Donepezil Hydrochloride contains NLT 98.0% and NMT 102.0% of C24H29NO3 · HCl, calculated on the anhydrous basis.

**DEFINITION**
Donepezil Hydrochloride contains NLT 98.0% and NMT 102.0% of C24H29NO3 · HCl, calculated on the anhydrous basis.

**IDENTIFICATION**

**Change to read:**

### A. INFRARED ABSORPTION (197K)

**NOTE—**If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the USP Donepezil Hydrochloride RS separately in dichloromethane, evaporate to dryness, and record new spectra using the residues.

### B. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

### C. IDENTIFICATION TESTS—GENERAL, Chloride (191)

Sample solution: 10 mg/mL

Acceptance criteria: Meets the requirements

**ASSAY**

**PROCEDURE**

Buffer: 3.9 g/L of sodium 1-decane sulfonate in water

Mobile phase: Acetonitrile and Buffer (35:65). Adjust with perchloric acid to a pH of 1.8.

**System suitability solution:** 0.4 mg/mL of USP Donepezil Hydrochloride RS and 0.016 mg/mL of USP Donepezil Related Compound A RS prepared as follows: Dissolve suitable quantities of USP Donepezil Hydrochloride RS and USP Donepezil Related Compound A RS using 40% of the flask volume of methanol, and dilute with water to volume.

**Standard solution:** 0.4 mg/mL of USP Donepezil Hydrochloride RS in Mobile phase

**Sample solution:** 0.4 mg/mL of Donepezil Hydrochloride in Mobile phase

**Chromatographic system**

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 271 nm

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

Flow rate: 1.4 mL/min

Injection size: 20 µL

**System suitability**

Samples: System suitability solution and Standard solution

[NOTE—Refer to Table 1 under Organic Impurities, Procedure 1 for relative retention times.]

Suitability requirements

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

Relative standard deviation: NMT 2.0%, Standard solution

**Analysis**

Samples: Standard solution and Sample solution

Calculate the percentage of donepezil hydrochloride (C24H29NO3 · HCl) in the portion of sample taken:

\[
\text{Result} = \left( \frac{r_1}{r_0} \right) \times \left( \frac{C_2}{C_1} \right) \times 100
\]

\(r_0\) = peak response of donepezil hydrochloride from the Sample solution

\(r_1\) = peak response of donepezil hydrochloride from the Standard solution

\(C_1\) = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)

\(C_2\) = concentration of Donepezil Hydrochloride in the Sample solution (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

**IMPURITIES**

- **HEAVY METALS, Method II (231):** NMT 20 ppm
- **RESIDUE ON IGNITION (281):** NMT 0.1%

**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 related compounds.]

**Mobile phase, System suitability solution, Sample solution, and Chromatographic system:** Proceed as directed in the Assay.

**Standard solution:** 0.8 µg/mL of USP Donepezil Hydrochloride RS in Mobile phase

**System suitability**

Samples: System suitability solution and Standard solution

[NOTE—Refer to Table 1 for relative retention times.]

**Suitability requirements**

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

Relative standard deviation: NMT 5.0%, Standard solution

**Analysis**

Samples: Standard solution and Sample solution

Calculate the percentage of any individual impurity in the portion of Donepezil Hydrochloride taken:

\[
\text{Result} = \left( \frac{r_1}{r_0} \right) \times \left( \frac{C_2}{C_1} \right) \times 100
\]

\(r_0\) = peak response of any individual impurity from the Sample solution

\(r_1\) = peak response of any individual impurity from the Standard solution

\(C_1\) = concentration of USP Donepezil Hydrochloride RS in the Standard solution (mg/mL)

\(C_2\) = concentration of Donepezil Hydrochloride in the Sample solution (mg/mL)

Acceptance criteria: See Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desbenzyl donepezil©</td>
<td>0.33</td>
<td>0.2</td>
</tr>
<tr>
<td>Hydroxydonepezil©</td>
<td>0.54</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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Table 1 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil related compound A</td>
<td>0.92</td>
<td>0.1</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
  2-{[1-Benzylpiperidin-4-yl](hydroxy)methyl]-5,6-dimethoxyindan-1-one.
  (E)-2-{[1-Benzylpiperidin-4-yl]methylene}-5,6-dimethoxyindan-1-one.

Add the following:

**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 2.

Table 2

<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: 1.0 mg/mL of Donepezil Hydrochloride in Diluent. Sonication may be used to aid the dissolution.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 286 nm

**Column:** 4.6-mm x 25-cm; 5-µm packing L1

**Column temperature:** 50 °C

**Flow rate:** 1.5 mL/min

**Injection size:** 20 µL

**System suitability**

Sample: Standard solution

Suitability requirements

- Column efficiency: NLT 40,000 theoretical plates
- Tailing factor: NMT 1.5
- Relative standard deviation: NMT 2.0%, for five replicate injections

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of any individual impurity in the portion of Donepezil Hydrochloride taken:

\[
\text{Result} = \left( \frac{r_i}{r_S} \right) \times \left( \frac{C_i}{C_S} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \(r_i\) = peak response of any individual impurity from the Sample solution
- \(r_S\) = peak response of donepezil hydrochloride from the Standard solution

Acceptance criteria: See Table 3.

Table 3

<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 donepezila</td>
<td>0.23</td>
<td>1.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezil pyridine analog (DPMI)°</td>
<td>0.49</td>
<td>1.9</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezilbenzyl bromide°</td>
<td>0.68</td>
<td>0.73</td>
<td>0.15</td>
</tr>
<tr>
<td>Donepezil hydrochloride°</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Dehydrodonepezila°</td>
<td>1.72</td>
<td>2.0</td>
<td>0.15</td>
</tr>
<tr>
<td>Deoxynonepezila°</td>
<td>2.12</td>
<td>0.67</td>
<td>0.15</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Relative retention times are based on 1 mL gradient delay volume.

- 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
- 5,6-Dimethoxy-2-(pyridin-4-ylmethyl)indan-1-one.
- 1,1-Dibenzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidinium.
- 1-Benzyl-4-[(5,6-dimethoxyinden-2-yl)methyl]piperidine.
- 1-Benzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidine.

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