

BRIEFING

Donepezil Hydrochloride Tablets. This proposal was published on the USP Website as a draft USP Pending Standard for public comments. 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: Two commenters requested the inclusion of identification by IR.

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

Comment 2: Two commenters requested the inclusion of water content to the monograph.

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

Comment 3: Two commenters requested that the proposed gradient elution method in the test for *Related compounds* be replaced with an isocratic HPLC method.

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

Comment 4: Two commenters requested the tightening of the *Assay* range from 90.0%–110.0% to 93.0%–107.0%.

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

The gradient elution HPLC procedures in the test for *Related compounds* are 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 procedures in the *Assay* are 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 Tablets**

v.1 Authorized January 28, 2008

» Donepezil Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of donepezil hydrochloride ($C_{24}H_{29}NO_3 \cdot HCl$).

Packaging and storage—Store at controlled room temperature.

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

Identification—

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

Dissolution (711)—[To come.]

Uniformity of dosage units (905): meet the requirements.

Related compounds—

Solution A—Add about 1 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 6.5. Pass through a filter having a 0.45- μ m or finer porosity.

Solution B: acetonitrile.

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

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

Standard solution—Accurately weigh a suitable amount of USP Donepezil Hydrochloride RS, and transfer 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, 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—Grind not fewer than 20 Tablets. Accurately weigh and transfer a quantity of powder, equivalent to about 50 mg of donepezil hydrochloride, to a 50-mL volumetric flask. Add 25 mL of the *Diluent*, sonicate for 15 minutes, and dilute with *Diluent* to volume to obtain a final solution having a nominal concentration of 1 mg per mL of donepezil hydrochloride.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 286-nm detector and a 4.6-mm \times 25-cm column that contains 5- μ m packing

2 / Donepezil Hydrochloride Tablets

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

Chromatograph the *Standard solution*. Record the peak responses as directed for *Procedure*: the column efficiency for the donepezil peak is not fewer 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 equal volumes (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. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

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

in which C_s is the concentration of USP Donepezil Hydrochloride RS, in mg per mL, in the *Standard solution*; C_T is the nominal concentration of donepezil hydrochloride, in mg per mL, in the *Test solution*, based on the label claim; 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, given in *Table 1*, for each of the impurities relative to donepezil hydrochloride. The appropriate limits are given in *Table 1*.

Assay—

Buffer—Dissolve about 6.8 g of monobasic potassium phosphate in 1000 mL of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 2.2. Pass through a filter having a 0.45-µm or finer porosity.

Mobile phase—Prepare a suitable quantity of a mixture of *Buffer* and methanol (3:2) (see *System Suitability* under *Chromatography* (621)).

Standard preparation—Accurately weigh a suitable amount of USP Donepezil Hydrochloride RS, and transfer 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 *Mobile phase* to the flask, sonicate to dissolve, and dilute with *Mobile phase* to volume. Dilute, quantitatively, a suitable volume of the resulting solution with *Mobile phase* to obtain a final solution having a known concentration of about 0.1 mg per mL of donepezil hydrochloride.

Assay preparation—Transfer a suitable number of Tablets, containing a total equivalent amount of 100 mg of donepezil hydrochloride, to a 500-mL volumetric flask. Add 100 mL of *Mobile phase*, sonicate with occasional shaking to disperse completely, then add 200 mL of *Mobile phase* to it, sonicate again for 30 minutes, cool, and dilute with *Mobile phase* to volume. Allow the excipients to settle completely. Quantitatively dilute a suitable volume of the resulting solution with *Mobile phase* to obtain a solution having a nominal concentration of 0.1 mg per mL of donepezil hydrochloride based on the label claim. Pass through a filter having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* (621))—The liquid chromatograph is equipped with a 268-nm detector and a 4.6-mm × 25-cm column that contains 5-µm 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 responses as directed for *Procedure*: the column efficiency is not fewer

Table 1

Related Compound	Relative Retention Time (RRT)*	Relative Response Factor (F)	Limit (%)
DNP1 ¹	0.23	1.5	NMT 0.15
DPMI ²	0.49	1.9	NMT 0.15
Donepezil benzyl bromide ³	0.68	0.73	NMT 0.15
Donepezil hydrochloride	1.0	1.0	—
Dehydrodeoxy donepezil ⁴	1.72	2.0	NMT 0.15
Deoxydonepezil ⁵	2.12	0.67	NMT 0.15
Any individual unspecified impurity	—	1.0	NMT 0.1
Total impurities	—	—	NMT 0.75

¹ 2,3-Dihydro-5,6-dimethoxy-2-(4-piperidinyl)methyl-indan-1-one hydrochloride

² 5,6-Dimethoxy-2-(4-pyridyl)methyl-indan-1-one

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

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

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

* Relative retention times are based on the system having a dwell volume of 1 mL.

than 7000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for five replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the donepezil peaks. Calculate the

percentage label claim of C₂₄H₂₉NO₃·HCl in the portion of Tablets taken by the formula:

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

in which C_u is the nominal concentration of donepezil hydrochloride in the *Assay preparation*, based on the label claim; C_s is the concentration of USP Donepezil Hydrochloride RS, in mg per mL, in the *Standard preparation*; and r_s and r_u are the responses obtained from the *Standard preparation* and the *Assay preparation*, respectively. ■