Edition: BP 2025 (Ph. Eur. 11.6 update)

Letrozole Tablets

General Notices

Action and use

Aromatase inhibitor; treatment of breast carcinoma.

DEFINITION

Letrozole Tablets contain Letrozole.

The tablets comply with the requirements stated under Tablets and with the following requirements.

Content of letrozole, $C_{17}H_{11}N_5$

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Carry out the method for *thin-layer chromatography*, Appendix III A, using the following solutions.
(1) Disperse a quantity of whole tablets containing 10 mg of Letrozole with 0.5 mL of *water*. Dilute to 5 mL with *methanol* and mix with the aid of ultrasound. Centrifuge and use the supernatant liquid.
(2) 0.2% w/v of *letrozole BPCRS* in *methanol*.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating *silica gel F_{254}* (Merck silica gel 60 F_{254} plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 5 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and examine under *ultraviolet light (254 nm)*.

MOBILE PHASE

1 volume of *methanol* and 9 volumes of *ethyl acetate*.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) is similar in position and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 500 mL of 0.1M *hydrochloric acid*, at a temperature of 37°, as the medium.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 30 minutes, withdraw a sample of the medium and centrifuge. Use the supernatant liquid, diluted with dissolution medium if necessary, to produce a solution expected to contain 0.0005% w/v of Letrozole.
(2) 0.05% w/v of *letrozole BPCRS* in *acetonitrile*. Dilute 1 volume of this solution to 100 volumes with dissolution medium.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5 C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 40 µL of each solution.

MOBILE PHASE

48 volumes of *acetonitrile* and 52 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of letrozole, $C_{17}H_{11}N_5$, in the medium from the chromatograms obtained and using the declared content of $C_{17}H_{11}N_5$ in *letrozole BPCRS*.

LIMITS

The amount of letrozole released is not less than 80% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in a mixture of 3 volumes of *acetonitrile* and 7 volumes of *water* (solution A).

(1) Shake a quantity of whole tablets containing 12.5 mg of Letrozole with 15 mL of solution A and dilute to 25 mL. Centrifuge and use the supernatant liquid.
(2) Dilute 1 volume of solution (1) to 100 volume. Dilute 1 volume of the resulting solution to 10 volumes.
(3) 0.05% w/v of *letrozole EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (12.5 cm × 4.6 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (5 µm) (Nucleosil 100-5 C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 230 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

Mobile phase A *water*.

Mobile phase B *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-4	70	30	isocratic
4-29	70→30	30→70	linear gradient
29-30	30→70	70→30	linear gradient
30-40	70	30	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to letrozole (retention time, about 11 minutes) are: impurity A, about 0.6 and impurity B, about 2.0.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to impurity A and letrozole is at least 5.0.

LIMITS

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity A is not greater than 3 times the area of the principal peak in the chromatogram obtained with solution (2) (0.3%);

the area of any other *secondary peak* is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (0.2%);

the sum of the areas of any *secondary peaks* is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Shake 10 whole tablets with 10 mL of *water*, add 30 mL of *acetonitrile* and shake until completely dispersed. Add sufficient *water* to produce 100 mL, mix well and centrifuge. Dilute 1 volume of the supernatant liquid with the mobile phase to produce a solution expected to contain 0.001% w/v of Letrozole.
(2) 0.025% w/v of *letrozole BPCRS* in a mixture of 3 volumes of *acetonitrile* and 7 volumes of *water*. Dilute 1 volume of the resulting solution to 25 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Dissolution may be used but with an injection volume of 20 µL.

DETERMINATION OF CONTENT

Calculate the content of letrozole, $C_{17}H_{11}N_5$, in the tablets from the chromatograms obtained and using the declared content of $C_{17}H_{11}N_5$ in *letrozole BPCRS*.

IMPURITIES

The impurities limited by the requirements of this monograph include those listed under *Letrozole*.