

LAW OFFICES
ROTHWELL, FIGG, ERNST & MANBECK

A PROFESSIONAL CORPORATION
1425 K STREET, N.W.
SUITE 800
WASHINGTON, D C 20005
TELEPHONE (202) 783-6040
FACSIMILE (202) 783-6031

OF COUNSEL
JEFFREY L IHNEN
GLENN E KARIA
MARK I BOWDITCH
STEPHEN B PARKER

G FRANKLIN ROTHWELL
E ANTHONY FIGG
BARBARA G ERNST
HARRY F MANBECK, JR
GEORGE R REPPER
STEVEN LIEBERMAN
VINCENT M DELUCA
JOSEPH A HYNDS
ELIZABETH A LEFF
RICHARD WYDEVEN
MARTIN M ZOLTICK
MINAKSI BHATT
MICHAEL G SULLIVAN
SHARON L DAVIS
ROBERT B MURRAY
MARTHA CASSIDY, Ph D
ROBERT H CAMERON
THOMAS E MCKIERNAN*
MICHAEL J MORAN, Ph D*
ANNE M STERBA
LISA N PHILLIPS*
LEIGH Z CALLANDER*
C NICHOLE GIFFORD
REGINA A BAILEY
MONICA S DAVIS*
PATRICK T SKACEL
BRIAN S ROSENBLUM
TARA J PATE
MONICA C KITTS*
BRIAN A TOLLEFSON*

April 17, 2003

Via Hand Delivery

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* NOT ADMITTED IN D.C

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Citizen Petition Requesting FDA Not Recommend the Mylan
Estradiol Transdermal System (ETS) as a Generic Substitute to the
Climara Once-A-Week Estradiol (TDS) Transdermal System
Docket No.: 02P-0029/CP 1

Dear Sir or Madam:

We represent Mylan Technologies, Inc. ("Mylan"), holder of ANDA Nos. 75-181 and 75-233 for a generic estradiol transdermal product. Pursuant to 37 C.F.R. §10.30(d), Mylan submits these comments in opposition to the above-referenced Citizen Petition filed by Berlex Laboratories, Inc. and 3M Pharmaceuticals (collectively "Berlex") on January 16, 2002 (the "Berlex Petition"), requesting that the FDA: (1) withdraw the A rating of the Mylan Estradiol Transdermal System (ETS) as a generic substitute for the Climara once-a-week estradiol transdermal system; (2) require Mylan to change its label to limit application of the ETS to the abdomen only, and (3) declare the Mylan ETS misbranded under §§ 502(a), (f) and (j) of the Federal Food, Drug and Cosmetic Act ("FFDCA"). Berlex also filed a supplement to the Berlex

02P-0029

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Petition on November 27, 2002 ("November Supplement"), requesting (4) that the FDA require Mylan to switch its 505(j) ANDA to an application under 505(b)(2).

Mylan has an interest in the outcome of the Berlex Petition because the granting of any of the petitioner's requests would substantially adversely effect Mylan. The granting of any of these four requests would have the net effect of removing from the market the only generic alternative to Climara. Mylan respectfully submits that the Berlex Petition should be denied for at least the following separate and independent reasons.

First, ANDA Nos. 75-181 and 75-233 have been reviewed and approved by the FDA, demonstrating that they are fully compliant with all current statutory and regulatory requirements designed to ensure the safety and efficacy of generic drug products, as well as current FDA practices and recommendations for demonstrating bioequivalence specifically of transdermal products.

