Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Leuprolide Mesylate

February 2023

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Leuprolide mesylate

Dosage Form; Route: Emulsion; subcutaneous

Strength: EQ 42 mg base

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Type of study: Bioequivalence study with pharmacokinetic endpoints
   Design: Single-dose, randomized, parallel, in vivo
   Strength: EQ 42 mg base
   Subjects: Prostatic carcinoma patients undergoing initial therapy or receiving a stable regimen of leuprolide mesylate (EQ 42 mg base) 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 subcutaneous leuprolide mesylate injection. 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 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 pharmacokinetic study.

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

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 Abbreviated New Drug Application (ANDA).

Additional information:

Device:
The Reference Listed Drug (RLD) is presented in a kit that consists of a pre-filled syringe (PFS) with drug emulsion, a 5/8" 18-gauge needle, and a Point-Lok needle protection device. The device constituent parts are the syringe, the 18-gauge needle, and the Point-Lok needle protection device.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD devices when designing the Test (T) devices including:

- Single-use, fixed-dose, pre-filled syringe format
- Needle gauge and length
- Needle protection system

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, 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]

Unique Agency Identifier: PSG_211488

[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.