Ropinirole Extended-Release Tablets

Type of Posting  Revision Bulletin
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Expert Committee  Chemical Medicines Monographs 4
Reason for Revision  Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Ropinirole Extended-Release Tablets monograph. The purpose for the revision is to revise the tolerances in Dissolution Test 2 to accommodate the FDA approved specifications for the sponsor product.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Ropinirole Extended-Release Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement of USP 41–NF 36.

Should you have any questions, please contact K. Kalyana Seela, Ph.D., Senior Scientific Liaison (kks@usp.org).
Ropinirole Extended-Release Tablets

**DEFINITION**
Ropinirole Extended-Release Tablets contain ropinirole hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of ropinirole free base (C₁₆H₂₄N₂O).  

**IDENTIFICATION**
- **A.** The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.
- **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**
  - **Buffer:** Dissolve 4.5 g of dibasic sodium phosphate dihydrate in 900 mL of water. Adjust with phosphoric acid to a pH of 7.0. Dilute with water to 1 L.
  - **Mobile phase:** Methanol and Buffer (75:25)
  - **Dilute phosphoric acid:** Dissolve 0.7 mL of phosphoric acid in 1 L of water.
  - **Diluent:** Acetonitrile and Dilute phosphoric acid (80:20)
  - **System suitability solution:** 0.1 mg/mL of USP Ropinirole Hydrochloride RS and 0.003 mg/mL of USP Ropinirole Related Compound B RS in Diluent. Sonication may be used to aid dissolution.
  - **Standard solution:** 0.11 mg/mL of USP Ropinirole Hydrochloride RS in Diluent. Sonication may be used to aid dissolution.
  - **Sample solution:** 0.05–0.2 mg/mL of ropinirole prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask containing 75% of the flask volume of Diluent. Sonicate for NLT 30 min. Allow to cool to room temperature. Dilute with Diluent to volume. Pass a portion of the solution through a nylon filter of 0.45-µm pore size and use the filtrate.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 250 nm. For Identification A, use a diode array detector in the range of 200–400 nm.
- **Column:** 4.6-mm × 12.5-cm; 5-µm packing L7
- **Column temperature:** 40°C
- **Flow rate:** 1 mL/min
- **Injection volume:** 10 µL
- **Run time:** NLT 1.5 times the retention time of ropinirole

**System suitability**
- **Samples:** System suitability solution and Standard solution
- **Suitability requirements**
  - **Resolution:** NLT 2.0 between ropinirole related compound B and ropinirole, System suitability solution
  - **Tailing factor:** NMT 1.5, Standard solution
  - **Relative standard deviation:** NMT 1.5%, Standard solution

**Analysis**
- **Samples:** Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of ropinirole (C₁₆H₂₄N₂O) in the portion of Tablets taken:
  \[ \text{Result} = \left( \frac{r_0}{r_s} \right) \times (C_s/C_o) \times (M_{ro}/M_{rb}) \times 100 \]
  - \( r_0 \) = peak response of ropinirole from the Sample solution
  - \( r_s \) = peak response of ropinirole from the Standard solution
  - \( C_s \) = concentration of USP Ropinirole Hydrochloride RS in the Standard solution (mg/mL)
  - \( C_o \) = nominal concentration of ropinirole in the Sample solution (mg/mL)
  - \( M_{ro} \) = molecular weight of ropinirole free base, 260.37
  - \( M_{rb} \) = molecular weight of ropinirole hydrochloride, 296.84

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**
  - **Test 1**
    - **Solution A:** 121.2 g/L of trishydroxymethylamino methane in water
    - **Buffer 1:** Dissolve 2.1 g of citric acid monohydrate in 900 mL of water. Adjust with Solution A to a pH of 4.0. Dilute with water to 1 L.
    - **Buffer 2:** Dissolve 3.9 g of ammonium acetate in 900 mL of water. Adjust with phosphoric acid to a pH of 2.5. Dilute with water to 1 L.
    - **Medium:** Buffer 1; 500 mL. Deaerate as appropriate.
    - **Apparatus 2:** 100 rpm with tablet holder. See Figure 7.

