

BRIEFING

**Donepezil Hydrochloride.** This monograph was posted on the USP Website as a draft USP Pending Standard for public comment. The MD-PP Expert Committee has reviewed all comments that were received and has approved the monograph as an Authorized USP Pending Standard. The following is a summary of the comments received and the Expert Committee's responses.

**Comment 1:** The molecular weight of the drug substance may not be correct. Upon checking the *USP Dictionary*, it became obvious that the molecular weight must be revised to 415.95. The commenter also pointed out that there may be errors in the chemical names in the table of impurities.

*Response:* Comments incorporated.

**Comment 2:** In the IR *Identification* test, there is evidence of polymorphism that may require the inclusion of a specific sample preparation.

*Response:* Comment not incorporated at this time due to lack of sufficient supporting data.

**Comment 3:** Request the inclusion of a test for particle size.

*Response:* Comment not incorporated because this requirement is more relevant for dosage form manufacturing.

**Comment 4:** In the test for *Related compounds*, request the replacement of the proposed gradient elution method with an isocratic HPLC method.

*Response:* Comment not incorporated due to lack of sufficient supporting documentation.

**Comment 5:** Request a requirement of 8.1% to 8.9% for the test for chloride content by silver nitrate.

*Response:* Comment not incorporated because the chloride range will be in conflict with the range of 98.0% to 102.0% given in the Definition.

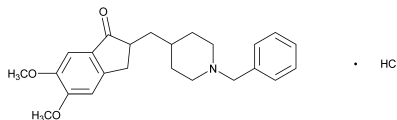
The gradient elution HPLC method for the test for *Related compounds* is based on analyses performed using the Kromasil C-18 brand of L1 column with a retention time between 12.5 and 15.5 minutes for the donepezil peak, depending on the gradient delay volume. The isocratic HPLC method for the *Assay* is based on analyses performed using the Kromasil C-18 brand of L1 column with a retention time of about 11.5 minutes for donepezil.

(MD-PP: R. Ravichandran) RTS—C41435

**Add the following:**

■ **Donepezil Hydrochloride**

v. 1 Authorized January 28, 2008



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

(±)-2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone hydrochloride [142057-77-0].

» Donepezil Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of  $C_{24}H_{29}NO_3 \cdot HCl$ , calculated on the anhydrous basis.

**Packaging and storage**—Preserve in well-closed containers. Store at room temperature.

**USP Reference standards** (11)—*USP Donepezil Hydrochloride RS*.

**Identification**—

**A:** *Infrared Absorption* (197K).

**B:** The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay*.

**C:** A solution (1 in 100) meets the requirements of the silver nitrate precipitate test for *Chloride* (191).

**Water, Method I** (921): 4.0% to 7.0%.

**Residue on ignition** (281): not more than 0.1%.

**Heavy metals, Method II** (231): not more than 20 ppm.

**Related compounds**—

**Diluent**—Prepare a suitable quantity of a mixture of water and acetonitrile (3 : 1). Mix and degas.

**Solution A**—Add about 1 mL of phosphoric acid in 1 L of water, and mix. Adjust the pH of this solution to 6.5 with triethylamine. Pass through a filter having a 0.45- $\mu$ m or finer porosity.

**Solution B:** acetonitrile.

**Mobile phase**—Use variable mixtures of *Solution A* and *Solution B* as directed under *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* (621)).

**Standard solution**—Transfer an accurately weighed quantity of USP Donepezil Hydrochloride RS to a suitable volumetric flask to obtain a solution having a known concentration of 1 mg per mL of donepezil hydrochloride. Add 40% of the flask volume of *Diluent* to the flask, sonicate to dissolve, and dilute with *Diluent* to volume. Dilute,

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quantitatively, a suitable volume of the resulting solution, successively if necessary, with *Diluent* to obtain a final solution having a known concentration of about 0.01 mg per mL of donepezil hydrochloride.

*Test solution*—Transfer an accurately weighed quantity of Donepezil Hydrochloride to a suitable volumetric flask to obtain a solution having a known concentration of 1 mg per mL of donepezil hydrochloride. Add 40% of the flask volume of *Diluent* to the flask, sonicate to dissolve, and dilute with *Diluent* to volume.

*Chromatographic system* (see *Chromatography* <621>)—The liquid chromatograph is equipped with a 286-nm detector and a 4.6-mm × 25-cm column that contains 5-μm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 50°. The chromatograph is programmed as follows.

Time (minutes)	Solution A (%)	Solution B (%)	Elution
0	75	25	isocratic
0–10	75→40	25→60	linear gradient
10–40	40	60	isocratic
40–41	40→75	60→25	linear gradient
41–50	75	25	re-equilibration

Inject the *Standard solution*. Record the peak responses as directed for *Procedure*: the column efficiency for the donepezil peak is not less than 40,000 theoretical plates; the tailing factor for the donepezil peak is not more than 1.5; and the relative standard deviation for five replicate injections is not more than 2.0% for the donepezil peak.

