**Letrozole Tablets**

**DEFINITION**
Letrozole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of letrozole (C\textsubscript{17}H\textsubscript{11}N\textsubscript{5}).

**IDENTIFICATION**

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST**
  - 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 × 15-cm; 5-µm packing L1
  - Flow rate: 1 mL/min
  - Injection volume: 20 µL

  **System suitability**
  - Sample: Standard solution
  - Suitability requirements: NMT 2.0%
  - Relative standard deviation: NMT 2.0%

  **Analysis**
  - Samples: Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of letrozole (C\textsubscript{17}H\textsubscript{11}N\textsubscript{5}) in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{C_0} \right) \times 100
  \]

  \(r_0\) = 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)

  \(C_0\) = nominal concentration of letrozole in the Sample solution (µg/mL)

**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\textsubscript{17}H\textsubscript{11}N\textsubscript{5}) dissolved:

  \[
  \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
  \]

  \(r_0\) = 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\textsubscript{17}H\textsubscript{11}N\textsubscript{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: NMT 25% relative standard deviation.
  - Tailing factor: NMT 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\textsubscript{17}H\textsubscript{11}N\textsubscript{5}) dissolved:

  \[
  \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100
  \]

  \(r_0\) = peak response from the Sample solution

  \(r_s\) = peak response from the Standard solution
**Letrozole**

\[ C_s = \text{concentration of USP Letrozole RS in the Standard solution (mg/mL)} \]

\[ L = \text{label claim (mg/Tablet)} \]

\[ V = \text{volume of Medium, 900 mL} \]

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

**Test 3**

<table>
<thead>
<tr>
<th>Medium</th>
<th>0.1 N hydrochloric acid; 500 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparatus</td>
<td>2: 75 rpm</td>
</tr>
<tr>
<td>Time</td>
<td>30 min</td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Acetonitrile and water (48:52)</td>
</tr>
<tr>
<td>Standard stock solution</td>
<td>0.25 mg/mL of USP Letrozole RS</td>
</tr>
<tr>
<td>Standard solution</td>
<td>0.005 mg/mL of USP Letrozole RS in Medium from the Standard stock solution</td>
</tr>
<tr>
<td>Sample solution</td>
<td>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.</td>
</tr>
</tbody>
</table>

**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 |
| Tailing factor | NMT 2.0% |
| Relative standard deviation | NLT 10.0% for letrozole, Standard solution |
| Acceptance criteria | See Table 2. Disregard any impurity peaks less than 0.05%. |

**Analysis**

Samples: Standard solution and Sample solution

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.

Relative standard deviation: NMT 10.0% for letrozole, Standard solution

Analysis

Sample solutions: Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100 \]

\[ r_0 = \text{peak response from the Sample solution} \]

\[ r_s = \text{peak response from the Standard solution} \]

\[ C_s = \text{concentration of USP Letrozole RS in the Sample solution (mg/mL)} \]

\[ L = \text{label claim (mg/Tablet)} \]

\[ V = \text{volume of Medium, 900 mL} \]

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

**Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

**Organic Impurities**

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See Table 1.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letrozole related compound A</td>
<td>0.67</td>
<td>—</td>
</tr>
<tr>
<td>Letrozole</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>4,4′,4″-Methanetriyltribenzonitrile</td>
<td>2.4</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total unspecified impurities</td>
<td>—</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**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′-(1H-1,3,4-Triazol-1-ylmethylene)tribenzonitrile

C\(_{17}H_{11}N_5\) 285.31

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