  Figure 1. 37-mm(l) × 19-mm(d) stainless steel sinker; screw cap drilled with seven 4-mm holes, bottom drilled with seven 5-mm holes, 12 longitudinal series of 5-mm holes alternately starting and ending with one 3-mm hole, polished electrochemically or with a suitably validated alternative

- **Times:** 2, 12, and 24 h
- **Mobile phase:** Acetonitrile, methanol, and Buffer 2 (14:6:80)
- **Standard solution:** (L/400) mg/mL of USP Ropinirole Hydrochloride RS in Medium where L is the label claim in mg/Tablet
- **Sample solution:** Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

**Chromatographic system**
(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 250 nm
- **Column:** 4.6-mm × 12.5-cm; 5-µm packing L7
- **Flow rate:** 1 mL/min
- **Injection volume:** 20 µL for 12-mg Tablets; 100 µL for all other strengths
- **Run time:** NLT 2 times the retention time of ropinirole
2 Ropinirole

System suitability
Sample: Standard solution
Suitability requirements
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 ropinirole (C_{16}H_{24}N_{2}O) dissolved at each time point (\(t\)):

\[
\text{Result} = \left( \frac{r_0}{r_S} \right) \times C_s \times V \times \left( \frac{1}{L} \right) \times \left( \frac{M_r}{M_o} \right) \times 100
\]

- \(r_0\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_s\) = concentration of USP Ropinirole Hydrochloride RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 500 mL
- \(L\) = label claim, mg/Tablet
- \(M_r\) = molecular weight of ropinirole hydrochloride, 296.84
- \(M_o\) = molecular weight of ropinirole free base, 260.37

Tolerances: See Table 1.

<table>
<thead>
<tr>
<th>Time Point ((t))</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>71±62 (RB 1-Nov-2017)</td>
</tr>
<tr>
<td>3</td>
<td>80±66 (RB 1-Nov-2017)</td>
</tr>
<tr>
<td>4</td>
<td>80±66 (RB 1-Nov-2017)</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of ropinirole (C_{16}H_{24}N_{2}O) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Solution A: 121.2 g/L of tris(hydroxymethyl)amino methane in water
Buffer 1: Dissolve 2.1 g of citric acid monohydrate and 11.7 mL of Solution A in 1000 mL of water. Adjust with Solution A to a pH of 4.0.
Buffer 2: Dissolve 4.2 g/L of monobasic potassium phosphate in water. Adjust with sodium hydroxide to a pH of 6.5.
Medium: Buffer 1; 500 mL
Apparatus 2: 100 rpm
Times: 2, 6, 12, and 24 h
Mobile phase: Acetonitrile and Buffer 2 (20:80)
Standard solution: (L/500) mg/mL of USP Ropinirole Hydrochloride RS in Medium where L is the label claim in mg/Tablet
Sample solution: Centrifuge a portion of the solution under test.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 50 µL
Run time: NLT 2 times the retention time of ropinirole

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration (\(C\)) of ropinirole (C_{16}H_{24}N_{2}O) in the sample withdrawn from the vessel at each time point (\(t\)):

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

- \(r_0\) = peak response of ropinirole from the Sample solution
- \(r_S\) = peak response of ropinirole from the Standard solution
- \(C_s\) = concentration of USP Ropinirole Hydrochloride RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of ropinirole (C_{16}H_{24}N_{2}O) dissolved at each time point (\(t\)):

\[
\text{Result} = C_s \times \left( \frac{1}{L} \right) \times \left( \frac{M_r}{M_o} \right) \times 100
\]

The percentages of the labeled amount of ropinirole (C_{16}H_{24}N_{2}O) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 3.

Buffer: 1.4 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.
Tolerances:
See System suitability

Medium: 0.1 N hydrochloric acid VS; 500 mL
Apparatus 2: 100 rpm, with sinkers
Times: 1, 6, 12, and 24 h
Mobile phase: Acetonitrile and Buffer (10:90)
Standard solution: \((L/500)\) mg/mL of USP Ropinirole Hydrochloride RS in Medium where \(L\) is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm \(\times\) 7.5-cm; 3.5-µm packing L1
Column temperature: 35°
Flow rate: 1.5 mL/min
Injection volume: 50 µL
Run time: NLT 2 times the retention time of ropinirole

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 1.5

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration \(C_i\) of ropinirole \((C_{16}H_{24}N_2O)\) in the sample withdrawn from the vessel at each time point \((i)\):

\[
\text{Result} = \left(\frac{r_i}{r_0}\right) \times C_i
\]

\(r_0\) = peak response of ropinirole and 3-oxo ropinirole from the Sample solution. [NOTE—The relative retention times for ropinirole and 3-oxo ropinirole are 1.0 and 1.21, respectively.]

