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Draft Guidance on Leuprolide Acetate

August 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 2014, FDA issued a draft product-specific guidance for industry on generic leuprolide acetate. We are now issuing revised draft guidance for industry that replaces the previously issued guidance.

Active Ingredient: Leuprolide acetate

Dosage Form; Route: Injectable; injection

Recommended Study: One study

1. Type of study: In vivo
   Design: Randomized, single dose, parallel
   Strength: 7.5 mg/vial
   Subjects: Prostatic carcinoma patients undergoing initial therapy or receiving a stable regimen of leuprolide acetate (7.5 mg/vial) via intramuscular injection route.
   Additional Comments: The test and reference groups should be balanced with respect to patient disease progression and treatment history. Furthermore, 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. The study should include exclusively prostatic

carcinoma patients undergoing initial therapy or exclusively prostatic carcinoma patients receiving a stable regimen of leuprolide acetate (7.5 mg/vial) via intramuscular injection route. If both types of patients are included in the study, proportions of the patients should be similar between test and reference groups.

Analyte to measure: Leuprolide in plasma

Bioequivalence based on (90% CI): Leuprolide

The 90% confidence intervals 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 plasma-concentration vs. time curve from Day 7 to the last sampling time point, $AUC_{0\text{-}t}$ is the area under the curve from 0 to the last sampling time point, and C_{max} is the maximum plasma concentration. Note that the last sampling time point 't' equals the dosing interval of the product used in the in vivo PK study.

In addition, for prostatic carcinoma patients undergoing initial therapy, after the PK study is completed, the treatment should not be discontinued or delayed for a second dose.

Waiver request of in vivo testing: 3.75 mg/vial, 11.25 mg/vial 1-month and 15 mg/vial based on: (1) an acceptable bioequivalence study on the 7.5 mg/vial strength (2) acceptable in vitro dissolution testing across all strengths and (3) qualitative (Q1) and quantitative (Q2) sameness to the respective reference listed drug (RLD) strength.

Note that leuprolide acetate for depot suspension, 3.75 mg/vial, leuprolide acetate for depot suspension, 7.5 mg/vial, and leuprolide acetate for depot suspension, 7.5 mg/vial, 11.25 mg/vial 1-month and 15 mg/vial are the subject of three separate reference products. For each strength for which a biowaiver is requested, it might be necessary to submit two separate applications comparing to the appropriate reference product.

An applicant may request a waiver of in vivo bioequivalence testing for the 3.75 mg/vial, 7.5 mg/vial, 11.25 mg/vial 1-month and 15-mg/vial strengths provided that it (1) submits an abbreviated new drug application (ANDA) containing an acceptable in vivo study on the 7.5-mg/vial strength; (2) if necessary, cross references the appropriate ANDA for the 7.5-mg/vial strength; and (3) documents Q1 and Q2 sameness to the respective RLD strength.

An applicant may request a waiver of in vivo bioequivalence testing for the 11.25 mg/vial 3-month and 30 mg/vial 3-month strengths provided that it (1) submits an ANDA containing an acceptable in vivo study on the 30-mg/vial strength; (2) if necessary, cross-references the appropriate ANDA for the 30-mg/vial strength; and (3) documents Q1 and Q2 sameness to the respective RLD strength.

Refer to the Guidance for Industry, *Variations in Drug Products That May Be Included in a Single ANDA*, located at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072892.pdf.

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 May 2010; Revised February 2014, August 2021

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