*Procedure*—Separately inject (about 20 μL) of the *Diluent* and the *Test solution* into the chromatograph and record the chromatograms. Identify the peaks in the *Test solution* chromatogram using the relative retention times provided in

*Table 1*, disregarding any peak observed in the chromatogram of the *Test solution* that corresponds to the peak in the *Diluent* chromatogram.

Table 1

Related Compound	Relative Retention Time (RRT)*	Relative Response Factor (F)	Limit (%)
DNP1 <sup>1</sup>	0.23	1.5	NMT 0.15
DPMI <sup>2</sup>	0.49	1.9	NMT 0.15
Donepezilbenzyl bromide <sup>3</sup>	0.68	0.73	NMT 0.15
Donepezil hydrochloride	1.0	1.0	—
Dehydrodeoxy donepezil <sup>4</sup>	1.72	2.0	NMT 0.15
Deoxydonepezil <sup>5</sup>	2.12	0.67	NMT 0.15
Any individual unspecified impurity	—	1.0	NMT 0.1
Total impurities	—	—	NMT 0.5

\* Relative retention times are based on 1 mL gradient delay volume.  
<sup>1</sup> 2,3-Dihydro-5,6-dimethoxy-2-(4-piperidinyl)methyl-indan-1-one hydrochloride.

<sup>2</sup> 5,6-Dimethoxy-2-(4-pyridyl)methyl-indan-1-one.

<sup>3</sup> 1,1-Dibenzyl-4-[(5,6-dimethoxy-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidinium bromide.

<sup>4</sup> 1-Benzyl-4-[(5,6-dimethoxy-1*H*-inden-2yl)methyl]piperidine hydrochloride.

<sup>5</sup> 1-Benzyl-4-[(5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-yl)methyl]piperidine hydrochloride.

Calculate the percentage of each impurity in the portion of Donepezil Hydrochloride taken by the formula:

$$100(C_s / C_v)(r_i / r_s)(1/F)$$

in which  $C_s$  and  $C_v$  are the concentrations of donepezil hydrochloride, in mg per mL, of the *Standard solution* and the *Test solution*, respectively;  $r_i$  is the peak response of each individual impurity;  $r_s$  is the response of the donepezil

hydrochloride peak obtained from the *Standard solution*; and  $F$  is the relative response factor for each of the impurities relative to donepezil hydrochloride, given in *Table 1*.

**Assay—**

*Buffer*—Dissolve about 6.8 g of potassium dihydrogen phosphate in 1000 mL of water. Add 5 mL of triethylamine and adjust the pH to 2.2 with orthophosphoric acid. Pass through a filter having a 0.45- $\mu$ m or finer porosity.

*Mobile phase*—Prepare a suitable quantity of a mixture of *Buffer* and methanol (3 : 2).

*Standard preparation*—Dissolve an accurately weighed quantity of USP Donepezil Hydrochloride RS in *Mobile phase* in a suitable volumetric flask to obtain a final solution having a known concentration of 0.1 mg per mL of donepezil hydrochloride. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

*Assay preparation*—Dissolve an accurately weighed quantity of Donepezil Hydrochloride in *Mobile phase* in a suitable volumetric flask to obtain a final solution having a known concentration of 0.1 mg per mL of donepezil hydrochloride. [NOTE—Sonication may be used to aid the dissolution of donepezil hydrochloride.]

*Chromatographic system* (see *Chromatography* (621))—The liquid chromatograph is equipped with a 268-nm detector and a 4.6-mm  $\times$  25-cm column that contains 5- $\mu$ m packing

L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation*, and record the peak response as directed for *Procedure*: the tailing factor for the donepezil peak is not more than 1.5; the column efficiency is not less than 7000 theoretical plates for donepezil; and the relative standard deviation for five replicate injections is not more than 1.0% for the donepezil peak.

*Procedure*—Separately inject equal volumes (about 20  $\mu$ L) of the *Standard preparation* and the *Assay preparation* into the chromatograph and record the chromatograms. Calculate the percentage of  $C_{24}H_{29}NO_3 \cdot HCl$  in the portion of Donepezil Hydrochloride taken by the formula:

$$100(C_s/C_u)(r_u/r_s)$$

in which  $C_s$  is the concentration of donepezil hydrochloride, in mg per mL, in the *Standard preparation*;  $C_u$  is the nominal concentration of donepezil hydrochloride in the *Assay preparation*; and  $r_u$  and  $r_s$  are the peak responses of donepezil hydrochloride obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■