Guidance for Industry

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

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This guidance updates the final guidance *Guidance for Clinical Evaluation of Combination Estrogen/Progestin - Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women,* published in March 1995. The guidance is intended to provide recommendations to industry for studies of estrogen and estrogen/progestin drug products for the treatment of moderate to severe vasomotor symptoms associated with the menopause and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The guidance also addresses the reduction of the risk of endometrial hyperplasia or adenocarcinoma from estrogen exposure in postmenopausal women who have a uterus. For other indications, such as prevention of osteoporosis, sponsors are asked to direct inquiries to the appropriate CDER Office of New Drugs review division.[2]

II. BACKGROUND

Estrogen therapy has been used for over one-half century for the management of menopausal symptoms, including vulvar and vaginal atrophy and vasomotor symptoms. Since the early 1980s, estrogen has also been used to help prevent the loss of bone mineral density.

The use of estrogen alone (unopposed by progestin drugs) therapy in women who have a uterus is associated with an increased incidence of endometrial hyperplasia and adenocarcinoma of the endometrium. A regimen that combines a progestin drug with estrogen has been shown to

[1] This guidance was developed by the Division of Reproductive and Urologic Drug Products (DRUDP) in the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA).

[2] Drugs for the prevention or treatment of osteoporosis are reviewed by the Division of Metabolic and Endocrine Drug Products, Office of New Drugs, CDER.

reduce the risk of estrogen-induced endometrial hyperplasia without compromising the positive effects of estrogen on vasomotor symptoms, vulvar and vaginal atrophy symptoms, or bone mineral density.

Although adding progestins to estrogens decreases the risk of endometrial hyperplasia in postmenopausal women, the addition of progestins to estrogen therapy may be associated with increases in the risk of a variety of serious adverse events, such as breast cancer, thromboembolic events, and myocardial infarction. Therefore, this guidance encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known. Sponsors are encouraged to investigate dosing schedules and drug delivery systems that can achieve efficacy with lowest possible exposures.

III. DRUG PRODUCTS CONTAINING ESTROGEN ALONE

A. Indications

There are two symptomatic indications for estrogen alone therapy.

1. Moderate to severe vasomotor symptoms associated with the menopause

Vasomotor symptoms in postmenopausal women are commonly known as *hot flushes or hot flashes*. The severity of vasomotor symptoms are defined clinically as follows:

Mild:	sensation of heat without sweating
Moderate:	sensation of heat with sweating, able to continue activity
Severe:	sensation of heat with sweating, causing cessation of activity

2. Moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause

Patient self-assessed symptoms of vulvar and vaginal atrophy include:

- Vaginal dryness (none, mild, moderate or severe)
- Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)
- Dysuria (none, mild, moderate or severe)
- Vaginal pain associated with sexual activity (none, mild, moderate or severe)
- Vaginal bleeding associated with sexual activity (presence vs. absence)

B. Study Considerations

The Agency recommends that prior to initiating phase 3 development, adequate dose ranging studies be conducted to identify the doses to be studied in the proof of efficacy studies. We recommend conducting one or more placebo-controlled trials to support efficacy of each indication in Section III.A. One adequately designed clinical trial to study both indications concurrently is possible. We recommend that studies be randomized, double-blinded and of 12-

week duration. In addition, we recommend that studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated.

If the drug product is considered to be a new molecular entity or poses an unexpected safety concern, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

We recommend that:

- Only postmenopausal women be included in studies. We define *postmenopausal* as 12 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy.
- For the indication of treatment of moderate to severe vasomotor symptoms, study participants be enrolled who have a minimum of 7 to 8 moderate to severe hot flushes per day, or 50 to 60 per week at baseline.
- For the indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy, study participants be enrolled who have self-identified at least one moderate to severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.
- Study participants not be taking estrogen alone or estrogen/progestin containing drug products. The following washout periods are recommended before baseline assessments are made for subjects previously on estrogen alone or estrogen/progestin containing products:
  - — 1 week or longer for prior vaginal hormonal products (rings, creams, gels)
  - — 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products
  - — 8 weeks or longer for prior oral estrogen and/or progestin therapy
  - — 8 weeks or longer for prior intrauterine progestin therapy
  - — 3 months or longer for prior progestin implants and estrogen alone injectable drug therapy
  - — 6 months or longer for prior estrogen pellet therapy or progestin injectable drug therapy
- Women >40 years have documentation of a negative screening mammogram (obtained at screening or within 9 months of study enrollment) and normal clinical breast examination prior to enrollment in clinical studies. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.
- All subjects who have a uterus have endometrial biopsy performed at screening. Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- All subjects who have a uterus undergo an endometrial biopsy at end-of-study.
- Any new findings noted during the conduct of the study or during the end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Sponsors provide plans for monitoring and/or reducing the risk of adverse endometrial effects in women who have a uterus.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For the treatment of moderate to severe vasomotor symptoms, we recommend the following co-primary endpoints:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

For the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, we recommend the following co-primary endpoints.

