Donepezil Hydrochloride Tablets

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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 *Dissolution Test 4* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using an ACE C8 brand of L7 column. The typical retention time for donepezil is about 3 min.

Existing references to reagents were updated for consistency with the reagent entry names. For additional information about reagent cross references, please see the related Compendial Notice. The revision also necessitates a change in the table numbering in the tests for *Organic Impurities, Procedure 1* and *Organic Impurities, Procedure 2.*

The Donepezil Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, 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

Change to read:

- **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 VS,▲ (RB 1-Mar-2019) and sonicate for 5 min. Cool the solution to room temperature, and dilute with ▲0.1 N hydrochloric acid VS▲ (RB 1-Mar-2019) 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 VS▲ (RB 1-Mar-2019) to volume.
  Analysis: Using a 1-cm cell, record the UV spectrum of the *Sample solution*.
  Acceptance criteria: The solution exhibits absorption maxima at 230, 271, and 315 nm.
- **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 VS▲ (RB 1-Mar-2019) (75:25)
  Mobile phase: Dissolve 2.5 g of sodium 1-decanesulfonate 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 × 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:

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩
  Test 1
  Medium: ▲0.1 N hydrochloric acid VS;▲ (RB 1-Mar-2019) 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 VS▲ (RB 1-Mar-2019) (75:25)
  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 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
  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: 50 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Column efficiency: NLT 5000 theoretical plates
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:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = 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:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = 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_i) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of donepezil from the *Sample solution*
r_S = peak response 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 ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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*.

Table 1

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	3	35–60
3	8	NLT 80

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) 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

Apparatus 2: 50 rpm
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: (*L*/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_i) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = (A_U/A_S) \times C_S$$

A_U = 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 ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–30
2	3	33–53
3	10	NLT 80

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 4:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: 0.05 M sodium phosphate buffer, pH 6.8 [0.1 N hydrochloric acid VS and 76 g/L of tribasic sodium phosphate (25:75) adjusted with 2 N hydrochloric acid TS or 2 N sodium hydroxide TS to a pH of 6.8]; 900 mL, degassed
Apparatus 2: 50 rpm, with sinkers; see *Dissolution* ⟨711⟩, *Figure 2a*.
Times: 1, 3, and 8 h
Buffer: 1.36 g/L of monobasic potassium phosphate prepared as follows. To each 1 L of 1.36 g/L of monobasic potassium phosphate in water, add 3 mL of triethylamine and adjust with phosphoric acid to a pH of 2.8.
Mobile phase: Methanol and *Buffer* (47:53)
Diluent: Methanol and water (50:50)
Standard stock solution: 0.53 mg/mL of USP Donepezil Hydrochloride RS in *Diluent*
Standard solution: 0.027 mg/mL of USP Donepezil Hydrochloride RS from *Standard stock solution* in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter. Replace the portion removed with the same volume of *Medium*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 268 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1.3 mL/min
Injection volume: 20 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 1.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the concentration (C_i) of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of donepezil from the *Sample solution*
r_S = peak response 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 ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	10–30
2	3	40–60
3	8	NLT 80

The percentages of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.▲ (RB 1-Mar-2019)

• **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 6*▲ (RB 1-Mar-2019) 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:

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

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 (see ▲*Table 4*)▲ (RB 1-Mar-2019)

Acceptance criteria: See ▲*Table 4*.

Table 4▲ (RB 1-Mar-2019)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[a]	0.33	1.0	0.5
Donepezil open ring[b]	0.70	0.6	0.5
Donepezil hydrochloride	1.0	—	—
Donepezil *N*-oxide[c]	1.2	1.0	0.5
Any individual unspecified degradation product	—	—	0.2

[a] 5,6-Dimethoxy-2-(piperidin-4-ylmethyl)indan-1-one.
[b] 2-(3-(1-Benzylpiperidin-4-yl)-2-oxopropyl)-4,5-dimethoxybenzoic acid.
[c] 2-[(1-Benzylpiperidin-4-yl)methyl]-5,6-dimethoxyindan-1-one *N*-oxide.

Change to read:

• **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 5*.

Table 5▲ (RB 1-Mar-2019)

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: Nominally 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 volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
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 each specified impurity or any individual degradation product in the portion of Tablets taken:

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

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 6*▲ (RB 1-Mar-2019)

Acceptance criteria: See ▲*Table 6*.

Table 6▲ (RB 1-Mar-2019)

Name	Relative Retention Time[a]	Relative Response Factor	Acceptance Criteria, NMT (%)
Desbenzyl donepezil[b]	0.23	1.5	0.15
Donepezil pyridine analog[c]	0.49	1.9	0.15
Donepezil quaternary salt[d]	0.68	0.74	0.15
Donepezil hydrochloride	1.0	1.0	—
Donepezil indene analog[e]	1.7	2.2	0.15
Deoxydonepezil[f]	2.1	1.3	0.15
Any individual degradation product	—	1.0	0.1
Total degradation products	—	—	1.0

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

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **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
  (*E*)-2-[(1-Benzylpiperidin-4-yl)methylene]-5,6-dimethoxyindan-1-one.
  $C_{24}H_{27}NO_3$ 377.48