Letrozole Tablets

DEFINITION

Letrozole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of letrozole ($C_{17}H_{11}N_5$).

IDENTIFICATION

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** ⟨**201**⟩
  Sample solution: Equivalent to 2 mg/mL of letrozole from powdered Tablets in methanol. [NOTE—Shake thoroughly, sonicate for 10 min, and centrifuge.]
  Application volume: 5 µL
  Developing solvent system: Ethyl acetate and methanol (9:1)
  Acceptance criteria: Meet the requirements
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**
  Mobile phase: Acetonitrile and water (48:52)
  Diluent: Acetonitrile and water (30:70)
  Standard stock solution: 0.2 mg/mL of USP Letrozole RS in *Diluent*. [NOTE—Dissolve letrozole in acetonitrile, and then dilute with water.]
  Standard solution: 10 µg/mL of USP Letrozole RS in *Mobile phase* from the *Standard stock solution*
  Sample stock solution: Equivalent to 50 mg of letrozole from Tablets in a 250-mL volumetric flask. Add 20 mL of water and shake for 5 min to dissolve the Tablets. Add 75 mL of acetonitrile, shake for 30 min, and dilute with water to volume. Centrifuge a portion of the solution.
  Sample solution: 10 µg/mL of letrozole in *Mobile phase* from the *Sample stock solution*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 230 nm
  Column: 4.6-mm × 12.5-cm; 5-µm packing L1
  Flow rate: 1 mL/min
  Injection volume: 20 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: 0.8–1.5
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of letrozole ($C_{17}H_{11}N_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Letrozole RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of letrozole in the *Sample solution* (µg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨**711**⟩
  Test 1
  Medium: 0.1 N hydrochloric acid; 500 mL
  Apparatus 2: 100 rpm
  Time: 30 min
  Standard solution: Transfer USP Letrozole RS to a suitable volumetric flask, dissolve in acetonitrile equivalent to 10% of the final volume, and dilute with *Medium* to volume to obtain a solution of 0.05 mg/mL of letrozole. Dilute this solution with *Medium* to obtain a solution of 0.005 mg/mL of letrozole.
  Sample solution: Centrifuge a portion of the solution under test at 4000 rpm for 5 min.
  Mobile phase and **Chromatographic system:** Proceed as directed in the *Assay*, except use an injection volume of 200 µL.
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of letrozole ($C_{17}H_{11}N_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Letrozole RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL
  Tolerances: NLT 80% (*Q*) of the labeled amount of letrozole ($C_{17}H_{11}N_5$) is dissolved.
  Test 2
  Medium: 0.1 N hydrochloric acid solution adjusted with 50% sodium hydroxide (NaOH) to a pH of 1.2; 900 mL, deaerated
  Apparatus 2: 75 rpm
  Time: 30 min
  Mobile phase: Acetonitrile and water (45:55)
  Standard stock solution: 0.3 mg/mL of USP Letrozole RS in *Mobile phase*
  Standard solution: 3.0 µg/mL of USP Letrozole RS in *Medium* from the *Standard stock solution*
  Sample solution: Pass a portion of the solution under test through a suitable filter of 35-µm pore size.
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 230 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Flow rate: 1 mL/min
  Injection volume: 100 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of letrozole ($C_{17}H_{11}N_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*

C_S = concentration of USP Letrozole RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of letrozole ($C_{17}H_{11}N_5$) is dissolved.

•**Test 3**
Medium: 0.1 N hydrochloric acid; 500 mL
Apparatus 2: 75 rpm
Time: 30 min
Mobile phase: Acetonitrile and water (48:52)
Standard stock solution: 0.25 mg/mL of USP Letrozole RS in *Mobile phase*
Standard solution: 0.005 mg/mL of USP Letrozole RS in *Medium* from the *Standard stock solution*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first few mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 50 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: 0.8–1.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of letrozole ($C_{17}H_{11}N_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Letrozole RS in the *Standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of letrozole ($C_{17}H_{11}N_5$) is dissolved.• (RB 1-Apr-2015)

• **Uniformity of Dosage Units** ⟨**905**⟩**:** Meet the requirements

IMPURITIES

• **Organic Impurities**
Solution A: Water
Solution B: Acetonitrile
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
25	30	70

Diluent: Prepare as directed in the *Assay*.
System suitability solution: 10 µg/mL of USP Letrozole RS and 2 µg/mL of USP Letrozole Related Compound A RS in *Diluent*. [Note—Dissolve letrozole and letrozole related compound A in acetonitrile, then dilute with water.]
Standard solution: 1 µg/mL of USP Letrozole RS in *Diluent*. [Note—Dissolve letrozole in acetonitrile, then dilute with water.]
Sample solution: Nominally 0.1 mg/mL of letrozole in *Diluent*. Shake the whole Tablets (NLT 10) for about 15 min in a portion of *Diluent* to aid in dissolution. Centrifuge, and use the supernatant.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 12.5-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 50 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between letrozole and letrozole related compound A, *System suitability solution*
Relative standard deviation: NMT 10.0% for letrozole, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of letrozole from the *Standard solution*
C_S = concentration of USP Letrozole RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of letrozole in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. Disregard any impurity peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Letrozole related compound A[a]	0.67	—
Letrozole	1.0	—
4,4′,4″-Methanetriyltribenzonitrile	2.4	—
Any unspecified impurity	—	0.1
Total unspecified impurities	—	0.3

[a] 4,4′-(1*H*-1,3,4-Triazol-1-ylmethylene)dibenzonitrile.

[Note—Letrozole related compound A and 4,4′,4″-Methanetriyltribenzonitrile are process impurities and are controlled in the drug substance monograph.]

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers at controlled room temperature.
• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
• **USP Reference Standards** ⟨**11**⟩
USP Letrozole RS
USP Letrozole Related Compound A RS
4,4′-(1*H*-1,3,4-Triazol-1-ylmethylene)dibenzonitrile.
$C_{17}H_{11}N_5$ 285.31