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Berlex Laboratories, Inc.

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir or Madam:

Re: Docket No. 03D-0007 – Draft Guidance for Industry On Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation

Reference is made to the Federal Register notice dated January 31, 2003 (Volume 68, Number 21, page 5025 ff.), and to the draft guidance to sponsors for the development of hormone therapy for moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms.

Berlex Laboratories, Inc. ("Berlex"), a subsidiary of Schering AG, Germany has a major US presence in the area of female healthcare, with products for estrogen therapy (ET), long-acting contraception, and oral contraception. Schering AG is a European leader in the field of Gynecology and Andrology products. Both Berlex and Schering AG appreciate the opportunity to provide comments on the draft guidance.

In general, both Berlex and Schering AG support the draft guidance and believes that it provides updated information for the development of compounds to treat vasomotor and vaginal symptoms. However, we offer the attached comments for your consideration. As requested in the Federal Register, our comments are being provided in duplicate.

Berlex and Schering AG hope you find our comments helpful; however if you have any questions, or need additional information, please contact the undersigned at (973) 487-2162 or via telefax at (973) 487-2016.

Sincerely,

BERLEX LABORATORIES

Sharon W. Brown
Director, Drug Regulatory Affairs

Attachment001
swb/htguidance

030-0007

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FDA Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms Recommendations for Clinical Evaluation

guidance text	comments
Study considerations/Inclusion exclusion criteria	
Line 97: only postmenopausal women to be included	• Please provide guidance as to how sponsors would be able to obtain indications for perimenopausal women • how does the Agency define "perimenopausal" • as the most severe hot flush symptomatology occurs in perimenopausal women the restriction to postmenopausal women is not in line with medical needs
Line 104-107: patients who have self identified at least one moderate to severe symptom (1. vaginal dryness, 2. vaginal / vulvar irritation / itching, 3. dysuria, 4. vaginal pain associated with sexual activity	• We suggest providing a definition for mild, moderate, severe similar to what was provided for vasomotor symptoms so there is consistency of data among patients as well as studies • as patients included will have different "most bothersome symptoms", how will the different symptoms be handled in the overall data analysis
Line 104-107: ..., have no greater than 5 percent superficial cells.	• We suggest the evaluation of clinical symptoms because the use of vaginal smears with cell counts is somewhat outdated
Lines 112-118: Washout periods for estrogen and/or progestin therapy	• We recommend that the wash-out period for oral estrogen is 4 weeks since it has been shown that the effect of oral estrogen has vanished at that time. Moreover, taking into account the half-lifes of potential components, a washout period of four weeks should be sufficient if not indicated otherwise based on pharmacokinetic results.

FDA Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms Recommendations for Clinical Evaluation

guidance text	comments
Line 124: Endometrial biopsy at screening: all subjects who have a uterus have endometrial biopsy performed at screening.	• We recommend that the requirement for biopsy at screening be evaluated in terms of whether the studies are short or long term studies. For short-term studies that are three months and less, these studies should not require a biopsy. These studies are too short for treatment to induce relevant changes of the endometrium. • For study entry into long term studies, if women have insufficient tissue from endometrial biopsy, we suggest that in the case of insufficient tissue an ultrasound of < 5 mm at screening qualifies the patient for inclusion.
Monitoring	
Line 132: Endometrial biopsy at end-of-study: all subjects who have an uterus undergo an endometrial biopsy at screening and at the end – of – study	• As mentioned previously, for short term (e.g. 3 months) studies, biopsies are not advisable because it is unlikely that three months of treatment will induce relevant endometrial changes. Biopsies should be limited to abnormal ultrasound findings (e.g. thickness >5 mm).
Line 139-140: safety assessment of lipids, carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.	• It is suggested that these genetic mutations such as factor V Leiden, Protein C and S deficiency be deleted because their predictive value is poorly defined.
Primary Endpoints	
Line 161: Primary Endpoints mean change from baseline to week 12 in vaginal pH	• It is suggested that mean change from baseline to week 12 for vaginal pH be deleted because it is an unreliable endpoint. Lowering of the vaginal pH can be easily influenced by other factors, such as a vaginal infection.
Lines 176-185: Statistical significance for all three endpoints	• It is proposed to use only one clinical parameter (urogenital symptoms) as the primary endpoint.

FDA Guidance for Industry

Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms Recommendations for Clinical Evaluation

guidance text	comments
Lines 261: Curricula vita for participating pathologist	• Please clarify at what point the CVs for the pathologist should be submitted. It's not clear whether the CVs should be submitted with the initial study protocol or upon completion of the clinical study report.
Line 279-282: ... the concurrence of two of the three pathologists be accepted as the final diagnosis. if there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis	• As a global company, we hope to conduct clinical trials that can be used worldwide. It would be helpful if the US and EU guidance on this topic were more harmonized in terms of pathology reading. • The final assessment of a biopsy (in case of discrepancies) should be performed during a final arbitration meeting between the involved at that stage unblinded pathologists, this expert discussion which is a reflection of usual medical decision making will most likely find the most adequate diagnosis rather than a formal procedure.
Line 287-288: digital recording of diagnostic areas of all slides have to be produced	• We suggest that the requirement for digital recording be deleted because this is not standard practice for pathologist. Also since the slides are available for 15 years in Europe and 20 years in the US; there is always the possibility of examining the slides.
Study Analysis	
Line 304-315: the results from the clinical trial demonstrate a hyperplasia rate that is ≤1 percent with an upper bound of the one-sided 95 percent confidence interval for that rate that does not exceed 4 percent.	• It should be clarified whether the point estimate of the hyperplasia rate is required to be 0.01 per year; if a rate of 1 percent is anticipated the probability to obtain a point estimate of 1 percent would be 50% only.

- **Additional comment**: Please provide guidance to sponsors who wish to develop a product for endometrial protection only.