Donepezil Hydrochloride Tablets

**Type of Posting**  
Revision Bulletin

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27–Jan–2017

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01–Feb–2017

**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 Donepezil Hydrochloride Tablets monograph. The purpose for the revision is to:

- Add two dissolution tests for approved products with dissolution conditions and tolerances that are different from the existing test for dissolution
- Revise the relative response factors for donepezil quaternary salt, donepezil indene analog, deoxydonepezil in *Organic Impurities, Procedure 2.*
- Widen the limit for total degradation products in *Organic Impurities, Procedure 2.*

*Dissolution Test 2* was validated using an Inertsil ODS-3V brand of L1 column. The typical retention time for donepezil is about 5.5 min.

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

The Donepezil Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *Second Supplement to USP 40–NF 35.*

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (301–998–6792 or hrj@usp.org).
Donepezil Hydrochloride Tablets

DEFINITION
Donepezil Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of donepezil hydrochloride (C_{24}H_{29}NO_{3} \cdot HCl).

IDENTIFICATION

• A. ULTRAVIOLET ABSORPTION (197U)

Wavelength range: 220–360 nm

Sample solution: Crush a suitable number of Tablets, and transfer an amount of powder, equivalent to 10 mg of donepezil hydrochloride, to a 100-mL volumetric flask. Add 80 mL of 0.1 N hydrochloric acid, and sonicate for 5 min. Cool the solution to room temperature, and dilute with 0.1 N hydrochloric acid to volume. Transfer a portion of this solution to a centrifuge tube, and centrifuge for 15 min. Transfer 5 mL of the clear supernatant to a 25-mL volumetric flask, and dilute with 0.1 N hydrochloric acid to volume.

Analysis: Using a 1-cm cell, record the UV spectrum of donepezil hydrochloride (C_{24}H_{29}NO_{3} \cdot HCl) in the prescribed wavelength range. 

• 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

Change to read:

• PROCEDURE

Diluent: Methanol and 0.1 N hydrochloric acid (75:25) (88.1-Feb-2017)

Mobile phase: Dissolve 2.5 g of sodium 1-decanesulfonate (88.1-Feb-2017) in 650 mL of water, and add 1.0 mL of perchloric acid and 350 mL of acetonitrile. If necessary, adjust with an additional 0.5 mL of perchloric acid to a pH of about 1.8.

System suitability solution: 0.2 mg/mL of USP Donepezil Hydrochloride RS and 0.008 mg/mL of USP Donepezil Related Compound A RS. (Note—Dissolve in 40% of the flask volume of methanol, swirl, and dilute with water to volume.)

Standard solution: 0.4 mg/mL of USP Donepezil Hydrochloride RS in Diluent. [Note—Dissolve in 60% of the flask volume of Diluent, swirl, and dilute with Diluent to volume.]

Sample solution: Nominally 0.4 mg/mL of donepezil hydrochloride prepared as follows. Dissolve a suitable number of Tablets in 75% of the flask volume of Diluent, and sonicate in an ultrasonic bath for 20 min. Swirl the mixture for 30 s, allow to cool to room temperature, and dilute with Diluent to volume. [Note—if necessary, add a magnetic stirring bar to the flask, and mix for 10 min on the magnetic stirrer, to aid in dissolution.] Allow a few min for the solids to settle. Pass through a suitable filter, discarding the first 2–3 mL of the filtrate.

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

Mode: LC
Detector: UV 271 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1.4 mL/min
Injection Volume: 20 µL

System suitability

Samples: System suitability solution and Standard solution
[Note—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]

Suitability requirements
Resolution: NLT 1.5 between donepezil related compound A and donepezil, System suitability solution
Tailing factor: NMT 1.5 for the donepezil peak, System suitability solution
Relative standard deviation: NMT 2.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of donepezil hydrochloride (C_{24}H_{29}NO_{3} \cdot HCl) in the portion of Tablets taken:

Result = \left(\frac{r_S}{r_U}\right) \times \left(\frac{C_S}{C_U}\right) \times 100

where:

\begin{align*}
 r_U & = \text{peak response of donepezil hydrochloride from the Sample solution} \\
 r_S & = \text{peak response of donepezil hydrochloride from the Standard solution} \\
 C_S & = \text{concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)} \\
 C_U & = \text{nominal concentration of donepezil hydrochloride in the Sample solution (mg/mL)}
\end{align*}

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)

Test 1 (88.1-Feb-2017)

Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 30 min

Analytical procedure: Determine the amount of donepezil hydrochloride (C_{24}H_{29}NO_{3} \cdot HCl) dissolved, by using one of the following methods.

