

## UPS OVERNIGHT

November 27, 2002

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

Re: Docket No. 02P-0029

Dear Sir/Madam:

Berlex Laboratories, Inc. (Berlex) and 3M Company (3M, formerly Minnesota Mining and Manufacturing) submit this supplement<sup>1</sup> to the January 16, 2002 citizen petition that Berlex submitted jointly with 3M Pharmaceuticals, now 3M Drug Delivery Systems, a division of 3M, which requested the Food and Drug Administration (FDA) to take actions adverse to the Mylan estradiol transdermal system (ETS). Berlex and 3M submit this supplement to request that FDA switch, or require Mylan to switch, its 505(j) application for the Mylan ETS to a 505(b)(2) application. This requested action is important for both legal and public health reasons because, absent action, the Mylan ETS may be misbranded and, as such, being illegally marketed, such marketing may be harming women by exposing them to higher levels of estrogen than expected.

As noted in Berlex's and 3M's January 16, 2002 citizen petition, Berlex conducted a study that compared the amount of estradiol delivered from the Mylan ETS and the Climara® once-a-week estradiol (TDS) transdermal systems on the buttock application site in healthy postmenopausal women.<sup>2</sup> The study found that the Mylan ETS and the Climara estradiol TDS were significantly different in the maximum serum level of estradiol ( $C_{max}$ ) delivered. The study evidenced that the

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<sup>1</sup> An original and two copies of this supplement are being submitted to the Dockets Management Branch.

<sup>2</sup> A complete Sponsor's report of the study was included in the citizen petition. A summary of the study was published in the Journal of Clinical Pharmacology, a peer-reviewed journal. See L. I. Harrison & D. Harari, "An Evaluation of Bioequivalence of Two 7-Day 17beta-Estradiol Transdermal Delivery Systems by Anatomical Site," 42 Journal of Clinical Pharmacology 1134-1141 (2002). An abstract entitled "Replacing Branded Estradiol Transdermal Systems and Generic Alternatives Does Not Result in Cost Savings," by J. P. Jones, M. M. Rowe, and L. I. Harrison, which focused on the pharmacoeconomic impacts of the study, was presented at the Academy of Managed Care Pharmacy, 14th Annual Meeting, Salt Lake City, UT, April 3-6, 2002.

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sup2

Mylan estradiol patch, when applied to the buttock, is not bioequivalent to Climara,<sup>3</sup> yet the labeling for the Mylan estradiol patch indicates that the product may be used on the buttock application site.

Berlex and 3M therefore requested in their citizen petition that FDA change the Therapeutic Equivalence Code of the Mylan ETS from being A-rated to B-rated; change the labeling of the Mylan ETS to not allow for placement of the patch on the buttock; and render the Mylan ETS misbranded under Section 502(a), (f), and (j) of the Federal Food, Drug, and Cosmetic Act (FDCA). In this supplement to the citizen petition, Berlex and 3M additionally request that FDA require Mylan to switch its 505(j) application to a 505(b)(2) application, for the reasons discussed below.

A 505(j) application requires, in pertinent part, that an applicant submit “information to show that [a] new drug is bioequivalent to the listed drug.” FDCA § 505(j)(2)(A)(iv). In addition, an applicant must also submit “information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug.” *Id.* § 505(j)(2)(A)(v). The Mylan ETS is not bioequivalent to the Climara patch at the buttock application site; therefore, the labeling’s reference to use on the buttocks misbrands the Mylan product. *See id.* § 502(a), (f), and (j). To avoid marketing a misbranded drug, Mylan will have to revise the labeling of the Mylan ETS. If the labeling of the Mylan ETS is not the same as that of Climara, then the Mylan ETS is not appropriate for a 505(j) application. *See id.* § 505(j)(2)(A)(v).

