Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Leuprolide Acetate

February 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in FDA guidances means that something is suggested or recommended, but not required.

This is a new draft product-specific guidance for industry on generic leuprolide acetate.

Active Ingredient: Leuprolide acetate

Dosage Form; Route: Powder; subcutaneous

Recommended Study: One study

1. Type of study: Bioequivalence study with pharmacokinetic (PK) endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: 45 mg
   Subjects: Prostatic carcinoma patients undergoing initial therapy or receiving a stable regimen of leuprolide acetate (45 mg) via subcutaneous injection.
   Additional comments:
   The test and reference groups should be balanced with respect to patient disease progression and treatment history. 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 those receiving a stable regimen of leuprolide acetate (45 mg) via

subcutaneous 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 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 prostate 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: 45 mg for pediatric use based on (1) an acceptable bioequivalence study on leuprolide acetate for injectable suspension, 45 mg and (2) qualitative (Q1) and quantitative (Q2) sameness to the respective reference listed drug (RLD).

Note that leuprolide acetate for injectable suspension, 45 mg, and leuprolide acetate for injectable suspension, 45 mg for pediatric use, are the subject of two separate reference products. It might be necessary to submit two separate applications comparing to the appropriate reference product if requesting a waiver for the 45 mg for pediatric use product.

An applicant may request a waiver of in vivo bioequivalence testing for the 45 mg for pediatric use provided that (1) submits an abbreviated new drug application (ANDA) containing an acceptable in vivo study; (2) if necessary, cross-references the ANDA for leuprolide acetate for injectable suspension, 45 mg; and (3) documents Q1 and Q2 sameness to the respective RLD.

Dissolution test method and sampling times: The applicant should develop and validate a method to determine in vitro drug release. Conduct comparative dissolution testing on 12 dosage units of the test and reference products. Specifications will be determined upon assessment of the abbreviated new drug application.

Additional Information:

Device:

This product is a drug-device combination product. Refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a] An ANDA for a proposed generic drug-device combination product should include complete comparative analyses.

Unique Agency Identifier: PSG_021731

[a] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.