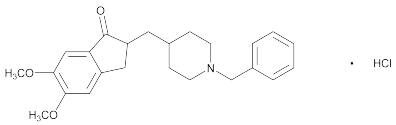
Donepezil Hydrochloride



$C_{24}H_{29}NO_3 \cdot HCl$ 415.95

(±)-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 $C_{24}H_{29}NO_3 \cdot HCl$, 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**⟩
  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
  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 ($C_{24}H_{29}NO_3 \cdot HCl$) in the portion of sample taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of donepezil hydrochloride 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)

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, 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.33	0.2
Hydroxydonepezil[b]	0.54	0.2
Donepezil related compound A[c]	0.92	0.1
Donepezil hydrochloride	1.0	—

[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)methylene]-5,6-dimethoxyindan-1-one.

Table 1 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any individual unspecified impurity	—	0.1
Total impurities	—	1.0

[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)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

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	40	60
40	40	60
41	75	25
50	75	25

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°
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 per centage of any individual impurity in the portion of Donepezil Hydrochloride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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*

Acceptance criteria: See *Table 3*.

Table 3

Name	Relative Retention Time*	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.23	1.5	0.15
Donepezil pyridine analog (DPMI)[b]	0.49	1.9	0.15
Donepezilbenzyl bromide[c]	0.68	0.73	0.15
Donepezil hydrochloride	1.0	1.0	—
Dehydrodeoxy donepezil[d]	1.72	2.0	0.15
Deoxydonepezil[e]	2.12	0.67	0.15
Any individual unspecified impurity	—	1.0	0.1
Total impurities	—	—	0.5

* Relative retention times are based on 1-mL gradient delay volume.
[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
[b] 5,6-Dimethoxy-2-(pyridin-4-ylmethyl)indan-1-one.
[c] 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidinium.
[d] 1-Benzyl-4-[(5,6-dimethoxyinden-2-yl)methyl]piperidine.
[e] 1-Benzyl-4-[(5,6-dimethoxyindan-2-yl)methyl]piperidine.

● (RB 1-May-2011)

SPECIFIC TESTS

Change to read:

• **WATER DETERMINATION,** *Method Ia* ⟨**921**⟩**:** NMT 0.4% •for the anhydrous form; NMT 7.0% for the monohydrate form ●(RB 1-May-2011)

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.● (RB 1-May-2011)

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.●(RB 1-May-2011)
$C_{24}H_{27}NO_3$ 377.48

Donepezil Hydrochloride Tablets

DEFINITION
Donepezil Hydrochloride Tablets contain NLT 93.0% and NMT 107.0% 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 T ablets, and transfer an amount of powder, equivalent to 10 mg of