 2.2.1 Limit test for chlorides; the chloride content is not more than 1.0 mg/g.

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

Loss on drying. Dry 1.0 g of the test substance to constant mass at 105 °C; it loses not more than 5.0 mg/g.

Related substances. Carry out the test as described under 1.14.4 High-performance liquid chromatography using a stainless steel column (1512.5 cm × 4.0–6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μm). Prepare the following solution to be used as the mobile phase: dissolve 1.0 g of sodium octanesulfonate R and 0.4 g of tetrabutylammonium hydrogen sulfate R in 1000 mL of a mixture of 80 volumes of a 3.4 mg/mL solution of potassium dihydrogen phosphate R, the pH of the solution adjusted to 3.0 with phosphoric acid (~1440 g/L), 18 volumes of methanol R and 2 volumes of tetrahydrofuran R.

Prepare the following solutions in mobile phase. For solution (1) dissolve 50 mg of the test substance in 20 mL and dilute to 25.0 mL with the test substance Atenolol in 5 mL of mobile phase. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3) dissolve 2 mg of atenolol for system suitability RS (containing atenolol and the impurities B, F, G, I and J) in 1.0 mL of the mobile phase. dissolve 0.05 g of Atenolol in 0.10 mL of dimethyl sulfoxide R, if
necessary applying gentle heat by placing the flask in a water bath for a few seconds, and
dilute with sufficient mobile phase to produce 25 mL; for solution (C) dilute 0.5 mL of
solution A with sufficient mobile phase to produce 100 mL; and for solution (D) dissolve
0.05 g of atenolol for column validation RS in 0.10 mL of dimethyl sulfoxide R, if
necessary applying gentle heat by placing the flask in a water bath for a few seconds, and
dilute with sufficient mobile phase to produce 25 mL.

Operate with a flow rate of 0.6 ± 0 mL per minute. As a detector use an ultraviolet
spectrophotometer set at a wavelength of about 226 nm.

Inject 10 μL of solution C. Adjust the sensitivity of the system so that the height of the
principal peak is at least 50% of the full scale of the recorder.

Inject 10 μL of solution (3)D. Record the chromatograms for about 5 times the retention
time of atenolol (retention time about 8 minutes). Use the chromatogram obtained with
solution (3) and the chromatogram supplied with atenolol for system suitability RS to
identify the peaks due to atenolol and the impurities B, F, G, I and J.

The test is not valid unless the resolution between the peaks due to the impurities J and I
is at least 1.4. The tracing obtained is similar to that of the specimen chromatogram
provided with atenolol for column validation RS, where the peak due to the bis-ether
precedes and is separated from the tertiary amine which normally appears as a doublet. If
necessary, adjust the concentration of sodium octanesulfonate R in the mobile phase: a
higher concentration would increase the retention time of the tertiary amine.

Inject alternately 10 μL each of solutions A(1) and B(2). Continue the recording of the
chromatogram for four times the retention time of the principal peak.

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 half the area of the principal peak obtained with solution C
(0.25%). The sum of the areas of all the peaks, other than the principal peak, is not
greater than that of the principal peak obtained with solution C (0.5%). Disregard any
peak with an area less than 0.1 times that of the principal peak obtained with solution C.
If the content of bisether in Atenolol is greater than 0.15%, repeat the chromatography
with 10ml of solution B to confirm its compliance.

In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity B is not greater than 2 times the area of
  the peak due to atenolol in the chromatogram obtained with solution (2) (0.2%);
- the area of any peak corresponding to either impurity F, G, I or J is not greater than 1.5
times the area of the peak due to atenolol in the chromatogram obtained with solution
  (2) (0.15%);
- the area of any other impurity peak is not greater than the area of the peak due to
  atenolol in the chromatogram obtained with solution (2) (0.10%);
the sum of the areas of all impurity peaks is not greater than 5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.5%). Disregard any peak with an area less than 0.5 times the area of the peak due to atenolol in the chromatogram obtained with solution (2) (0.05%).

**Assay.** Dissolve about 0.200 g, accurately weighed, in 80 mL of glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/L) VS as described under 2.6 *Non-aqueous titration*, Method A, determining the end-point potentiometrically.

Each mL of perchloric acid (0.1 mol/L) VS is equivalent to 26.63 mg of \( \text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_3 \).

**Impurities**

A. 2-(4-hydroxyphenyl)acetamide

and enantiomer

B. 2-[4-[(2RS)-2,3-dihydroxypropoxy]phenyl]acetamide

and enantiomer

D. 2-[4-[(2RS)-3-chloro-2-hydroxypropoxy]phenyl]acetamide

E. 2,2′-[2-hydroxypropane-1,3-diyl]bis(oxy-4,1-phenylene)]diacetamide

F. 2,2′-[(propan-2-yl)azanediyl]bis[(2-hydroxypropane-3,1-diyl]oxy-4,1-phenylene)]diacetamide


I. 2-[4-[(2RS)-3-(ethylamino)-2-hydroxypropoxy]phenyl]acetamide

J. 2-[4-[(2RS)-3-amino-2-hydroxypropoxy]phenyl]acetamide

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