

Draft Guidance on Scopolamine

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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.

Active Ingredient: Scopolamine

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence (BE) study with pharmacokinetic (PK) endpoints
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 1 mg/72 hr
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- 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 *patches* or *extended release films*.
- Unless otherwise justified, the scopolamine TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference listed drug (RLD) product, and worn for 72 hours. Applicants should randomize subjects to receive either the test or RLD product 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.
- Contact of the TDS with the skin is essential for the in vivo performance of the TDS, and the PK 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 PK study. The PK samples should be collected and analyzed from all subjects at all sampling times regardless of the adhesion scores of the TDS. 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.
- The applicant should follow FDA's current thinking in the guidance "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" for the design and conduct of the PK BE study.

Analytes to measure (in appropriate biological fluid): Scopolamine in plasma

Bioequivalence based on (90% CI): Scopolamine

- The confidence intervals of the geometric mean test/reference (T/R) ratios for the metrics (C_{max} , AUC_{0-24} , $AUC_{0-tlast}$, and $AUC_{0-\infty}$) should fall within the limits of 80.00-125.00%, where AUC_{0-24} is the area under the plasma concentration vs. time curve from 0 to 24 hours.
- Adequate PK samples are needed, particularly during the first 2-3 hours, to enable the evaluation of drug release into systemic circulation following TDS application.
- Develop an analytical method with adequate sensitivity to measure plasma scopolamine concentrations especially in the first 2 -3 hours.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of the test and RLD products. Information on a dissolution method for this drug product can be found on the FDA Dissolution Methods web site, accessible at: <http://www.accessdata.fda.gov/scripts/cder/dissolution/>.

2. Type of study: Adhesion study
 Design: Single-dose, two-treatment, two period crossover in vivo
 Strength: 1 mg/72 hr
 Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- The applicant may elect to evaluate the PK BE (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 BE, and independently, the comparative assessment of adhesion.
- The applicant should follow FDA's current thinking in the guidance "Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs" for the design and conduct of the independent adhesion study or the combined study to evaluate both PK BE and adhesion.

3. Type of study: Skin irritation and sensitization study
 Design: Randomized, evaluator-blinded, within-subject repeat in vivo
 Strength: Vehicle TDS and positive control (TDS containing active pharmaceutical ingredient should not be used in this study due to safety concerns)
 Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., vehicle TDS¹, positive control of low irritancy² and optional negative control³) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved RLD labeling.
- Sequential TDS applications should be made to the same application site every 72 hours, for a total of 21 consecutive days. The TDS applied on Day 19 should be removed on Day 22.
- The applicant should follow FDA’s current thinking in the guidance “Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs” for the design and conduct of the skin irritation and sensitization study.

Additional comments relating 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.

- Exclusion Criteria (the applicant may add additional criteria):
 - a. Subjects with a history of angle closure or open angle glaucoma
 - b. Subjects with a history of pyloric obstruction or urinary bladder neck obstruction.
 - c. Subjects with a history of seizures or psychosis
- The RLD product contains aluminum. Subjects should be advised to remove all TDS prior to magnetic resonance imaging or cardioversion to avoid skin burns.

¹ The optional vehicle TDS should contain all the inactive ingredients in the test product, and be identical to the test product in every manner except for the absence of the active ingredient.

² Safety concerns preclude the use of comparative studies with the test and RLD products, therefore, the test product can be evaluated by testing a vehicle TDS versus a positive control TDS that produces mild irritation (e.g., $\leq 0.1\%$ sodium lauryl sulfate).

³ An example of the optional negative control treatment is an occlusive cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.