Contains Nonbinding Recommendations

Draft Guidance on Estradiol; Norethindrone Acetate

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies (Note: Studies on one strength of the drug product may not be used to support the approval of the other strength. All three studies should be conducted independently for 0.05 mg/24 hr; 0.14 mg/24 hr and 0.05 mg/24 hr; 0.25 mg/24 hr strengths.)

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.05 mg/24 hr; 0.14 mg/24 hr or 0.05 mg/24 hr; 0.25 mg/24 hr
   Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
   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 estradiol; norethindrone acetate TDS should be applied to the same anatomical site on all subjects, as recommended for dosing in the approved labeling for the reference product and worn for 3.5 days (84 hours). Applicants should randomize subjects to receive either the test or reference 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 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.

- 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 pharmacokinetic bioequivalence study.

Analytes to measure (in appropriate biological fluid): Estradiol and norethindrone in plasma. An average baseline correction is obtained for estradiol by averaging the 3 pre-application sampling times (-1, -0.5 and 0 hours).

Bioequivalence based on (90% CI): Estradiol (using both baseline corrected and uncorrected data) and norethindrone.

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 reference 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/.

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2. Type of study: Adhesion study
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 0.05 mg/24 hr; 0.14 mg/24 hr or 0.05 mg/24 hr; 0.25 mg/24 hr
Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
Additional comments:

- 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.

- 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 pharmacokinetic bioequivalence and adhesion.

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3. Type of study: Skin irritation and sensitization study
Design: Randomized, evaluator-blinded, within-subject repeat in vivo
Strength: 0.05 mg/24 hr; 0.14 mg/24 hr (Dose: One-half of TDS) or
0.05 mg/24 hr; 0.25 mg/24 hr (Dose: One-half of TDS)
Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy
Additional comments:

- All test articles (i.e., one-half of the 0.05 mg/24 hr; 0.14 mg/24 hr or 0.05 mg/24 hr; 0.25 mg/24 hr test product[1], one-half of the 0.05 mg/24 hr; 0.14 mg/24 hr or 0.05 mg/24 hr; 0.25 mg/24 hr reference 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 in the approved labeling for the reference product.

- Sequential TDS applications should be made to the same application site every 84 hours for a total of 21 consecutive days. The TDS applied on Day 18 should be removed on Day 22.

- There is insufficient information to determine whether it is safe to simultaneously apply two whole, active, 0.05 mg/24 hr; 0.14 mg/24 hr or 0.05 mg/24 hr; 0.25 mg/24 hr estradiol; norethindrone acetate TDS on the same subject during a 21-day skin irritation and sensitization study. Since the reference product has a matrix design that can be safety cut in half, one half of the reference product can be used for these studies. If the test product also has a design that can be safety cut into 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 reference 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 TDS has a design that cannot be safety 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.

- 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.

- As a safety precaution, the subject's seated blood pressure should be evaluated at all visits.

- Inclusion Criteria (the applicant may add additional criteria):
  a. Non-smoking, postmenopausal female subjects with no contraindication to

[1] The test product evaluated should be the actual TDS to be marketed.
[2] 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.
[3] An example of the optional negative control treatment is an occlusion cover or device with normal saline applied on a polyester pad under the cover or within the device chamber.

estrogen therapy. “Postmenopausal” is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.

b. Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg.
c. Subjects >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and a normal clinical breast examination prior to enrollment in study.
d. Subjects with an intact uterus have baseline vaginal ultrasonography demonstrating inactive endometrial lining with endometrial thickness less than 4 mm.

- Exclusion Criteria (the applicant may add additional criteria):
  a. Male subject
  b. Premenopausal, perimenopausal, pregnant or lactating subject
  c. Undiagnosed abnormal genital bleeding
  d. Known, suspected, or history of breast cancer
  e. Known or suspected estrogen-dependent neoplasia
  f. History of endometrial cancer or risk factors for endometrial cancer
  g. Subject with tobacco use or body weight >90 kg
  h. Active deep venous thrombosis, pulmonary embolism, or a history of these conditions
  i. High risk of venous thrombosis or arterial thrombosis
  j. Active arterial thromboembolic disease (e.g., stroke and myocardial infarction), or a history of these conditions
  k. Anaphylactic reaction or angioedema with the reference product
  l. Liver impairment or disease
  m. Protein C, protein S, or antithrombin deficiency, or other thrombophilic disorders.
  n. History of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas
  o. History of narcotic abuse, drug abuse or alcoholism
  p. Within 6 months prior to dosing, estrogen pellet therapy or progestin injectable drug therapy
  q. Within 3 months prior to dosing, progestin implants and estrogen alone injectable drug therapy
  r. Within 8 weeks prior to dosing, oral estrogen and/or oral or intrauterine progestin therapy
  s. Within 4 weeks prior to dosing, transdermal estrogen alone or transdermal estrogen/progestin products
  t. Within 1 week prior to dosing, vaginal hormonal products (rings, creams, gels)
  u. Within 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

v. Taking thyroid hormone replacement therapy
w. Taking inducers of CYP3A4 such as St. John's wort, anticonvulsants, phenylbutazone, rifampin, rifabutin, nevirapine and efavirenz
x. Taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice

- A listing of the prescription and over-the-counter drug products that are contraindicated during the study should be provided, such as:
  a. Antihypertensives and pressor agents
  b. Estrogens, other than study medication