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Dockets Management Branch
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

CITIZEN PETITION

The undersigned, Berlex Laboratories, Inc. ("Berlex") and 3M Pharmaceuticals, a division of Minnesota Mining & Manufacturing Company ("3M"), submit this petition under section 505(j) of the Federal Food, Drug and Cosmetic Act ("FDC Act") and 21 C.F.R. § 10.30 to request that the Agency not recommend the Mylan estradiol transdermal system (ETS) as a generic substitute to the Climara® once-a-week estradiol (TDS) transdermal system.

ACTION REQUESTED

Berlex and 3M request that the Agency take the following actions:

1. Change the Therapeutic Equivalence Code of the Mylan ETS A-rated to B-rated.
2. Change the labeling for the Mylan ETS to not allow placement of the patch on the buttock.
3. Render the Mylan ETS misbranded under Sections 502 (a), (f), and (j) of the FDC Act.

STATEMENT OF GROUNDS

BACKGROUND

To obtain approval of an Abbreviated New Drug Application (ANDA), the generic drug sponsor must demonstrate that its product is "bioequivalent" to the reference listed drug (RLD). FDC Act § 505(j)(2)(A)(iv). Under the FDC Act, a generic drug is considered "bioequivalent" to a RLD if there is no "significant difference" in the "rate

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and extent of absorption” of the generic drug. Id. § 505(j)(8)(B). See also, 21 C.F.R. § 320.1(e).

The Mylan ETS is a generic estradiol patch that used the Climara multi-day estradiol TDS as its RLD. Berlex and 3M jointly manufacture and market Climara pursuant to NDA 20-375. The labeling for Climara states that the product can be affixed either to the user’s lower abdomen, or to the upper quadrant of the buttock.

In 1998, the Mylan ANDA was under review by the Agency, and Berlex/3M filed a Citizen Petition [Docket 98P-0434] with the Agency in order to address several concerns regarding this application. Chief among these was the concern that the Mylan application demonstrated that its product was only bioequivalent to Climara at the abdomen application site, and provided no clinical evidence in support of its bioequivalence at the buttock site. This petition argued that the Agency should establish approval standards for generic transdermal estradiol patches that require a demonstration of bioequivalence at all sites of administration.

Despite these concerns, the Agency approved the Mylan ANDA in February of 2000 with labeling that allows use of the product at either the abdomen or the buttock sites. The Agency, in its reply to the Berlex/3M Citizen Petition, stated that:

If a bioequivalent product is placed on the same site as the reference listed drug product, it will yield equivalent plasma concentrations. If the same two products are placed on an alternate site on the body, different plasma concentrations may result, but the products will still yield equivalent plasma concentrations.

The Agency concluded by stating that:

The Agency's scientific opinion and practice is that two transdermal products shown to be bioequivalent at one site are also bioequivalent at an alternate site.

The original Citizen Petition was filed to address concerns that were based on scientific information from other transdermal products. However, this current filing presents concrete evidence to demonstrate that those concerns were warranted.

I. MYLAN GENERIC ESTRADIOL TRANSDERMAL SYSTEM IS NOT BIOEQUIVALENT TO CLIMARA ESTRADIOL TRANSDERMAL SYSTEM AT THE BUTTOCK APPLICATION SITE.

In order to evaluate the concerns that were presented to the Agency, Berlex conducted a statistically powered (n=40) bioequivalence study which compared the bioequivalence of estradiol delivery from the Mylan and Climara transdermal systems on the buttock application site in healthy postmenopausal women. A commentary on the study (Attachment 1) is attached. The full study report (Attachment 2) was submitted to the Food and Drug Administration's Office of Generic Drugs on December 3, 2001.

A. Description of Study

This study was a single-center, open label, randomized, 3-period, cross-over bioequivalence study with two test transdermal systems and a reference transdermal system (Climara), all designed to deliver 0.1mg estradiol/day. One test transdermal system was a modified Climara formulation under investigation; the other test transdermal system was the Mylan generic.

Forty-two postmenopausal women were enrolled in the study and forty completed. The subjects remained in-house at the study site for the first 48 hours after

the application of each transdermal system; thereafter, the subjects returned to the study site at a predetermined schedule for blood sample collection and other study procedures. Discontinued and withdrawn subjects were not replaced.

One transdermal system was applied for a week (7 days) to the upper buttock of each subject, according to a randomization schedule generated for a three-period crossover design. Preliminary investigations indicated that 7-day adhesion was a potential problem with the Mylan generic so taping of either Climara or Mylan patches that were beginning to lift was allowed. Blood samples were drawn prior to application (time zero) and at 12, 18, 24, 30, 36, 42, 48, 72, 96, 120, 144 and 168 hours after application; and post patch removal at 174 and 180 hours. There was 2 weeks between the start of each study period, providing for a one-week washout interval between periods.

The primary objectives of the study were to determine the bioequivalence of 17β -estradiol, estrone, and estrone sulfate from the Mylan ETS and from a modified Climara estradiol TDS with that from the reference Climara estradiol TDS.

