ATTACHMENT 1

Commentary on Study 304100 Findings: Mylan Generic Transdermal Estradiol System is not Bioequivalent to Climara Transdermal System at Buttock Application Site

Background

Berlex/3M Pharmaceuticals had grave concerns (which have now been shown to be justified) when OGD approved Mylan's ANDA for a 7-day transdermal estradiol system as bioequivalent to the reference listed drug Climara at both listed sites of application. Mylan conducted only one clinical study on the abdomen site and none on the buttock application site. As pointed out in our Citizen's Petition of June 12, 1998 (Docket # 98P-0434/CP1), the Mylan ANDA contained, in our opinion, an inadequate amount of information on the bioequivalence performance of the Mylan transdermal estradiol system, lacking data on both multiple dosing and on the buttock application site.

The Climara NDA contained safety, efficacy and pharmacokinetic studies at only the abdomen application site and on December 22, 1994, Climara was approved for application at the abdomen site only. Subsequently, Berlex (the NDA holder) performed a bioequivalence study that compared the buttock with the abdomen application site. Results of this study, submitted on April 10, 1996 in Supplement 006 to the NDA, showed that the two sites were not bioequivalent. Cmax and AUC values for the buttock application site were greater than allowed by the confidence interval analysis. Despite the finding of bioinequivalence, the medical reviewer of the Division of Endocrine and Reproductive Products accepted the study as showing therapeutic equivalence. Thus, the buttock application site for Climara was granted on April 11, 1997.

Given that estradiol absorption from Climara is not equivalent from the buttock and abdomen application sites, and that the buttock site maintains the higher levels, we had two concerns when the Mylan generic transdermal system was given an approval that was based on only a single abdomen application site study. Our first concern was that the Mylan generic and Climara transdermal systems were not bioequivalent at the buttock application site. Our second, more serious, concern was that the Mylan generic might produce significantly higher serum drug levels than that of Climara.

To investigate these two concerns Berlex conducted an appropriately powered (N = 40) bioequivalence study which compared the bioequivalence of estradiol delivery from the Mylan generic and Climara transdermal systems on the buttock application site in healthy postmenopausal women.

Study 304100 Synopsis

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 0.1 mg estradiol/day. One test transdermal system was a modified Climara formulation being investigated as a possible product improvement; the other test transdermal system was the Mylan generic.

Forty-two postmenopausal women were enrolled in the study. 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 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. At 30 minutes after removal of a transdermal system, skin irritation was assessed. There was 2 weeks between the start of each study period, providing for a one-week washout interval between periods.

Analytes

Estradiol and estrone were measured simultaneously in the serum by a validated GC/MS assay. The lower limits of quantitation for estradiol and estrone were 5 and 10 pg/mL, respectively. Estrone sulfate was quantitated with a validated LC/MS/MS assay. The lower limit of quantitation for estrone sulfate was 50 pg/ml. Descriptions of the procedures and validations for these assays can be found in the study report.

Pharmacokinetics

The primary objectives of the study were to determine the bioequivalence of 17β-estradiol, estrone, and estrone sulfate from the Mylan generic transdermal system and from a modified Climara transdermal system with that from the reference Climara transdermal system. 17β-estradiol was the primary analyte.

The primary derived variables of interest were AUC to the last quantifiable concentration (AUCtlast), Cmax, and AUC calculated to the population median Tmax of the reference product (AUCtmax) for each analyte. All variables were calculated from the measured concentrations before and after baseline subtraction.

Statistical Plan

Because this study involved two test transdermal systems and a reference system, the principle of multiple inferences (simultaneous confidence intervals in this case) was applied. This principle recognizes that the overall coverage probability of the confidence intervals would be lower than the nominal coverage probability of 90% if the size of each confidence interval were kept at 90%. The appropriate Bonferroni analysis requires the calculation of a 95% confidence interval for the log transformed data for inferring bioequivalence of each of the pairs (1) modified formulation and Climara, and (2) Mylan generic and Climara.

The statistical plan was modified to incorporate FDA guidelines that recommend a 90% confidence interval analysis for bioequivalence assessments. Thus, as an additional analysis for the Cmax and AUC variables for estradiol, a 90% confidence interval was constructed for each of these assessments without multiplicity adjustment.

