

Contains Nonbinding Recommendations

Draft – Not for Implementation

## Draft Guidance on Donepezil Hydrochloride

February 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

---

**Active Ingredient:** Donepezil hydrochloride

**Dosage Form; Route:** System; transdermal

**Recommended Studies** One in vivo bioequivalence study with pharmacokinetic endpoints, one in vivo adhesion study, and one in vivo skin irritation study

1. Type of study: Bioequivalence study with pharmacokinetic endpoints  
Design: Single-dose, two-treatment, two-period crossover in vivo  
Strength: 10 mg/day  
Subjects: Healthy males and non-pregnant, non-lactating females  
Additional comments:
  - a. In this document, this dosage form is referred to as a transdermal delivery system (TDS) and includes products that may be described elsewhere or known as *systems, patches* or *extended release films*.
  - b. Unless otherwise justified, the donepezil hydrochloride TDS should be applied to the same anatomical site on all subjects, selected from among those recommended for dosing in the approved labeling for the reference standard, and worn for seven days. Applicants should randomize subjects to receive either the test product or reference standard in a given study period. When possible, the TDS administered in the second study period should be applied to the same anatomical site as in the first study period, but on the contralateral side of the body.
  - c. Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the pharmacokinetics may be altered when a TDS loses its adherence to the skin. Therefore, the adhesion of each TDS should be monitored and recorded throughout the pharmacokinetic study. The applicant should prespecify their inclusion criteria for the statistical analysis of pharmacokinetic endpoints and perform their primary pharmacokinetic analysis on the per protocol population, however, pharmacokinetic samples should be collected and analyzed from all

subjects at all sampling times regardless of the adhesion scores of the TDS and regardless of the inclusion criteria for the statistical analysis of pharmacokinetic endpoints. Provisions should be included in the study protocol to ensure that deliberate actions with the intent to re-apply a detached area of the TDS, to apply pressure to the TDS, or to reinforce TDS adhesion with the skin (e.g., overlays) are avoided throughout the study.

- d. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA*<sup>a</sup> for the design and conduct of the pharmacokinetic bioequivalence study.

**Analyte to measure:** Donepezil in plasma

**Bioequivalence based on (90% CI):** Donepezil

**Waiver request of in vivo testing:** The 5 mg/day strength of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (i) an acceptable bioequivalence study with the 10 mg/day strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths.

**NOTE:** The proportional similarity of the TDS formulation across all strengths means (i) that the amounts of active and inactive ingredients per unit of active surface area are identical for the different strengths of the test product, and (ii) that the ratios of the active surface areas of each strength of the test product compared to the 10 mg/day strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference listed drug (RLD) compared to the 10 mg/day strength of the RLD.

**Dissolution test method and sampling times:** The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test product and reference standard. Specifications will be determined upon review of the Abbreviated New Drug Application (ANDA).

2. Type of study: Adhesion study

Design: Single-dose, two-treatment, two-period crossover in vivo

Strength: 10 mg/day

Subjects: Healthy males and non-pregnant, non-lactating females

Additional comments:

- a. The applicant may elect to evaluate the pharmacokinetic bioequivalence (study 1) and the adhesion (study 2) in a single study with a combined purpose, or in independent studies. In either case, the studies should be adequately powered to evaluate the bioequivalence, and independently, the comparative assessment of adhesion.
- b. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs*<sup>a</sup> for the design and conduct of the

independent adhesion study or the combined study to evaluate both pharmacokinetic bioequivalence and adhesion.

3. Type of study: Skin irritation study

Design: Randomized, evaluator-blinded, within-subject repeat design in vivo

Strength: 5 mg/day (Administered as one-half of the test and one-half of the lowest strength of the reference standard)

Subjects: Healthy males and non-pregnant, non-lactating females

Additional comments:

- a. All test articles (i.e., 5 mg/day administered as one-half of the test<sup>1</sup> and one-half of the lowest strength of the reference standard, optional vehicle TDS<sup>2</sup> and optional negative control<sup>3</sup>) should be applied simultaneously to each subject at different positions on an application site recommended in the approved labeling for the reference standard.
- b. Sequential TDS applications should be made to the same application site weekly (i.e., every 7 days; the intended duration of wear) for a total of 21 consecutive days.
- c. There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 5 mg/day donepezil hydrochloride TDS on the same subject during a 21-day skin irritation study. Since the RLD/reference standard has a matrix design that can be safely cut in half, one-half of the lowest strength of the reference standard can be used for these studies. If the test product also has a design that can be safely cut to a smaller size, it should also be cut in half, and one half of the test product may be applied simultaneously with one-half of the lowest strength of the reference standard (to separate skin sites). It would not be acceptable to manufacture a separate batch of the test product in order to use a smaller TDS in this study. If the test TDS has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes a study design different than what is recommended above, the prospective applicant may submit a pre-abbreviated new drug application (pre-ANDA) meeting request to discuss the proposed approach.
- d. The applicant should follow FDA's current thinking in the most recent version of the FDA guidance for industry on *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs*<sup>a</sup> for the design and conduct of the skin irritation study.

---

<sup>1</sup> The test product evaluated should be the actual TDS to be marketed.

<sup>2</sup> The optional vehicle TDS should contain all of the inactive ingredients in the test product and be identical to the test product in every manner except for the absence of the active ingredients

<sup>3</sup> An example of the optional negative control is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

### **Additional comments related to all studies:**

In addition to the recommendations in the general guidances referenced above, and the product specific recommendations related to the individual studies, the following product specific recommendations should be considered.

1. Inclusion Criteria (the applicant may add additional criteria):
  - a. Healthy adult males or non-pregnant, non-lactating females
  - b. Female subjects agree to use effective contraception during the study
2. Exclusion Criteria (the applicant may add additional criteria):
  - a. Medical history or presence of cardiovascular disorder, gastrointestinal tract disorders, asthma or chronic obstructive pulmonary disease, urinary obstruction, or seizures
  - b. Clinically relevant heart rhythm abnormalities in a screening 12-lead electrocardiogram, such as sick sinus syndrome, second- or third-degree atrioventricular block or complete bundle branch block
  - c. Planned surgery procedure under general anesthesia that requires the use of muscle relaxants
  - d. Skin condition on the application sites (e.g., significant skin damage, diffuse skin, scars, tattoos, or excessive hairy skin) that could potentially have interfered with drug absorption or skin tolerability assessments
  - e. Pregnant or lactating females
  - f. Use of cholinergic compounds within 3 weeks prior to dosing
3. A listing of the prescription and over-the-counter drug products that are prohibited during the study should be provided, such as:
  - a. Cholinomimetic drugs
  - b. Anticholinergic drugs
  - c. Beta blockers
  - d. Muscle relaxants
4. Subjects who are not tolerant to nausea or vomiting can be treated with an anti-emetic drug as a rescue medication. Ensure that there is no drug-drug pharmacokinetic and pharmacodynamic interaction between the anti-emetic drug and donepezil.

### **Additional information:**

Device:

The RLD is presented as a transdermal delivery system and is a drug-device combination product.

FDA recommends that prospective applicants examine the external critical design attributes of the RLD device when designing the test device.

User interface assessment:

An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.<sup>a</sup>

---

**Unique Agency Identifier:** PSG\_212304

---

<sup>a</sup> For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.