Second, the "new data" that Berlex presents with its petition is derived from a flawed, under-powered study, the design of which encourages a finding that the two products are not bioequivalent (i.e., the result Berlex desired), and which, when published in a peer-reviewed journal, was presented with so many qualifications and hedging that it was virtually conceded to be inconclusive. The Berlex study was based on an assumption of the ratio between test and reference product that was too low, resulting in the use of too few test subjects to provide any meaningful results. The procedures used for base-line correction and for re-applying patches that fall off were not in accordance with specific recommendations provided to Berlex by the FDA for the conduct of such studies with estradiol patches. See March 17, 2000 letter from FDA to Berlex, responding to the First Petition (Exhibit 1, attached hereto), page 10. While the under-powered Berlex study fails to demonstrate that the Mylan ETS meets the bioequivalence standards of the FDCA when compared to Climara, it does not demonstrate that the two products are inequivalent. This type of study would, at best, be considered a pilot used to design an appropriately-powered study that would conclusively show whether the two products were bioequivalent, or inequivalent. Such a flawed and inconclusive study as Berlex now presents cannot be considered as a reliable measure of the relative bioavailability of the two products.

Third, the very issues raised in the Berlex Petition have been previously considered and rejected by the FDA in a prior Citizen's Petition filed by Berlex (Docket # 98P-0434) (the "First Petition"). Specifically, the First Petition, like the present Berlex Petition, alleged that the Mylan ETS product should not be considered equivalent to Climara because of an alleged difference in absorption of estradiol between the abdomen and buttock application sites, and that the adhesion of the Mylan ETS is inferior to that of Climara. After due consideration of all of the arguments and evidence presented by Berlex, the FDA appropriately denied Berlex's request that bioequivalence studies be carried out at both sites of patch application, and that an application under 505(b)(2), rather than an ANDA, be required for a generic drug product relying on Climara as a reference listed drug. See Ex. 1, page 26. The present petition adds nothing to support the arguments that the FDA has already rejected.

In sum, Berlex presents nothing new in the present petition, and the data presented as allegedly demonstrating non-bioequivalence is from a study containing fundamental flaws in its design that render its results essentially meaningless. This second attempt by Berlex to eliminate generic competition for its Climara product should be rejected, and the Berlex Petition, including the request in the November Supplement, denied.

I. THE MYLAN ANDAs MEET ALL STATUTORY AND REGULATORY REQUIREMENTS

The Berlex Petition alleges that the Mylan ETS product is not bioequivalent at the buttock application site, and so should not have been approved for market. Berlex Petition, pages 2-3. The flaws in Berlex's position require little discussion or elaboration. The process by which the FDA reviews ANDAs follows a rigorous, well-established procedure that applies proven, scientifically sound principles to the determination as to whether or not a proposed generic product can be considered an appropriate substitute for the branded reference product. The FDA reviewed these principles and procedures in detail, along with their scientific validity and relevance, in its March 17, 2000 letter in response to the First Petition. See Ex. 1. The FDA has already determined that the Mylan ETS products meet every one of the criteria necessary to establish bioequivalence, and an "AB" Therapeutic Equivalence rating.

II. THE NEW STUDY ALLEGEDLY SHOWING NON-BIOEQUIVALENCE IS FLAWED AND INCONCLUSIVE

In its new petition, Berlex presents the results of a bioequivalence study between the Mylan ETS and Climara at the buttock application site, which it claims provides "concrete evidence" (Berlex Petition, page 3) that "clearly illustrates" (Berlex Petition, page 6) that the Mylan ETS and Berlex's Climara are not bioequivalent when applied to the buttock. Berlex also asserts that their study "demonstrates" that Mylan's ETS has significantly worse adhesion at the buttock site than does Climara. Berlex Petition, page 6. Contrary to these allegations, in the peer-reviewed publication of this same study,¹ the authors could only say that the study "indicated" that the products were not bioequivalent, and "suggests" that bioequivalence at one site is not indicative of bioequivalence at another (see Ex. 2, Abstract). In fact, even a cursory look at the data presented in the published study shows that the mean serum concentration profiles of the two products are virtually identical. Ex. 2, Figure 1. Nonetheless, it is argued in the Berlex Petition that the ratio of C_{max} of the Mylan ETS relative to that of Climara, which should fall within a 90% confidence interval between 0.8 - 1.25, the FDA's criteria for bioequivalence (BE), shows that the two products are not bioequivalent. According to the Berlex study, the ratio of C_{max} for Mylan's ETS relative to Climara has a 90% confidence interval of 1.068 - 1.266 for baseline corrected data. It is worth noting that the reported ratio of $AUC_{0-tlast}$ for Mylan's ETS relative to Climara has a 90% confidence interval of 1.046 - 1.237 for baseline corrected data. Berlex Petition, Attachment 1, Table I.² As will be explained below in more detail, the study in fact seems biased in a way that would erroneously lead one to conclude that the products are "not bioequivalent." Also, the study was flawed in a way to make it unsuited for