\(r_i\) = peak response of ropinirole from the Standard solution

\(C_i\) = concentration of USP Ropinirole Hydrochloride RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of ropinirole \((C_{16}H_{24}N_2O)\) dissolved at each time point \((i)\):

\[
\text{Result} = C_i \times \left(\frac{L}{M_i/M_0}\right) \times 100
\]

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 25</td>
</tr>
<tr>
<td>2</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>65–85</td>
</tr>
<tr>
<td>4</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of ropinirole \((C_{16}H_{24}N_2O)\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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

### Impurities

#### Organic Impurities
Solution A: 0.05% (v/v) trifluoroacetic acid in water
Solution B: Acetonitrile and methanol (80:20)
Mobile phase: See Table 4.

#### Change to read:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>23</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>36</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>36.1</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>50</td>
<td>84</td>
<td>16</td>
</tr>
</tbody>
</table>

Diluent 1: Acetonitrile and Solution A (80:20)
Diluent 2: Diluent 1 and Solution A (20:80)

System suitability solution: 0.03 mg/mL of USP Ropinirole Hydrochloride RS and 0.001 mg/mL of USP Ropinirole Related Compound B RS in Diluent 2. Sensitivity may be used to aid dissolution.

Sensitivity solution: 0.015 µg/mL of USP Ropinirole Hydrochloride RS in Diluent 2

Standard solution: 0.15 µg/mL of USP Ropinirole Related Compound B RS in Diluent 2

Sample stock solution: Nominally 0.13–0.14 mg/mL of ropinirole from a suitable number of Tablets containing 20–50 mg of ropinirole prepared as follows. Homogenize an appropriate number of Tablets in a suitable volume of Diluent 1. Pass a portion of the solution through a syringe filter of 0.45-µm pore size and use the filtrate.

Sample solution: Nominally 26–28 µg/mL of ropinirole from the Sample stock solution and Solution A

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm \(\times\) 25-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1 mL/min
Injection volume: 100 µL

System suitability
Samples: System suitability solution, Sensitivity solution, and Standard solution

Suitability requirements
Resolution: NLT 2.0 between ropinirole related compound B and ropinirole, System suitability solution

Relative standard deviation: NMT 10% for ropinirole related compound B, Standard solution

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Signal-to-noise ratio:  NLT 10 for ropinirole, Sensitivity solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of ropinirole related compound B in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_u}{r_S} \right) \times \left( \frac{C_u}{C_S} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100
\]

where:
- \( r_u \) = peak response of ropinirole related compound B from the Sample solution
- \( r_S \) = peak response of ropinirole related compound B from the Standard solution
- \( C_u \) = concentration of USP Ropinirole Related Compound B RS in the Standard solution (µg/mL)
- \( C_S \) = nominal concentration of ropinirole in the Sample solution (µg/mL) (E81.1-Apr-2017)
- \( M_{r1} \) = molecular weight of ropinirole related compound B free base, 274.36
- \( M_{r2} \) = molecular weight of ropinirole related compound B′ hydrochloride, 310.82

Calculate the percentage of each degradation product in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_u}{F} \right) / \left( \Sigma \left( \frac{r_u}{F} \right) + r_R \right) \times 100
\]

where:
- \( F \) = relative response factor for the corresponding degradation product from Table 5
- \( r_u \) = peak response of ropinirole from the Sample solution
- \( r_R \) = peak response of ropinirole from the Sample solution

Acceptance criteria: See Table 5. Disregard peaks less than 0.05%.

### Table 5 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ropinirole N-hydroxymethyl(^a)</td>
<td>0.94</td>
<td>0.71</td>
<td>0.5</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ropinirole N-oxide(^c)</td>
<td>1.31</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Ropinirole methylene dimer(^e)</td>
<td>1.82</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Propyldiene ropinirole(^f)</td>
<td>1.96</td>
<td>2.0</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) 4-(2-(Propylamino)ethyl)indoline-2,3-dione
\(^b\) 4-(2-(Dipropylamino)ethyl)-1-(hydroxymethyl)indol-2-one
\(^c\) N-[2-(2-Oxindol-4-yl)ethyl]-N-propylpropan-1-amine oxide
\(^d\) 4-[2-(Dipropylamino)ethyl]-3-[2-(2-(dipropylamino)ethyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]methyl]-2,3-dihydro-1H-indol-2-one
\(^e\) (Z)-4-[2-(Dipropylamino)ethyl]-3-propylideneindolin-2-one
\(^f\) Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

### Add the following:

- **LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used. (E81.1-Nov-2017)
- **USP Reference Standards (11)**
  - USP Ropinirole Hydrochloride RS
  - USP Ropinirole Related Compound B RS
  - 4-(2-(Dipropylamino)ethyl)indoline-2,3-dione hydrochloride.

\( C_{18}H_{23}N_2O_2 \cdot HCl \) 310.82

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