Contains Nonbinding Recommendations

Draft Guidance on Progesterone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Progesterone

Form/Route: Insert/Vaginal

Recommended studies: 2 studies

1. Type of study: Bioequivalence (BE) study with Pharmacokinetic (PK) endpoints
   Design: Single-dose, two-treatment, two-period, crossover, fasting in vivo
   Strength: 100 mg (dose: 1x100 mg)
   Subjects: Healthy premenopausal, nonpregnant females, general population.
   Additional comments: Specific recommendations are provided below.

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2. Type of study: BE study with clinical endpoint
   Design: Multiple-dose, 2-treatment, parallel, randomized in vivo
   Strength: 100 mg
   Subjects: Infertile women participating in an Assisted Reproductive Technology (ART) treatment program
   Additional comments: It is recommended that a protocol be submitted to the OGD for review prior to initiating the study.

Analytes to measure (in appropriate biological fluid): Progesterone in plasma (for PK endpoint)

Bioequivalence based on (90% CI): Progesterone (for PK endpoints) and clinical pregnancy, defined as the presence of a gestational sac and fetal heart activity beginning at six weeks and maintained to ten weeks post embryo transfer (for clinical endpoint)

Waiver request of in vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a **Dissolution Method Database** is available to the public at the Office of Generic Drug (OGD) website at http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

Additional comments regarding the BE study with PK endpoints:

1. Divide the study into 6 phases: i) screening, ii) down regulation with a GnRH agonist (e.g., a single leuprolide acetate depot 3.75 mg intramuscular injection provides suppression for one month), iii) estrogen priming for approximately 14 days, iv) randomization/treatment period 1 with continued estrogen administration, v) wash-out

period with continued estrogen administration, vi) treatment period 2 with continued estrogen administration.

2. Exclusion Criteria (the sponsor may add additional criteria)
   a. Pregnant, breast feeding, or planning a pregnancy.
   b. History of hypersensitivity or allergy to progesterone and/or any of the study medication ingredients.
   c. Known missed abortion or ectopic pregnancy
   d. Liver disease
   e. Known or suspected breast cancer
   f. Active arterial or venous thromboembolism, or severe thrombophlebitis or a history of these events

3. Progesterone is known to be highly variable. It is the sponsor's responsibility to enroll sufficient subjects for the study to demonstrate bioequivalence between the products.

4. The protocol should include a listing of the prescription and over-the-counter drug products, procedures, and activities that are prohibited during the study, such as:
   a. Any vaginal products other than study treatments (e.g., antifungal products), as they may alter progesterone release and absorption from the vaginal insert.
   b. Drugs known to induce hepatic cytochrome P450 3A4 (e.g., rifampin and carbamazepine).

5. Measure baseline progesterone levels at -1.0, -0.5, and 0 hours before dosing. The mean of the pre-dose progesterone levels should be used for the baseline adjustment of the post-dose levels. Baseline concentrations should be determined for each dosing period, and baseline corrections should be period specific. If a negative plasma concentration value results after baseline correction, this should be set to 0 prior to calculating the baseline-corrected AUC. The progesterone pharmacokinetic parameters should be determined based on both baseline-adjusted and baseline-unadjusted plasma concentration data.