However, the Mylan product may be appropriate for a 505(b)(2) application. A 505(b)(2) application is appropriate when an applicant seeks “approval of a drug product that represents a modification of a listed drug.” 21 C.F.R. § 314.54(a); *see also* FDA, “Applications Covered by Section 505(b)(2)” (Draft Guidance) (Oct. 1999) (hereinafter “FDA 505(b)(2) Guidance”), at 3 (“For changes to a previously approved drug product, an application may rely on the Agency’s finding of safety and effectiveness of the previously approved product, coupled with the information needed to support the change from the approved product.”). Mylan’s product “represents a modification” of Climara – namely, the Mylan ETS is appropriate for use on the abdomen only – and the labeling of the Mylan ETS needs to reflect this difference. Because Mylan’s 505(j) application cannot take this labeling difference into account, FDA should reclassify the Mylan ETS application as a 505(b)(2) application, or Mylan should be required to change its application to a 505(b)(2) application. In addition, the Therapeutic Equivalence Code of the Mylan ETS will need to be changed from being A-rated to B-rated.

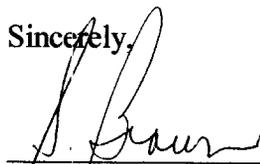
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<sup>3</sup> In its regulations, FDA lists criteria that could indicate actual or potential bioequivalence problems, including “[e]vidence from well-controlled bioequivalence studies that such products are not bioequivalent drug products.” 21 C.F.R. § 320.33(b). Berlex has provided evidence of the non-equivalence of the Mylan product to the Climara product when applied on the buttock. In the well-controlled bioequivalence study noted above, Berlex demonstrated that the Mylan ETS and the Climara estradiol TDS were significantly different in the maximum serum level of estradiol ( $C_{max}$ ) delivered, and that the 90% confidence interval exceeded the 125% acceptable limit ( $p=0.004$ ; Mylan ETS was higher). These findings demonstrate unequivocally that the Mylan and Climara transdermal systems are “not bioequivalent drug products,” thus fitting FDA’s definition of “pharmaceutical equivalents” that are not “bioequivalent drug products.” *Id.* § 320.33.

Recognizing Mylan's ETS application as a 505(b)(2) application is consistent with FDA's policies on 505(b)(2) applications. FDA does not consider as an appropriate 505(b)(2) application the following: (1) "[a]n application that is a duplicate of a listed drug and eligible for approval under section 505(j)," (2) "[a]n application in which the *only* difference from the reference listed drug is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than the listed drug," or (3) "[a]n application in which the *only* difference from the reference listed drug is that the rate at which its active ingredient(s) is absorbed or otherwise made available to the site of action is *unintentionally* less than that of the listed drug." FDA 505(b)(2) Guidance at 6; see also 21 C.F.R. § 314.54(b)(1) and (2). A 505(b)(2) application for the Mylan ETS would not be a "duplicate" of the Climara estradiol TDS because the labeling of the Mylan ETS would indicate use of the product on the abdomen only. In addition, FDA has already found that there is no difference in the Mylan ETS from the Climara estradiol TDS in terms of rate of absorption at the abdomen site. Accordingly, a 505(b)(2) application for use of the Mylan ETS on the abdomen would be appropriate.

In sum, the Berlex study confirms that when the Mylan ETS is placed on the buttocks, it is not bioequivalent to the Climara estradiol TDS, and it indicates that women switching from the Climara estradiol TDS to the Mylan ETS will experience an increase in drug exposure when the patch is placed on the buttocks. No studies have shown that this increase in drug exposure is not harmful to women's health; therefore, it is imperative that FDA take immediate action to prevent the Mylan ETS product from being used on the buttock. FDA can accomplish this by recognizing the Mylan ETS application as a 505(b)(2) application or by requiring Mylan to switch its 505(j) application to a 505(b)(2); in both cases, it is imperative that Mylan remove the buttocks site of administration information from its labeling in order to avoid being illegally in interstate commerce as a misbranded drug product. In the alternative, Berlex requests that FDA take the actions specified in the Berlex/3M January 16, 2002 citizen petition.

Sincerely,



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