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Draft Guidance on Esterified Estrogens

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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: 2 studies

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:

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Analytes to measure (in appropriate biological fluid): Unconjugated estrone, total estrone, unconjugated equilin and total equilin in plasma

Please provide baseline correction for unconjugated and total estrone in the analysis. Please measure baseline unconjugated and total estrone levels at -48, -24, and 0 hours. The mean of the pre-dose unconjugated and total estrone levels should be used for the baseline adjustment of the post-dose levels.

Bioequivalence based on (90% CI): Baseline-adjusted unconjugated estrone, baseline-adjusted total estrone, unconjugated equilin, total equilin

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.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.

NOTE: the USP 32 monograph for Esterified Estrogens does not reflect the standard of identity of the Reference Listed Drug. The USP 32 monograph for Esterified Estrogens cross-references Identification Test A of the Conjugated Estrogens monograph, which includes requirements for 17α-dihydroequilin. The RLD label includes sodium equilin sulfate, 17α-estradiol, and sodium estrone sulfate as components of Esterified Estrogens.