¹Harrison, L.I. & D. Harari, "An Evaluation of Bioequivalence of Two 7-Day 17 β -Estradiol Transdermal Delivery Systems by Anatomical Site," J. Clin. Pharmacol., 42:1134-41 (2002) (Exhibit 2, attached hereto).

²Once again, in their peer-reviewed publication, the authors candidly conceded that "[i]t is unclear why the generic patch was found not to be bioequivalent at the buttock site in the present study but was bioequivalent at the abdomen site in a previous study." Harrison & Harari (Ex. 2), page 1140. The authors also concede that "[i]t is not known whether the higher estradiol serum levels maintained by the generic Estradiol Transdermal System are safe and efficacious." Id., page 1139.

FDA submission, even if bioequivalence had been concluded. The data presented in the Berlex study has not proven bioequivalence, and is at best inconclusive.

A. The Berlex Study Was Underpowered

Simply stated, the Berlex study utilized too few subjects to confirm bioequivalence. Berlex states that its study was "statistically powered" (Berlex Petition, page 3) and "as robust and fair as possible." Harrison & Harari (Ex. 2), page 1140. However, the basic design of the Berlex study not only deviates significantly from the Mylan study showing bioequivalence between the ETS and Climara at the abdomen application site, it deviates from both industry and FDA-accepted guidelines for conducting and powering such a study. In its March 17, 2000 letter denying in part Berlex's First Petition, the FDA stated that bioequivalence studies must, "using the best available method, [give] a demonstration of rate and extent of absorption consistent with good medicine and science." Ex. 1, pages 25-26. For reasons it does not explain, Berlex assumed in its statistical analysis a mean ratio between the relevant pharmacokinetic parameters of the compared products which deviated by no more than 5% from a ratio of 1.0, and an intra-subject variability of 25% for log-transformed parameters (%CV). There are numerous examples in which mean ratio deviates by more than +/-5%, yet bioequivalence can be clearly demonstrated. Mylan's pivotal study was publicly available from any number of sources (for example, the New Jersey Formulary), and Berlex could have (and should have) consulted it when designing this new study accompanying the Berlex Petition. Using a limited number of subjects to power a study for a ratio of 0.95 to 1.05 (i.e. <5% difference) essentially "stacks the deck" against a fair assessment of bioequivalence. The only conclusion that can be drawn from the Berlex study is that it is inconclusive.

As a statistical tool, the mean ratio between the compared products is used to determine the magnitude of any difference between compared products (the greater the deviation from a ratio of 1, the greater the difference); intra-subject variability is an estimate of how variable a particular product is within the same individual (reproducibility). Berlex also powered its study for 95% confidence and 80% power, based on a mean ratio that would deviate 5% or less from

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1.00.³ The FDA has set the criteria for bioequivalence such that the 90% confidence intervals for the ratio of test to reference must fall in the range of 0.8 and 1.25. Thus, it is quite possible, for example, for two bioequivalent products to have a point-estimate mean ratio ranging from approximately 0.85 to 1.18 (or more), such that the associated 90% confidence intervals would fall within 0.8 to 1.25. This would require that such a study be powered with a greater number of subjects to account for that degree of difference from a ratio of one, for any given %CV.

