Contains Nonbinding Recommendations

Draft Guidance on Mifepristone

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: Mifepristone

Form/Route: Tablets/Oral

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, two-way, crossover in vivo
   Strength: 200 mg
   Subjects: Healthy males and postmenopausal females, general population.
   Additional comments: Specific recommendations are provided below.

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2. Type of study: Fed
   Design: Single-dose, two-way, crossover in vivo
   Strength: 200 mg
   Subjects: Healthy males and postmenopausal females, general population.
   Additional comments: Specific recommendations are provided below

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Analytes to measure (in appropriate biological matrix): Mifepristone and its two primary metabolites, N-monodemethylated (RU 42 633) and hydroxylated (RU 42 698).

Bioequivalence based on (90% CI): Both primary metabolites of mifepristone, N-monodemethylated (RU 42 633) and hydroxylated (RU 42 698).

Please submit the data of the parent drug, mifepristone, as supportive evidence of comparable therapeutic outcome. For the parent drug, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times: Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. 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 Fasting and Fed Bioequivalence (BE) studies:

1. Due to the anti-gestational effects of mifepristone, both studies should be conducted in healthy male volunteers and/or postmenopausal females. “Postmenopausal” is defined as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40

mIU/ml or at least 6 weeks postsurgical following bilateral oophorectomy with or without hysterectomy.

2. Because there is limited information regarding the effect of food on the bioavailability of mifepristone, it is especially important to confirm bioequivalence and therefore therapeutic equivalence of a generic product to the Reference Listed Drug product under fed conditions. This is consistent with the bioequivalence recommendations presently being applied to most solid oral dosage form drug products.

3. To ensure that the fasting and fed bioequivalence studies incorporate the appropriate safeguards against exposure of pregnant women to the drug, the Agency strongly recommends that complete protocols be submitted to the Office of Generic Drugs for review and comment prior to conducting the studies. For additional information regarding protocols, please refer to the CDER Manual of Policies and Procedures (MaPP) 5210.6.

4. Both protocols for the fed and fasted bioequivalence studies must incorporate rigorous safety measures including:

    a. Providing a Mifeprex® Medication Guide to each female subject. Enroll female subjects who are able to read the Mifeprex® Medication Guide either in English or in a provided translation.

    b. Placing in the Informed Consent all of the pertinent elements listed in the current Mifeprex® labeling [Section PATIENT AGREEMENT, Mifeprex (mifepristone) Tablets, of the labeling].