Donepezil Hydrochloride

\[
\text{C}_{24}\text{H}_{29}\text{NO}_3 \cdot \text{HCl} \quad 415.95
\]

(t)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride [120011-70-3].

**DEFINITION**

Donepezil Hydrochloride contains NLT 98.0% and NMT 102.0% of \(\text{C}_{24}\text{H}_{29}\text{NO}_3 \cdot \text{HCl}\), 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.] (RB 1-May-2011)
  - **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)**

**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
- **Column temperature:** 35°
- **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 the 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 \(\text{C}_{24}\text{H}_{29}\text{NO}_3 \cdot \text{HCl}\) in the portion of sample taken:
  
  \[
  \text{Result} = \left( \frac{r_i}{r_s} \right) \times \left( \frac{C_i}{C_s} \right) \times 100
  \]

**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, per form either Procedure 1 or Procedure 2. Procedure 2 is recommended if any of the impurities included in Table 3 are potential related compounds.] (RB 1-May-2011)

**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 the relative retention times.]

**Suitability requirements**

- **Resolution:** NLT 1.5 between donepezil related compound A and donepezil, System suitability solution
- **Relative standard deviation:** NLT 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:
    
    \[
    \text{Result} = \left( \frac{r_i}{r_s} \right) \times \left( \frac{C_i}{C_s} \right) \times 100
    \]

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desbenzyl donepezil (^a)</td>
<td>0.33</td>
<td>0.2</td>
</tr>
<tr>
<td>Hydroxydonepezil (^b)</td>
<td>0.54</td>
<td>0.2</td>
</tr>
<tr>
<td>Donepezil related compound A (^c)</td>
<td>0.92</td>
<td>0.1</td>
</tr>
<tr>
<td>Donepezil hydrochloride</td>
<td>1.0</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.

\(^b\) 2-[1-Benzylpiperidin-4-yl](hydroxy)methyl]-5,6-dimethoxyindan-1-one.

\(^c\) (E)-2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one.
Table 1 (Continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<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.

Acceptance criteria: See Table 3.

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 × 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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times (1/F) \times 100
\]

\(r_U\) = peak response of any 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)
\(C_U\) = concentration of Donepezil Hydrochloride in the Sample solution (mg/mL)
\(F\) = relative response factor for the corresponding impurity peak from Table 3

Donepezil Hydrochloride Tablets

DEFINITION

Donepezil Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% of the labeled amount of donepezil hydrochloride (C24H29NO3 · 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

SPECIFIC TESTS

Change to read:

• WATER DETERMINATION, Method la (921): NMT 0.4% for the anhydrous form; NMT 7.0% for the monohydrate form.

ADDITIONAL REQUIREMENTS

• PACKAGING AND STORAGE: Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

• LABELING: Label to indicate whether it is the monohydrate form. If a test for Organic Impurities other than Procedure 1 is used, the labeling states the test with which the article complies.

Change to read:

• USP REFERENCE STANDARDS (11)
USP Donepezil Hydrochloride RS
USP Donepezil Related Compound A RS
*(E)-2-[(1-Benzylpiperidin-4-yl)methylene]-5,6-dimethoxyindan-1-one.
C24H27NO3 377.48

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