To further illustrate the point of proper powering, refer to the industry-accepted method appearing in Hauscke et al., "Sample Size Determination for Bioequivalence Assessment Using a Multiplicative Model," *J. Pharmacokinetics and Biopharmaceutics*, 20: 557-561 (1992) (Exhibit 3, attached hereto), for some examples:

Sample Size Estimates to meet 90% Confidence Interval Criteria, with 80% Power [from Hauscke et al.]		
True Population Ratio	True Population %CV	Sample Size N
1.05	25%	28
1.10	25%	48
1.15	25%	110
1.15	15%	41
1.15	20%	72
1.15	25%	110

Using a constant %CV of 25% as an example, it may be seen that as the ratio deviates from unity (1.0) the appropriate sample size quickly increases. Correspondingly, at a constant ratio of 1.15,

³ Ninety-five percent (95%) confidence interval specifies that the probability that the ratio will fall in that range. Eighty percent (80%) power represents the percent chance of correctly concluding that the two products are bioequivalent, but it also means there is a 20% chance that two products will be falsely concluded to be not bioequivalent.

as %CV increases, the sample size requirements also increase. Any single bioequivalence study may not estimate the exact, true population ratio or %CV; and, as the study in question has some flaws associated with it, one cannot rely on the study results for estimates of true ratio or %CV.

Based on the assumed values for the mean ratios (i.e. 1.05) and intra-subject variability (25%), Berlex selected a sample size of 42 test subjects (n=42), of which only 40 completed the study, and of which only 39 were used in the final data analysis (while the published version of the study notes that one subject who completed the study was not included in the pharmacokinetic analysis, neither the Berlex Petition, nor the Commentary on the study provided as Attachment 1 to the Berlex Petition, note this fact).⁴ Based on the industry standard method of Hauscke et al., it would normally be reasonable to power a pivotal study to a degree somewhat larger than that used in the Berlex study. Also, it is common for subjects to drop out of a study such as that executed by Berlex (and in fact, two did), thus one would normally recruit even higher numbers of subjects to account for that. Had the study completed 48 subjects rather than 39, it is probable that the 0.8 to 1.25 bioequivalence criteria would have been met. However, Berlex's prior assumptions used to estimate appropriate sample size of the study limit their ability to draw a conclusion with respect to assessment of bioequivalence. In other words, if one wanted to truly assess bioequivalence, one would err on the side of choosing a larger number of subjects, for greater power, but if one were interested in a result that did not meet FDA bioequivalence standards, one would design the study to use as few subjects as possible, just as Berlex did.

B. The Berlex Study Was Not Properly Base-Line Corrected

The Berlex study was further biased in its design in failing to correct properly for base-line levels of estradiol in the test subjects. In the Berlex study, only a single base-line measurement was taken (at t_0 , or "time zero"). It is customary to obtain at least three separate base serum level measurements, and use the average of those measurements as the base-line for

⁴ In fact, if Berlex had performed a proper base-line correction of the subject data (see section II.B, below), it is possible that this subject need not have been excluded from the pharmacokinetic analysis.

the study data, and in fact this is the procedure recommended by the FDA in its March 17, 2000 letter responding to Berlex's First Petition. Ex. 1, page 10. The use of a single "base-line" value instead of an average base-line value introduces an unacceptable degree of inaccuracy into the results. This is a further reason to consider the Berlex study unreliable.

III. BERLEX'S SUGGESTION THAT THE SAMPLING INTERVAL USED IN THE ORIGINAL MYLAN STUDY MASKED NON-BIOEQUIVALENCE AT THE ABDOMEN SITE IS BASELESS.

