

UPS OVERNIGHT



Berlex, Inc.

December 3, 2004

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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**Re: Docket No. 03D-0007 – Draft Guidance for Industry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is made to the Federal Register notice dated January 31, 2003 (Volume 68, Number 21, page 5025 ff.), and to the draft guidance for industry for the development of hormone therapy for moderate to severe vasomotor symptoms and moderate to severe vulvar and vaginal atrophy symptoms. Berlex provided comments to the docket on March 29, 2003. Through interaction with the Division of Reproductive and Urologic Drug Products, Berlex learned that the Division is interested in obtaining any additional comments or suggestions. Berlex/Schering AG hereby submits the attached additional comments, in duplicate, to Docket No. 03D-007.

Berlex Inc. ("Berlex"), a subsidiary of Schering AG, Germany has a major US presence in the area of female healthcare, with products for hormone therapy (HT), 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 applaud the Agency's effort in providing clinical guidance for estrogen and progestin containing drug products for the use in vasomotor symptoms. Berlex and Schering AG appreciate the opportunity to provide additional comments on the draft guidance especially during this critical time as it relates to the treatment of postmenopausal women.

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 INC

A handwritten signature in black ink, appearing to read "S. Brown", is written over the typed name.

Sharon W. Brown
Director, Drug Regulatory Affairs

Attachment
swb/htguidance/013
cc Dr Daniel Shames

03D-0007

C7

FDA Guidance for Industry
Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms
Recommendations for Clinical Evaluation-January 2003

guidance text	comments
Indications	
Line 66: Definition of Severe	<ul style="list-style-type: none"> We suggest that the definition should read "sensation of heat with sweating, causing impairment of activity instead of cessation
Primary Endpoints	
Line 147-154: - Currently there are four endpoints	<ul style="list-style-type: none"> Instead of 4 primary endpoints, we suggests that only one endpoint should be included. It should be the relative change from baseline in frequency of moderate to severe hot flashes to week 12. We propose a new section for secondary endpoints and the other three primary endpoints would shift to this new section. The new section "secondary endpoints" would include response defined as 80% reduction of hot flashes versus baseline The endpoints on "mean change in severity of moderate to severe vasomotor symptoms" should be changed. If the wording is applied exactly, all subjects without moderate to severe symptoms during treatment would yield missing values. Especially for very efficacious medications it would be impossible to power and to conduct reasonably such an analysis. Please clarify.
Study Considerations	
Lines 221-223 – Ineffective dose	<ul style="list-style-type: none"> There is a need to define an ineffective dose. We propose that a dose should be considered as ineffective if the relative change in frequency does not exceed the placebo effect by 20%. The lowest effective dose would be determined by increments usually accepted in dose-finding studies. A statement such as "a dose exceeding the lowest effective dose can be supported by a dose response study should be included

Monitoring

Lines 255-260-Safety and Efficacy Reading

- Clarification is needed because it does not specifically provide for a "safety read" for all subjects as they come off study - the potential exists that a subject could complete the study, have a biopsy, and not have that biopsy read for several months until sufficient slides were collected to begin the efficacy readings. Provisions need to be made for the women who may not bleed on drug and continue until the end of study then has a biopsy. This biopsy may not be read immediately and how does one rule out the possibility that the subject could have hyperplasia or adenocarcinoma of the endometrium.

Appendix

- We are seeking clarification regarding the procedure of efficacy evaluation regarding the determination of the final diagnosis:
1. Categories used for the determination of an agreement:
The final diagnosis depends on the used pathology categories due to the definition of an agreement between two readers. It should be stated which of the following categories should be used for the definition of an agreement:
 - (A) Blaustein categories as given in the appendix including different categories for Blaustein sub-categories 4a, 4b, 4c, and as well for 5a, 5b (12 categories not considering insufficient tissue and no tissue)
 - (B) Blaustein categories as given in the appendix not using the Blaustein sub-categories 4a, 4b, 4c, and as well for 5a, 5b (9 categories not considering insufficient tissue and no tissue))
 - (C) Atypical hyperplasia, complex hyperplasia, simple hyperplasia, benign endometrium as stated in section IV D.
 - (D) Hyperplasia yes/no

Monitoring (con't)

Appendix (con't)

2. Evaluation procedure:
It should be clarified whether the agreement between two readers always overrules even a worse diagnosis of the third pathologist. Otherwise the proposed procedure would always lead to the worst case diagnosis. Hence, it should be stated which of the following procedures should be used, if the categories are ordered from the most benign diagnosis upwards to the most severe one and the result of reader i is given by x_i .

(1) Final diagnosis = $\max(x_1, x_2, x_3)$

(2) Final diagnosis =

$$\left\{ \begin{array}{ll} \max(x_1, x_2, x_3) & \text{if } x_1 \neq x_2 \text{ and } x_1 \neq x_3 \text{ and } x_2 \neq x_3 \\ x_1 & \text{if } x_1 = x_2 \text{ or } x_1 = x_3 \\ x_2 & \text{if } x_1 = x_2 \text{ or } x_2 = x_3 \\ x_3 & \text{if } x_1 = x_3 \text{ or } x_2 = x_3 \end{array} \right.$$

Regarding the incidence estimation on the dichotomous variable hyperplasia yes/no the different evaluation procedures are not all equivalent if the final diagnosis is determined by (2). C and D are equivalent. However, A, B, and C lead to different final diagnoses.

Example 1: $x_1 = \text{simple hyperplasia}$, $x_2 = \text{weakly proliferative}$, $x_3 = \text{disordered proliferative}$
leads to the final diagnoses
A = simple hyperplasia, B = proliferative, i.e. no hyperplasia, C = benign endometrium i.e. no hyperplasia.

Example 2: $x_1 = \text{simple hyperplasia}$, $x_2 = \text{weakly proliferative}$, $x_3 = \text{inactive}$
leads to the final diagnoses
A = B = simple hyperplasia, C = benign endometrium i.e. no hyperplasia

Monitoring (con't)

Appendix (con't)

Example 3: x_1 = complex hyperplasia with atypia, x_2 = disordered proliferative, x_3 = disordered proliferative
leads to the final diagnoses
 A = disordered proliferative, i.e. no hyperplasia, B = proliferative, i.e. no hyperplasia, C = benign endometrium i.e. no hyperplasia.

3. Depending on the evaluation procedure, the incidence estimation can be biased. The worse case procedures (1) lead to the highest upward bias depending mainly on the specificity of the diagnostic procedure. Even a very high specificity of 99% for each reader would lead to an expected incidence estimation of approximately 4% if the true incidence is only 1% and independence between the readers is assumed. Consequently, the criterion on the upper confidence limit being less than 4%