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Dockets Management Branch (HFA 305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Reference: Citizen Petition 2005 P-0037
Estrace Vaginal Cream, USP, 0.01%

The undersigned hereby submits the following comments in opposition to the Citizen Petition reference number 2005P-0037 filed by Warner Chilcott requesting a stay of approval and or effective date of final approval of any estradiol vaginal cream ANDAs unless the applications contain data to address the special bioequivalence and therapeutic equivalence issues. For the reasons listed below, Warner Chilcott's petition should be denied.

Warner Chilcott's petition is nothing more than an ANDA approval delay tactic which will cause the Agency to spend valuable scientific reviewer time and resources on evaluation when FDA policy and regulations already provide guidance for therapeutic equivalence of topical drug products. In fact, the drug product mentioned in this petition which is the referenced listed drug (RLD) Estrace Vaginal Cream, USP, 0.01% is itself approved by FDA as an Abbreviated New Drug Application (ANDA) utilizing the abbreviated application requirements.

Basis for Denial

Estrace Cream is a topically applied estradiol drug product used in the treatment of vulval and vaginal atrophy associated with menopause. Estradiol is absorbed orally and when applied topically is absorbed through the skin and mucous membranes providing for localized therapy. The usual dose of vaginal cream contains one-fifth (1/5) the amount of estradiol administered orally resulting in less systemic absorption. Although systemic absorption does occur from topical application, the primary effect of the drug is achieved at the local site of application. There is no question that a topically applied drug product needs to be evaluated from a safety and efficacy perspective to demonstrate therapeutic bio-equivalent efficacy. Since the systemic absorption of topically applied estradiol

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results in lower and more variable blood levels of estradiol than that of orally administered estradiol an in vivo bioequivalence study is not practical to demonstrate bioequivalence of a topically applied estradiol drug product. Thus, a well-controlled clinical end-point bioequivalency study is an acceptable mechanism to demonstrate therapeutic bioequivalency. There is no reason to require or evaluate a dose ranging study since the RLD drug product is only available in one strength (0.01%) and dose titrated downward (4gr to 1gr) over a period of 3 to 6 months per the approved Dosage and Administration Section of the approved Estrace Vaginal Cream labeling. Additionally, the Federal Food Drug and Cosmetic Act section 505(J)(2)(iv) only requires information to show that a new drug is bioequivalent to the referenced listed drug. In addition, 21 CFR 320.24 outlines other acceptable approaches for demonstrating bioequivalence of the same active ingredient one of which in section (b)(4) is a well controlled clinical study to demonstrate comparative safety and efficacy.

Relative Systemic Absorption

The issue of relative systemic absorption of a topically applied drug product can be evaluated through in-vitro release testing. In the current FDA SUPAC guidance for Industry on Nonsterile Semisolid Dosage Forms the agency presents several standard methods to evaluate diffusion of different topical drug product formulations. The Guidance presents various approaches to measure in vitro release and diffusion of active drug substances as well as limits and criteria to evaluate the comparative data.

In summary in-vitro test data when combined with clinical data from a well controlled clinical end point study evaluating safety and efficacy is a reasonable alternative to an in-vivo bioequivalence study. In addition, there is no rationale basis to expose additional women subjects to estrogen in a demonstration of bioequivalence of a vaginal cream drug product when in-vitro methods are available to access this parameter and so much is already known about estradiol absorption and metabolism in women.

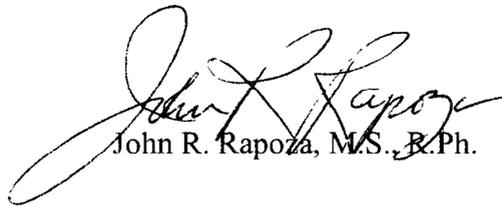
Inactive Ingredients

In the FDA regulations 21 CFR 314.94 (a)(9)(v), the Agency presents the issue of inactive ingredients in topical drug products. Specifically, the FDA recommends that topical products contain the same inactive ingredients as the referenced listed drug. Given that the qualitative composition of the cream product is listed in the product labeling a generic drug product should contain the same inactive ingredients. In addition these inactive ingredients would be included at levels at or below those currently found in the FDA's Inactive Ingredient Guide (IIG). Thus, the issue of drug product formulation safety should not be of concern.

Conclusion

Warner Chilcott's petition requests an excessive amount of clinical testing to demonstrate bioequivalency of a locally administered topical vaginal cream drug product and therefore should be denied. The Congressional objective of the ANDA and the review process is to make available bioequivalent drug products an economic alternative to the American Consumer without the burden of unnecessary repetitive clinical trials. In addition, the FDA, through its guidance documents and regulation, has provided the industry an approach to the demonstration of therapeutic bioequivalence without the need for excessive clinical testing of already approved drug products.

Respectfully,



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