B. Results of Study

The Mylan ETS and the Climara estradiol TDS were significantly different in the maximum serum level of estradiol (C_{max}) delivered. The C_{max} was on average about 16% higher with the Mylan generic system than with Climara. The 90% confidence interval for Mylan C_{max} ranged from 107% to 126% of the C_{max} for Climara ($p=0.004$), exceeding the 125% acceptable limit, and was statistically significantly different. Consequently, patients who are switched to the Mylan estradiol transdermal system will likely experience higher maximum levels than when they were receiving Climara. These patients will also experience higher levels at all time points and will receive almost 14% more drug over the 7-day interval than with Climara. This represents a substantial increase in drug exposure when switching patients from Climara to the Mylan generic product. Clearly, the Mylan estradiol patch applied to the buttock is not bioequivalent to Climara, and therefore such use should not be permitted as a matter of law.

This study has been submitted for publication in the Journal of Clinical Pharmacology.

C. Importance of Proper Study Design

Adequate blood sampling is the most essential component of a well designed pharmacokinetic study. This parameter enables a study to provide an accurate characterization of the pharmacokinetics of the study drug. Adequate blood sampling takes on additional significance when conducting bioavailability studies for the extended-release dosage form of a 7-day estradiol transdermal system.

The blood sampling times utilized in the original Mylan bioequivalence study that was included in its ANDA resulted in pharmacokinetic profiles that were not truly comparable to those of Climara. In the Mylan study, blood samples were collected at 6, 12, 24, 48, 72, 96, 120, 144, and 168 hours after patch application and before patch removal. This sampling schedule incorrectly assumes that the peak absorption from the estradiol patch occurs by the 24 hour period. Numerous figures in the Climara product labeling, however, show a characteristic peak concentration of estradiol near 36 hours. The presence or absence of this peak in the Mylan estradiol pharmacokinetic profile cannot be confirmed due to the lack of blood sampling during the 24-48 hour interval in the study design. This inconsistency leads to the erroneous conclusion that the profiles of the Mylan estradiol transdermal system and that of Climara's are equivalent.

The recent Berlex/3M bioequivalence study directly compared the pharmacokinetic profiles of the Mylan ETS to that of Climara's using a blood sampling schedule to capture the true maximum concentration: 12, 18, 24, 30, 36, 42, 48, 72, 96, 120, 144 and 168 hours after patch application.

II. ADHESION PROPERTIES OF THE MYLAN PRODUCT

In the original Citizen Petition filed by Berlex/3M in 1998, an additional concern raised was the issue of skin adhesion of the Mylan ETS. In order to be considered bioequivalent, the Mylan product must possess similar skin adhesion characteristics to Climara in order to ensure consistent estradiol dosing. The recent Berlex/3M bioequivalence study demonstrates that this is not the case. Patch lift or fall-off occurred in 59% of the applications of the Mylan ETS, compared with 18% of the Climara applications. The median lift-off time for the Mylan product was 35.5 hours after application (23 occurrences), while the median lift-off time for Climara was 119 hours (6 occurrences). This disparity results in a significant pharmacoeconomic impact due to the increased costs associated with taping and replacing the less adherent Mylan ETS patches.¹

CONCLUSION

The recent Berlex and 3M bioequivalence study clearly illustrates that the Mylan ETS applied to the buttock is not bioequivalent to Climara. In addition to highlighting this legal deficiency, the study also indicates that Mylan patches applied to the buttock can be expected to deliver estradiol into the bloodstream at rates and to extents higher than Climara, and this increased exposure may pose an unnecessary health risk. The current labeling for Mylan's ETS allows it to be used on the buttock application site despite the fact that it has been shown that the product is not bioequivalent to Climara at this site. This evidence renders the drug misbranded under Sections 502 (a), (f), and (j) of the FDC Act.

¹ Jones, J.P., Rowe, M.M., and Harrison, L.I. 2001. Replacing branded estradiol transdermal systems with generic alternatives does not result in a cost savings. Abstract to be presented at the Academy of Managed Care Pharmacy, 14th Annual Meeting, Salt Lake City, UT, April 3-6, 2000.

ENVIRONMENTAL IMPACT

The subject matter of this petition does not fall within any of the categories of action for which an environmental assessment is required pursuant to 21 C.F.R. § 25.22, and is exempt under 21 C.F.R. § 25.24(a)(8) in that it is concerned with FDA's procedures in administering the FDC Act.

ECONOMIC IMPACT

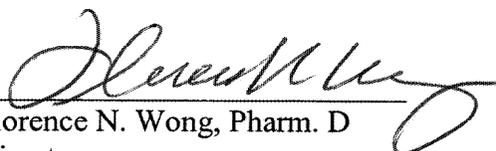
Information on the economic impact of this petition will be submitted if requested by the Commissioner.

CERTIFICATION STATEMENT

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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Enclosures

cc: Gary Buehler (w/o attachments)
Director, Office of Generic Drugs