Berlex suggests as a possible explanation for the earlier finding of bioequivalence between Mylan's ETS and Climara when applied to the abdomen, and their present finding of not bioequivalent at the buttock application site, that Mylan's sampling interval failed to accurately determine the time at which peak plasma concentrations (C_{max}) were reached (called " T_{max} "). Berlex Petition, pages 5-6. Berlex asserts that with Climara, peak serum concentrations are reached near 36 hours after application. Berlex Petition, page 5. According to Berlex, Mylan's failure to measure serum estradiol levels at six-hour intervals from 24 to 48 hours after application "leads to the erroneous conclusion that the profiles of the Mylan estradiol transdermal system and that of Climara's are equivalent." Id.

The Berlex argument must fail. First, similarity between the plasma concentration profiles, per se, is not, and never has been, a requirement for bioequivalence. Ex. 1, page 13 ("The Agency's position is that matching of plasma concentration profiles of the parent drug or metabolites is not currently used as a regulatory method or criterion for the approval of ANDAs for any drug product approved by the FDA.") Thus, Berlex's assertion, even if it were true, is irrelevant.⁵ Second, contrary to Berlex's assertion, the times at which peak mean serum estradiol concentrations are reached with both Mylan's ETS and Climara is at approximately 18 hours when applied to the buttocks. Harrison & Harari (Ex. 2), Figure 1, first panel. This finding is consistent with Mylan's own bioequivalence study, which showed that approximately 94% of the observations on subjects administered Climara to the abdomen showed peak plasma estradiol concentrations at ≤ 24 hours and 73% showed peak levels at ≤ 18 hours. In addition, in

⁵ The FDA went so far as to state that "[t]he Agency considers T_{max} so variable that it does not apply strict statistical criteria to this parameter." Ex. 1, page 9.

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discussing differences in rate of absorption, Harrison and Harari comment that absorption is expected to be faster (and hence T_{max} occurs earlier) when Climara is applied to the buttocks compared to the abdomen. Mylan's sampling interval, therefore, was entirely appropriate.

IV. BERLEX'S ASSERTION THAT ADHESION IS WORSE WITH MYLAN'S ETS IS UNSUPPORTED

Finally, Berlex curiously reaches the conclusion that its study shows that adhesion of Mylan's ETS is worse than that of Climara (Berlex Petition, page 6), even though the study was not designed to measure adhesion. Once again, greater candor was required in the peer-reviewed publication of the study, in which the authors conceded that "given that [adhesion and irritation] were not the primary outcomes of the study, further data are required to assess the validity of these observations." Harrison & Harari (Ex. 2), page 1140. In other words, the authors concede that the "data" on adhesion is inconclusive.

It is customary to assess adhesion, either in a separate study or together with a bioequivalence study, in a controlled clinical environment with trained personnel making the observations. In the Berlex study, test subjects were simply provided with tape, and told to tape the patch down if it lost adherence. There were no criteria whatsoever provided to the subjects for assessing what constituted a loss of adhesion, or for assessing the degree of loss of adhesion. The application of tape was left entirely up to the discretion of the test subject, and therefore all data gathered was anecdotal. Furthermore, subjects were even instructed to re-apply a patch that had fallen off, in contradiction to customary and accepted procedures for either an adhesion or a bioequivalence study. Because the study presented in the Berlex Petition was not designed, or conducted, in a way that would provide meaningful data on the comparative adhesion of the Mylan ETS and Climara, no reliable conclusions can be reached based upon its results.

CONCLUSION

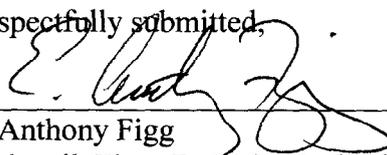
Because Berlex did not present any arguments in the present Petition that were not addressed and rejected by the FDA in Berlex's First Petition, and because the allegedly

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“concrete” data presented in the present Petition was obtained from a flawed and biased study design, and is inconclusive, the Berlex Petition should be denied.

Respectfully submitted,



E. Anthony Figg
Rothwell, Figg, Ernst & Manbeck, P.C.
1425 K Street NW, Suite 800
Washington, DC. 20005
tel. (202) 783-6040
fax (202) 783-6031

Enclosures: Exhibits 1-3