Contains Nonbinding Recommendations

Draft Guidance on Nitroglycerin

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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: 0.4 mg/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 nitroglycerin 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 listed drug (RLD) product, and worn for 12 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): Nitroglycerin and its metabolites, 1,2- dinitroglycerol and 1,3- dinitroglycerol, in plasma. If nitroglycerin

plasma concentrations can be reliably measured and its PK parameters accurately determined, the nitroglycerin data should be analyzed using the confidence interval approach. The 1,2- dinitroglycerol and 1,3- dinitroglycerol data can be used to provide supportive evidence of comparable therapeutic outcome. A highly selective assay capable of a low pg/mL limit of quantitation should be used.

Bioequivalence based on (90% CI): Nitroglycerin

Waiver request of in vivo testing: The 0.1 mg/hr, 0.2 mg/hr, 0.6 mg/hr and 0.8 mg/hr strengths of the TDS may be considered for a waiver of in vivo BE testing based on (i) an acceptable BE study with the 0.4 mg/hr strength TDS, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the TDS formulation across all strengths. If the 0.8 mg/hr strength of the RLD is not available, dissolution studies should be conducted on all available strengths of the RLD product in addition to all strengths of the test product.

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 0.4 mg/hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the RLD product compared to the 0.4 mg/hr strength of the RLD product.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths 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 design, in vivo
Strength: 0.4 mg/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: 0.1 mg/hr (or one-half of a 0.2 mg/hr TDS)
Subjects: Males and non-pregnant, non-lactating females, general population

Additional comments:

- All test articles (i.e., 0.1 mg/hr test product[1], 0.1 mg/hr RLD product, optional vehicle TDS[2] and optional negative control[3]) should be applied simultaneously to each subject at different positions on an application site recommended for dosing in the approved labeling of the RLD product.
- Sequential TDS applications should be made to the same application site every 24 hours, for a total of 21 consecutive days. The TDS applied on Day 21 should be removed on Day 22.
- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 0.2 mg/hr nitroglycerin TDS on the same subject during a 21-day skin irritation and sensitization study. Since the RLD product has a matrix design that can be safely cut in half, one half of the RLD product 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 a RLD product (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 product has a design that cannot be safely cut to a smaller size, and/or if a prospective applicant proposes study design different than what is recommended above, the prospective applicant may submit a pre-Abbreviated New Drug Application meeting request to discuss the proposed approach.
- 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:

[1] The test product evaluated should be the actual TDS to be marketed..
[2] The optional vehicle TDS should have all of the inactive ingredients of the test product and be identical to the test product in every manner except for the absence of the active ingredient.
[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.

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.

- Inclusion Criteria (the applicant may add additional criteria):

  Normotensive subjects with no history of hypotension.

- Exclusion Criteria (the applicant may add additional criteria):

  Within 72 hours prior to dosing, use of phosphodiesterase inhibitors, antihistamines or use of topical drugs at the site of TDS application.

- Provide a listing of the prescription and over-the-counter drug products that are contraindicated during the study, such as:

  a. Antihypertensives

  b. The soluble guanylate cyclase stimulator riociguat

  c. Narcotics and certain analgesics (e.g., cocaine, meperidine, methadone, pentazocine, propoxyphene, tramadol)

  d. Nitrates and nitrites other than study medication, (e.g., buccal, intravenous, lingual, sublingual, or topical nitroglycerin, amyl nitrite, isosorbide dinitrate, nitric oxide)

  e. Phosphodiesterase inhibitors (e.g., sildenafil citrate, tadalafil, vardenafil hydrochloride)

  f. Vasodilators (e.g., alprostadil, ambrisentan, bosentan, dipyridamole, papaverine hydrocholoride)

- Subjects should be advised that the use of alcohol is not recommended while taking study drug due to possible hypotension.

- Standing and supine blood pressure and pulse should be assessed at each visit. Due to the risk of hypotension, subjects should be informed of the symptoms of orthostatic hypotension and cautioned to rise slowly from supine to seated positions. Subjects with significant orthostatic hypotension (decrease of 20 mmHg systolic or 15 mmHg diastolic) should be discontinued from the study.