- 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 to her
- Mean change from baseline to week 12 in vaginal pH
- Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells)

F. Study Analysis

For estrogen alone products intended to treat moderate to severe vasomotor symptoms, we recommend that the primary efficacy analyses show a clinically and a statistically significant

reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups. Subjective measures (e.g., daily patient diary entries) can be used as primary efficacy endpoints. Alternatively, objective measures (e.g., thermography) can be used both as primary efficacy endpoints and as validation of subjective endpoints. We recommend that study results clearly identify the lowest effective dose of estrogen to support the indication by demonstrating an ineffective lower dose.

For estrogen alone drug products intended to treat moderate to severe symptoms of vulvar and vaginal atrophy, we recommend that the primary efficacy analyses demonstrate a statistically significant improvement versus placebo from baseline to week 12 of treatment in all three of the following parameters:

1. Maturation Index (decrease of parabasal vaginal cells and increase in superficial vaginal cells)
2. Lowering of the vaginal pH
3. The moderate to severe symptom identified by the subject as being most bothersome to her

IV. DRUG PRODUCTS CONTAINING ESTROGEN PLUS PROGESTIN

The approval of specific fixed dose estrogen/progestin drug products for estrogen class labeling indications in women who have a uterus will be based on two criteria: (1) that each component contribute to the efficacy and safety as defined in the combination drug policy (see 21 CFR 300.50) and (2) the determination that a combination drug contains the lowest effective dose of each of its active components for their respective labeled indications.

A. Indications

1. Estrogen Component

The symptomatic indications for estrogen/progestin therapy are the same as those previously discussed under Section III.A of this guidance.

2. Progestin Component

The progestin component is added to estrogen alone regimens for safety purposes to oppose the adverse effects of estrogen on the endometrium in women who have a uterus. We recommend that sponsors propose low-dose combination estrogen/progestin regimens and dosing schedules that demonstrate endometrial safety and have acceptable endometrial bleeding profiles.

B. Study Considerations

To support the indication of the treatment of moderate to severe vasomotor symptoms or the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, see Section III.B in this guidance.

To demonstrate protection of the endometrium, we recommend that a single, 12-month, randomized, double-blind, dose-ranging phase 3 clinical trial be conducted and include two or more progestin drug treatment arms for each estrogen dose studied. However, the indications in Section III.A can be studied as part of the 12-month endometrial protection study, provided all entrance criteria for each indication are met and the study is powered adequately for each endpoint. We recommend that study results clearly identify the lowest effective dose of estrogen (as described in Section III.B) and the lowest effective dose of progestin to support endometrial safety by demonstrating an ineffective lower dose on the endometrium.

If the drug to be studied is considered to be a new molecular entity or if it poses unique safety concerns, two placebo-controlled phase 3 clinical trials are recommended to establish safety and efficacy.

C. Inclusion and Exclusion Criteria

Please refer to the criteria set out in Section III.C., except as specified below.

We recommend that:

- All subjects have a uterus and have an evaluable screening endometrial biopsy (i.e., endometrial tissue sufficient for diagnosis). Findings indicating endometrial hyperplasia or cancer would result in exclusion from enrollment and subjects would be referred for *standard of care* clinical management.
- A negative screening mammogram (obtained at screening or within 3 months of study enrollment) and normal clinical breast examination be documented prior to enrollment in clinical studies for women > 40 years old. Findings indicating any suspicion of breast malignancy would result in exclusion from enrollment.

D. Monitoring

We recommend that:

- The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory.
- Endometrial biopsies and not uterine ultrasounds be used for the evaluation of endometrial hyperplasia (sponsors interested in establishing a correlation between transvaginal ultrasound and endometrial biopsy results may perform transvaginal ultrasound immediately preceding endometrial biopsies).
- A single pathologist reader (any one of the three blinded pathologists) initially assess the slides from the endometrial biopsies obtained at screening or because of participant bleeding while on study drug (safety reading).

