Contains Nonbinding Recommendations

Draft Guidance on Estradiol

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Dosage Form; Route: Film, extended release; transdermal

Recommended Studies: Three studies

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 0.1 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 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 product, and worn for 7 days (168 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 in plasma. An average baseline correction is obtained 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.

Waiver request of in vivo testing: The 0.014 mg/24 hr, 0.025 mg/24 hr, 0.0375 mg/24 hr, 0.05 mg/24 hr, 0.06 mg/24 hr and 0.075 mg/24 hr strength of the TDS may be considered for a waiver of in vivo bioequivalence testing based on (1) an acceptable bioequivalence study with the 0.1 mg/24 hr strength, (2) acceptable in vitro dissolution testing of all strengths, and (3) proportional similarity of the TDS formulations 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 0.1 mg/24 hr strength of the test product are the same as the corresponding ratios for the active surface areas of each strength of the reference product compared to the 0.1 mg/24 hr strength of the reference product. The ratios of labeled strength across all strengths may not be precisely proportional to the ratios of active surface areas across all strengths, and so the labeled strengths should not be used as the basis for determining the proportionality of the TDS formulations across all strengths.

Dissolution test method and sampling times: Comparative dissolution testing should be conducted on 12 dosage units each, of all strengths 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: 0.1 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: 0.025 mg/24 hr
Subjects: Non-smoking, postmenopausal women with no contraindication to estrogen therapy

Additional comments:

- All test articles (i.e., 0.025 mg/24 hr test product[1], 0.025 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 7 days for a total of 21 consecutive days.

- 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.

- Please note that estradiol TDS 0.014 mg/24 hr is the subject of a separate new drug application (NDA). For this strength, a separate abbreviated new drug application (ANDA) should be submitted. If the specified criteria are met, a waiver may be requested for the in vivo bioequivalence testing requirement for the 0.014 mg/24 hr strength based on Study 1 and Study 2 (discussed above) conducted on the 0.1 mg/24 hr strength, and Study 3 (discussed above) conducted on the 0.025 mg/24 hr strength.

[1] The test TDS 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 ingredient.
[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.

Applicants should cross-reference the aforementioned studies, conducted on the 0.1 mg/24 hr and 0.025 mg/24 hr strengths, along with the waiver request.

- The applicant should follow FDA's current thinking in the guidance *Variations in Drug Products that May Be Included in a Single ANDA* for information relevant to the development of a 0.014 mg/24 hr strength estradiol TDS.

- If an applicant intends to market only the 0.014 mg/24 hr strength estradiol TDS, it may be acceptable to conduct the Study 1, Study 2, and Study 3 (discussed above) using the 0.014 mg/24 hr strength. However, if the applicant thereafter seeks to market higher strengths of this estradiol TDS in the future, the applicant should conduct an additional Study 1 and Study 2 using the 0.1 mg/24 hr strength estradiol TDS.

- 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 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