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Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Docket No. 03D-0007. Estrogen and estrogen/progestin drug products

Comments

Dear Sir, dear Madam,

Reference is made to the FDA draft guidance for industry titled "Estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms- Recommendations for clinical evaluation". At this time, we would like to submit comments to the draft guidance. Please find them below.

1/ Lines 68-77 and 104-107:
a/ The indication of vulvar and vaginal atrophy (VVA) could previously be granted as part of the class labeling. In the new draft guidelines, it is not clear whether for new applications the FDA requires to have VVA endpoints included in clinical trials as co-primaries or as secondary endpoint to obtain the VVA indication.

b/ The first endpoint for VVA "Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as being the most bothersome" is not well defined. It is difficult to assess a mean change if there are two different scales, i.e. none, mild, moderate and severe for four VVA symptoms but only presence versus absence for "vaginal bleeding associated with sexual activity".

2/ Lines 124-126 and 132-140:
With respect to the requirement of an endometrial biopsy for a postmenopausal symptoms (PMS) study utilizing an estrogen/progestin combination therapy, we believe that there is a difference between a 3-month PMS study with an estrogen only product (possibly justifying a biopsy) versus a 3-month PMS study with a combination product. This combination product will undergo a full one-year endometrial safety evaluation. Therefore, we believe that collection of endometrial biopsies at the entrance and end of the study in the 3-months PMS study in women administered an estrogen/progestin combination is not needed. We propose the following alternative: A transvaginal ultrasonography (TVS) to be performed at study entry. All women with an endometrial thickness more than 4 mm should be excluded from the study. At study end, a TVS is repeated and an endometrial biopsy is only recommended for those women with TVS higher than 4 mm.

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Lines 139-140 and 293/294:
If a study is conducted with a comparator, we would like to know whether the numerical results of the safety assessment of the lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) can be included in the label (data form the investigational drug and comparator).

Line 141: A separate and adequate pharmacokinetics study could be performed with the final formulation and would measure parent compounds and certain metabolites, if appropriate, prior to a PMS study. We believe that these measurements do not need to be repeated in the clinical program

Line 142-163:
We have the same comments as for lines 68-77 and 104-107. It is not clear whether VVA and PMS endpoints are all co-primaries. If the PMS and VVA indications are sought, it is not clear whether studies need to be powered for both indications. To obtain both indications, we propose to either keep VVA secondary and power only for PMS or to define hierarchy of families of hypotheses, e.g. first on PMS, second on VVA, keeping the significance level for each family with the second only tested in a confirmatory way if the first is significant.

Line 217:
The draft guidelines require endometrial safety studies to be run double-blind. When not combining an endometrial safety with a PMS study and if biopsies are read blinded to the pathologists, we believe that the endometrial safety study could be an open label study.

Line 255-260:
The draft guidelines recommend that a single pathologist assess the slides from the endometrial biopsies obtained at screening or all the unscheduled biopsies performed during the study taken for safety reasons. We recommend that two independent pathologists assess these biopsies. This recommendation is to avoid the inclusion of false negative patients in the study (Some cases of hyperplasia could be missed by a single reviewer).

The draft guidelines recommend that 3 pathologists read the slides at the study-end. We favor having 2 pathologists read them and in case of disagreement, the 3rd pathologist used as an adjudicator.

The draft guidelines recommend that when discrepancies exist between the diagnosis of the 3 pathologists (Line 279), the most severe pathologic diagnosis would be the final diagnosis. We think that this comment should only apply to characteristics 7-11 (Line 348) and that disagreement within categories 2-6 will not be taken into account. Also, we recommend to maintain the 2 readers, plus one adjudicator pathologist.

If you have any questions or comments in regard to this submission, please do not hesitate to contact me at (862) 778-6521. Thank you very much.

Sincerely,

Paul M. Vancutsem, DVM, PhD
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