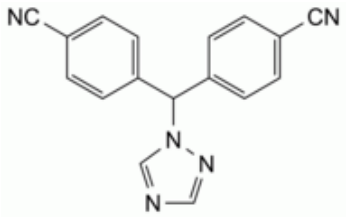
Edition: BP 2025 (Ph. Eur. 11.6 update)

Letrozole

General Notices

(Ph. Eur. monograph 2334)



$C_{17}H_{11}N_5$ 285.3 *112809-51-5*

Action and use

Aromatase inhibitor; treatment of breast carcinoma.

Preparation

Letrozole Tablets

Ph Eur

DEFINITION

4,4′-[(1*H*-1,2,4-Triazol-1-yl)methylene]dibenzonitrile.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or yellowish, crystalline powder.

Solubility

Practically insoluble in water, freely soluble in methylene chloride, sparingly soluble in methanol.

IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

Comparison *letrozole CRS*.

TESTS

Related substances

Liquid chromatography (2.2.29).

Test solution (a) Dissolve 25.0 mg of the substance to be examined in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*.

Test solution (b) To 2.0 mL of test solution (a) add 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Reference solution (a) Dilute 2 mL of test solution (a) to 10 mL with a mixture of 30 volumes of *acetonitrile R* and 70 volumes of *water R*. Dissolve the contents of a vial of *letrozole impurity A CRS* in 1 mL of this solution.

Reference solution (b) To 2.0 mL of test solution (a) add 30.0 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*. To 1.0 mL of this solution add 6.0 mL of *acetonitrile R* and dilute to 20.0 mL with *water R*.

Reference solution (c) Dissolve 25.0 mg of *letrozole CRS* in 15 mL of *acetonitrile R* and dilute to 50.0 mL with *water R*. To 2.0 mL of this solution add 30 mL of *acetonitrile R* and dilute to 100.0 mL with *water R*.

Column:

— *size*: *l* = 0.125 m, Ø = 4.6 mm;

— *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:

— *mobile phase A*: *water for chromatography R*;

— *mobile phase B*: *acetonitrile for chromatography R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	70	30
4 - 29	70 → 30	30 → 70

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 230 nm.

Injection 20 µL of test solution (a) and reference solutions (a) and (b).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A.

Relative retention With reference to letrozole (retention time = about 13 min): impurity A = about 0.6.

System suitability Reference solution (a):

— *resolution*: minimum 5.0 between the peaks due to impurity A and letrozole.

Calculation of percentage contents:

— for each impurity, use the concentration of letrozole in reference solution (b).

Limits:

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.3 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.3 per cent, determined on 1.00 g.

ASSAY

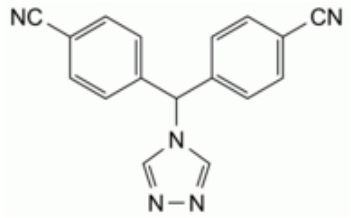
Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications.

Injection Test solution (b) and reference solution (c).

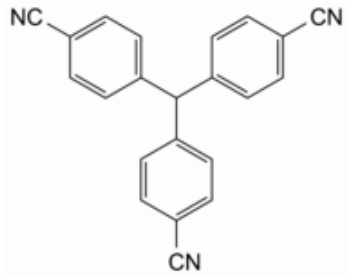
Calculate the percentage content of $C_{17}H_{11}N_5$ from the assigned content of *letrozole CRS*.

IMPURITIES

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use) A, B.



A. 4,4′-[(4*H*-1,2,4-triazol-4-yl)methylene]dibenzonitrile,



B. 4,4′,4″-methanetriyltribenzonitrile.

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