- For the efficacy evaluation, three independent expert pathologists, blinded to treatment group and to each other's readings, determine the diagnosis for endometrial biopsy slides during the conduct of the study.
- Curricula vitae for participating pathologists be provided to the FDA and document expertise in gynecologic pathology.
- Participating study pathologists be from different institutions with independent fiduciary and organizational reporting, and these pathologists not meet to review slides before or during the conduct of the clinical trial.
- Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) be used for the diagnosis of endometrial hyperplasia (see Appendix for recommended histologic characteristics of the endometrium).
- Endometrial polyps be fully characterized as to the glandular proliferation and atypia (see Appendix for additional histologic characteristics of the specimen).
- Subjects found to have endometrial hyperplasia or adenocarcinoma of the endometrium be excluded from further drug treatment (if discovered during study drug treatment period) and referred for *standard of care* clinical management and followed to complete resolution, and the report of any medical or surgical procedures and the resultant pathology be provided to the FDA.
- If hyperplasia is diagnosed by the single safety reader for a subject who has bled while on study drug, this diagnosis be maintained for the efficacy evaluation and the slides become part of the slide set given to the two other pathologists for reading.
- For the efficacy evaluation, 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.
- The slide set distributed to each of the three pathologists for the end-of-study pathology review incorporate control sides representing a randomly selected 10 percent of the screening normal slides and all slides from subjects excluded for the diagnosis of hyperplasia or cancer to insure quality control.
- Digital recording of diagnostic areas of the slides be maintained by the central laboratory and be made available upon FDA request.
- Any new findings noted during the conduct of the study and on end-of-study physical examination (including findings related to the breast) receive careful and appropriate evaluation and be monitored until there is complete clinical resolution of any diagnosed condition.
- Safety assessments of lipids and of carbohydrate and coagulation parameters (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- Serum levels of the parent compounds and metabolites be measured.

E. Primary Endpoints

For protection of the endometrium, we recommend the evaluation of the incidence rate of endometrial hyperplasia at 12 months.

F. Study Analysis

See Section III.F. for analysis of primary endpoints for treatment of moderate or severe vasomotor symptoms or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The objective of the clinical trial is to demonstrate the lowest effective dose of the progestin drug that reduces the estimated risk of endometrial hyperplasia after 1 year of estrogen/progestin treatment. The reported 1-year background incidence rate for endometrial hyperplasia in postmenopausal women and in postmenopausal women treated with currently marketed combination estrogen/progestin drugs is approximately 0-1 percent. We recommend that 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. The frequency of atypical hyperplasia and cancer are important additional factors to be considered in determining approvability of the drug product. The incidence of hyperplastic polyps and associated atypia would be considered in the safety review.

APPENDIX: HISTOLOGIC DESCRIPTIONS RECOMMENDED FOR USE WHEN READING ENDOMETRIAL BIOPSY SLIDES

Histologic Characteristics of the Endometrium

0. No tissue

1. Tissue insufficient for diagnosis

2. Atrophic

3. Inactive

4. Proliferative

    a. Weakly proliferative

    b. Active proliferative

    c. Disordered proliferative

5. Secretory

    a. Cyclic type

    b. Progestational type (including stromal decidualization)

6. Menstrual type

7. Simple hyperplasia without atypia

8. Simple hyperplasia with atypia

9. Complex hyperplasia without atypia

10. Complex hyperplasia with atypia

11. Carcinoma (specify type)

Additional Histologic Characteristics

If there are any polyps, please specify the type or types.

- Functional
- Atrophic
- Hyperplastic without atypia
- Hyperplastic with atypia
- Carcinomatous

If there is any stromal tissue, please specify the type or types.

- Smooth muscle tissue, normal
- Features suggestive of adenomyoma
- Features suggestive of stromal nodule
- Sarcoma (specify type)

If there is any metaplasia, please specify the type or types.

- Squamous
- Papillary
- Eosinophilic
- Ciliated
- Mucinous
- Syncytial
- Other type (specify type)

If there is any cervical tissue, please specify the type or types.

- Fragments of negative cervical epithelium
- Endocervical polyp
- Atypical endocervical glandular epithelium
- Atypical squamous metaplasia
- Squamous dysplasia
- Cervical carcinoma