Chromatographic method

Diluent: Methanol and 0.1 N hydrochloric acid (75:25) (88.1-Feb-2017)

Mobile phase: Acetonitrile, water, and perchloric acid (35:65:0.1)

Standard stock solution A: 1.1 mg/mL of USP Donepezil Hydrochloride RS in Diluent

Standard stock solution B: 0.11 mg/mL of USP Donepezil Hydrochloride RS from Standard stock solution A in Medium

Standard stock solution: (L/1000) mg/mL of USP Donepezil Hydrochloride RS from Standard stock solution B in Medium, where L is the label claim in mg/Tablet (88.1-Feb-2017)
Donepezil

**Sample solution**: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first few mL of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode**: LC

**Detector**: UV 271 nm

**Column**: 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature**: 35°

**Flow rate**: 1.0 mL/min

**Injection volume**: (88.3-Feb-2017) 50 µL

**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 donepezil hydrochloride \((C_{24}H_{29}NO_3 \cdot HCl)\) dissolved:

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

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_i\) = concentration of the Standard solution (mg/mL)
- \(L\) = label claim (mg/Tablet)
- \(V\) = volume of Medium, 900 mL

**Spectrometric method**

**Standard stock solution**: 0.11 mg/mL of USP Donepezil Hydrochloride RS in water

**Standard solution**: (L/900) mg/mL of USP Donepezil Hydrochloride RS from the Standard stock solution 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 0.45-µm pore size.

**Instrumental conditions**

(See Ultraviolet-Visible Spectroscopy (857).)

**Mode**: UV

**Analytical wavelength**: 230 nm

**Blank**: Medium

Calculate the percentage of the labeled amount of donepezil hydrochloride \((C_{24}H_{29}NO_3 \cdot HCl)\) dissolved:

\[
\text{Result} = \left(\frac{A_U}{A_S}\right) \times \left(\frac{C_i}{L}\right) \times V \times 100
\]

- \(A_U\) = absorbance of the Sample solution
- \(A_S\) = absorbance of the Standard solution
- \(C_i\) = concentration of 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 donepezil hydrochloride is dissolved.

**For Tablets which contain 23 mg of donepezil hydrochloride**

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

**Medium**: pH 6.8 phosphate buffer, 900 mL

**Apparatus 2**: 50 rpm

**Times**: 1, 3, and 8 h

**Buffer**: 5.0 g/L of monobasic ammonium phosphate in water adjusted with phosphoric acid to a pH of 2.3

**Mobile phase**: Acetonitrile and Buffer (25:75)

**Standard stock solution**: 0.26 mg/mL of USP Donepezil Hydrochloride RS prepared as follows. Transfer a suitable quantity of USP Donepezil Hydrochloride RS to an appropriate volumetric flask. Add 70% of the flask volume of Medium. Sonicate to dissolve and dilute with Medium to volume.

**Standard solution**: (L/900) mg/mL of USP Donepezil Hydrochloride RS from Standard stock solution in Medium, where \(L\) is the label claim in mg/Tablet. Pass the solution through a suitable filter, discarding the first 3 mL of the filtrate.

**Sample solution**: Pass a portion of the solution under test through a suitable filter, discarding the first 3 mL of the filtrate.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode**: LC

**Detector**: UV 210 nm

**Column**: 4.6-mm × 15-cm; 5-µm packing L1

**Column temperature**: 35°

**Flow rate**: 1.5 mL/min

**Injection volume**: 50 µL

**Run time**: NLT 1.7 times the retention time of donepezil

**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 donepezil hydrochloride \((C_{24}H_{29}NO_3 \cdot HCl)\) in the sample withdrawn from the vessel at each time point (\(t\)):

\[
\text{Result} = \left(\frac{r_u}{r_s}\right) \times C_i
\]

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_i\) = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride \((C_{24}H_{29}NO_3 \cdot HCl)\) dissolved at each time point (\(t\)):

\[
\text{Result}_1 = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = \left(\frac{[C_i \times (V - V_S)] + [C_i \times V_S]}{V} \right) \times (1/L) \times 100
\]

\[
\text{Result}_3 = \left(\frac{[C_i \times (V - (2 \times V_S))] + [(C_i + C_i) \times V_S]}{V} \right) \times (1/L) \times 100
\]

- \(C_i\) = concentration of donepezil hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Tablet)
- \(V_S\) = volume of the Sample solution withdrawn at each time point (mL)

**Tolerances**: See Table 1.
Donepezil

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (b)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>35–60</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of donepezil hydrochloride (C$_{24}$H$_{29}$NO$_{3}$ · HCl) 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.

**Medium:** pH 6.8 phosphate buffer; 900 mL hydrochloride (C$_{24}$H$_{29}$NO$_{3}$ · HCl) dissolved at the time point (mL).

**Times:** 1, 3, and 10 h

**Standard stock solution:** 0.25 mg/mL of USP Donepezil Hydrochloride RS prepared as follows:

Transfer a suitable quantity of USP Donepezil Hydrochloride RS to an appropriate volumetric flask. Add 70% of the flask volume of water. Sonicate to dissolve and allow to cool to room temperature. Dilute with water to volume.

**Standard solution:** (1/900) mg/mL of USP Donepezil Hydrochloride RS from Standard stock solution 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.

**Instrumental conditions**

(See Ultraviolet-Visible Spectroscopy (857).)

