Contains Nonbinding Recommendations

Draft Guidance on Esterified Estrogens

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Fasting
Design: Single-dose, two way crossover *in-vivo*
Strength: 2.5 mg
Subjects: Normal healthy post menopausal or surgically sterile females.
Additional comments:

Analytes to measure (in appropriate biological fluid): Estrone sulfate and Equilin sulfate in plasma.

1. Please provide baseline correction for endogenous estrone sulfate in the analysis. Please measure baseline estrone sulfate levels at -1, -0.5 and 0 hours. The mean of the pre-dose estrone sulfate levels should be used for the baseline adjustment of the post-dose levels. Any negative values obtained from baseline correction should be designated as zero (0) and any subject with baseline-adjusted pre-dose concentrations (at time 0 hour) greater than 5% of their Cmax should be excluded from the bioequivalence statistical analysis and the 90% confidence interval based on the remaining subjects.

2. The selected blood sampling schedule should include sufficient time points around Tmax for the best estimate of Cmax, and should be sufficiently long for the best characterization of the elimination phase of both analytes (at least 96 hours).

3. The analytical assay method selected should be sufficiently sensitive and specific to measure estrone sulfate and equilin sulfate concentrations in plasma and should have a lower limit of quantitation of 50 pg/mL or less for both analytes.

4. Based on the estimated half-life of the two analytes, the washout duration should be greater than five times the half-life, therefore at least a two-week washout period between doses is recommended.

Bioequivalence based on (90% CI): Estrone sulfate and Equilin sulfate

Waiver request of in-vivo testing: 0.3 mg, 0.625 mg and 1.25 mg based on (i) acceptable bioequivalence studies on the 2.5 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

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.fda.gov/cder/ogd/index.htm. 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.