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Draft Guidance on Leuprolide Acetate; Norethindrone Acetate

November 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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In February 2018, FDA issued a draft product-specific guidance for industry on generic leuprolide acetate; norethindrone acetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredients: Leuprolide acetate; Norethindrone acetate

Dosage Forms; Routes: Injectable, tablet; intramuscular, oral

Recommended Studies: Three studies

1. Type of study: In vivo
   Design: Randomized, single-dose, parallel
   Strength: 11.25 mg/vial (leuprolide acetate injectable depot 3-month)
   Subjects: Endometriosis patients who are receiving treatment with leuprolide acetate and norethindrone acetate for their condition
   Additional comments: Exclude pregnant or lactating patients. Patients should be on 5 mg norethindrone acetate tablet daily during the study. The test and reference study groups should be balanced with respect to patient disease progression and treatment history. The treatment regimen during the study should be identical between the test and reference

groups. The same injection site should be used for test and reference products, which should be pre-specified prior to conducting the study.

2. Type of study: In vivo
Design: Randomized, single-dose, parallel
Strength: 3.75 mg/vial (leuprolide acetate injectable depot 1-month)
Subjects: Endometriosis patients who are receiving treatment with leuprolide acetate and norethindrone acetate for their condition
Additional comments: See comments above

3. Type of study: In vivo
Design: Steady state, crossover
Strength: 5 mg (norethindrone acetate tablet)
Subjects: Endometriosis patients who are enrolled in Study 1 or Study 2
Additional comments: This is a co-packaged product containing leuprolide acetate (3.75 mg/vial or 11.25mg/vial) and 5 mg norethindrone acetate tablet.
For the above studies, the assay method(s) used should be free of interference for each component, and the sampling scheme should be adequate to accommodate each product.

Analytes to measure: Leuprolide and norethindrone in plasma

Bioequivalence based on (90% CI): Leuprolide and norethindrone

For leuprolide, the 90% confidence intervals (CIs) of the following pharmacokinetic (PK) parameters should meet the acceptable limits of [80.00-125.00%]: Log-transformed $AUC_{7\text{-}t}$, $AUC_{0\text{-}t}$, and C_{max}, where $AUC_{7\text{-}t}$ is the area under the concentration (AUC) vs. time curve from Day 7 to the last sampling time point, $AUC_{0\text{-}t}$ is the AUC from 0 to the last sampling time point, and C_{max} is the maximum concentration. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo PK study.

For norethindrone, the 90% CIs of the following PK parameters should meet the acceptable limits of [80.00-125.00%]: Log-transformed $AUC_{0\text{-}tau}$, and C_{max}, where $AUC_{0\text{-}tau}$ is the AUC vs. time curve to the end of the dosing period at steady state, and C_{max} is the maximum concentration during the dosing interval.

Additional comments: The proposed test leuprolide acetate drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference product for both strengths. Provide characterization data on polylactic acid (PLA) or poly(lactide-co-glycolide) (PLGA) for both the test and reference products including, but not limited to, polymer composition (ratio between glycolic acid and lactic acid), molecular weight and weight distribution, and polymer architecture (e.g., linear or star-branched). Additional PLA or PLGA

[1] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[2] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

polymer, and drug product characterization data may be requested during the review of the abbreviated new drug application (ANDA).

Alternative to the recommended studies above, applicants may conduct in vivo studies independently for 5 mg norethindrone acetate tablet and leuprolide acetate for intramuscular injectable use. For norethindrone acetate portion of the co-package, the applicants may follow the recommendations in individual product-specific guidance for 5 mg norethindrone acetate. If an ANDA applicant has an approved ANDA for the single entity of 5 mg norethindrone acetate tablet, the applicant may cross reference its approved ANDA for this co-packaged product. For leuprolide acetate portion of the co-package, the applicants may refer the appropriate individual product-specific guidance for leuprolide acetate that recommends the in vivo study and request a waiver of in vivo bioequivalence study for the 3.75 mg/vial for 1 month or 11.25 mg/vial for 3-month or applicants can cross reference the appropriate ANDA(s) for the 3.75 mg/vial for 1-month and/or 11.25 mg/vial for 3-month strength. In either case, the applicants should document Q1 and Q2 sameness to the respective reference listed drug strength.

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 ANDA.

Revision History: Recommended February 2008; Revised November 2021

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