**Mode:** UV-Vis

**Analytical wavelength:** 315 nm

**Blank:** Medium

**System suitability**

Sample: Standard solution

Suitability requirements

Relative standard deviation: NMT 2.0%

**Analysis**

Samples: Standard solution and Sample solution

Calculate the concentration (C) of donepezil hydrochloride (C$_{24}$H$_{29}$NO$_{3}$ · HCl) in the sample withdrawn from the vessel at each time point (i):

$$\text{Result}, = (A_i / A_S) \times C_S$$

$A_i$ = absorbance of donepezil from the Sample solution

$A_S$ = absorbance of donepezil from the Standard solution

$C_S$ = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of donepezil hydrochloride (C$_{24}$H$_{29}$NO$_{3}$ · HCl) dissolved at each time point (i):

$$\text{Result}, = C_i \times V \times (1/L) \times 100$$

$C_i$ = concentration of donepezil hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)

$V$ = volume of Medium, 900 mL

**Tolerances:** See Table 2.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (b)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>33–53</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of donepezil hydrochloride (C$_{24}$H$_{29}$NO$_{3}$ · HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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

**Impurities**

Change to read:

- **Organic Impurities, Procedure 1**

[NOTE—On the basis of the synthetic route, perform either Procedure 1 or Procedure 2. Procedure 2 is recommended if any of the impurities included in Table 3 are potential degradation products.]

**Diluent, Mobile phase, System suitability solution, Sample solution, and Chromatographic system:**

Proceed as directed in the Assay.

**Standard solution:** 0.0008 mg/mL of USP Donepezil Hydrochloride RS in Diluent

**System suitability**

Samples: System suitability solution and Standard solution

[NOTE—The relative retention times for donepezil related compound A and donepezil are about 0.92 and 1.0, respectively.]

**Suitability requirements**

Resolution: NLT 1.5 between donepezil related compound A and donepezil, System suitability solution

Relative standard deviation: NMT 8.0%, Standard solution

**Analysis**

Samples: Standard solution and Sample solution

[NOTE—Identify the impurities using the relative retention times given in Table 3.]

Calculate the percentage of any individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_i/r_S) \times (C_S/C_I) \times (1/L) \times 100$$

$C_I$ = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)

$C_S$ = nominal concentration of donepezil hydrochloride in the Sample solution (mg/mL)

$F$ = relative response factor (see Table 3)

Acceptance criteria: See Table 3.
4 Donepezil

**Table 3** (RB 1-Feb-2017)

<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>Desbenzyl donepezil</td>
<td>0.33</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Donepezil open ring</td>
<td>0.70</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Donepezil N-oxide</td>
<td>1.2</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>—</td>
<td>0.2</td>
</tr>
</tbody>
</table>

\*5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
\*2-(3-(1-Benzylpiperidin-4-yl)-2-oxopropyl)-4,5-dimethoxybenzoic acid.
\*2-{(1-Benzylpiperidin-4-yl)methyl}-5,6-dimethoxyindan-1-one N-oxide.

**Table 4** (RB 1-Feb-2017)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>40</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>41</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>50</td>
<td>75</td>
<td>25</td>
</tr>
</tbody>
</table>

Standard solution: 0.01 mg/mL of USP Donepezil Hydrochloride RS in Diluent. Sonication may be used to aid the dissolution.

Sample solution: Nominally 1.0 mg/mL of donepezil hydrochloride in Diluent. Sonication may be used to aid the dissolution.

**Organic Impurities, Procedure 2**

Diluent: Acetonitrile and water (25:75)

Solution A: Add 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 6.5. Pass through a filter of 0.45-µm or finer pore size.

Solution B: Acetonitrile

Mobile phase: See Table 4.

**Table 5** (RB 1-Feb-2017)

<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>Desbenzyl donepezil</td>
<td>0.23</td>
<td>1.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezil pyridine analog</td>
<td>0.49</td>
<td>1.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezil quaternary salt</td>
<td>0.68</td>
<td>0.74</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>1.0</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Donepezil indene analog</td>
<td>1.7</td>
<td>2.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Deoxydonepezil</td>
<td>2.1</td>
<td>1.3</td>
<td>0.15</td>
</tr>
<tr>
<td>Any individual degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**ADDITIONAL REQUIREMENTS**

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

**Change to read:**

- **Labeling:** If a test for Organic Impurities other than Procedure 1 is used, the labeling states the test with which the article complies. If a test for Dissolution other than Test 1 is used, the labeling states the test with which the article complies.
- **USP Reference Standards (11)**
  - USP Donepezil Hydrochloride RS
  - USP Donepezil Related Compound A RS
  - (5)-2-{(1-Benzylpiperidin-4-yl)methylene}-5,6-dimethoxyindan-1-one.
  - C₂₄H₂₇NO₃ 377.48

\( r_U \) = peak response of each individual impurity from the Sample solution
\( r_S \) = peak response of donepezil hydrochloride from the Standard solution
\( C_S \) = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)
\( C_U \) = nominal concentration of donepezil hydrochloride in the Sample solution (mg/mL)
\( F \) = relative response factor for the corresponding impurity peak from Table 5

Acceptance criteria: See Table 5.