Only the results from the analysis of the Mylan generic and Climara pair are presented in this commentary. All the study comparisons are included in the sponsor's final study report.

Results

General Observations

Forty subjects completed the study. One subject voluntarily withdrew because of personal reasons before receiving drug, and one subject withdrew after completing the Mylan generic system treatment because of adverse events.

Patch lift/patch fall-off occurred in 18% of the patch applications with Climara and in 59% of the patch applications with the Mylan generic system. The median lift-off time relative to dosing was 119 hours for Climara (6 occurrences) and 35.5 hours for the Mylan generic (23 occurrences).

Serum Levels of Estradiol (Primary Analyte)

The Mylan generic system consistently maintained serum estradiol levels that were on average greater than those from the reference Climara system for all times points over the entire 7-day application interval. Bioequivalence analysis of this data is given in Table 1 for both estradiol concentrations that were and were not corrected for endogenous levels.

Table 1: Statistical summary of estradiol bioequivalence (95% and 90% confidence intervals) for the Mylan generic estradiol patch in relation to the reference Climara patch

PK Variable	Ratio, Test/Reference	p-value	Confidence Interval 95%	Interval 90%
Cmax				
Baseline uncorrected	1.159	0.004	1.049, 1.281	1.066, 1.260
Baseline corrected	1.163	0.004	1.051, 1.288	1.068, 1.266
AUC(0-tlast)				
Baseline uncorrected	1.133	0.011	1.030, 1.247	1.046, 1.227
Baseline corrected	1.138	0.012	1.024, 1.257	1.046, 1.237
AUC(0-Tmax,ref)				
Baseline uncorrected	1.058	0.247	0.961, 1.166	0.976, 1.148
Baseline corrected	1.057	0.280	0.955, 1.171	0.971, 1.151

Results from the statistical analyses of estradiol, the primary analyte, show that the Mylan generic transdermal system fails the Cmax test for bioequivalence (90% CI and 95% CI) both when calculated with or without baseline subtract (Table 1).

It can be concluded that the Mylan generic system is not bioequivalent to Climara at the buttock application site for estradiol.

Conclusions

Study 304100 confirmed our hypothesis that the absorption of estradiol from the Mylan generic transdermal system was not bioequivalent to that from the reference Climara transdermal system for the buttock application site.

The major difference between the products was in the Cmax value. The maximum serum concentration of estradiol was on average about 16% higher with the Mylan generic system than with Climara. Therefore, patients switched to the Mylan generic 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.

It is unknown whether or not the higher estradiol serum levels maintained by the Mylan generic system are safe and efficacious. From the Climara NDA, a therapeutic serum level range was established for transdermal delivery of estradiol at the lower abdomen site. Further Phase IV study by Berlex extended the therapeutic serum level range to cover the buttock site of application. Approval of this application site, however, was based upon medical opinion, not bioequivalence documentation. It does not seem prudent to us to extend the therapeutic serum level range for estradiol even further during ANDA review without bioequivalence documentation.

Every attempt was made in this study to have a fair comparison of Climara with the Mylan generic system. It was feared that if Mylan patches preferentially lifted (since our preliminary data suggested that the Mylan product had the poorer adhesion), then the product comparison could be biased. To prevent such a bias, taping (but not overlays) was allowed. Indeed, the results show 59% taping for the Mylan product compared with 18% for Climara.

The blood-sampling schedule in the study was also selected to afford a fair comparison of the two products. Frequent sampling was included in the first 48 hours (every 6 hours between 12 and 48 hours) to accurately characterize Cmax and AUC(tmax). This sampling schedule was in contrast to that used in the Mylan bioequivalence study. In the latter study, no samples were taken between 24 and 48 hours, despite the fact that Climara's Cmax often occurs within this interval. This could have introduced a substantial bias in that study.

Overall, the present study was adequately powered and properly designed to conclude that the Mylan generic transdermal estradiol system and the reference transdermal system Climara are not bioequivalent at the buttock application site. Patients switched from Climara to the Mylan generic system will experience a substantial increase in drug exposure of approximately 14% over 7 days when using this site of application. It is recommended that the FDA resolve this issue expeditiously, by removing the buttock application site indication from the Mylan generic labeling.