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# 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### *DRAFT GUIDANCE*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  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)**

**January 2003  
Clinical/Medical**

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## Table of Contents

<b>I. INTRODUCTION.....</b>	<b>1</b>
<b>II. BACKGROUND .....</b>	<b>1</b>
<b>III. DRUG PRODUCTS CONTAINING ESTROGEN ALONE .....</b>	<b>2</b>
<b>A. Indications.....</b>	<b>2</b>
1. <i>Moderate to severe vasomotor symptoms associated with the menopause.....</i>	<i>2</i>
2. <i>Moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.....</i>	<i>2</i>
<b>B. Study Considerations.....</b>	<b>2</b>
<b>C. Inclusion and Exclusion Criteria .....</b>	<b>3</b>
<b>D. Monitoring .....</b>	<b>4</b>
<b>E. Primary Endpoints.....</b>	<b>4</b>
<b>F. Study Analysis .....</b>	<b>4</b>
<b>IV. DRUG PRODUCTS CONTAINING ESTROGEN PLUS PROGESTIN .....</b>	<b>5</b>
<b>A. Indications.....</b>	<b>5</b>
1. <i>Estrogen Component.....</i>	<i>5</i>
2. <i>Progestin Component .....</i>	<i>5</i>
<b>B. Study Considerations.....</b>	<b>5</b>
<b>C. Inclusion and Exclusion Criteria .....</b>	<b>6</b>
<b>D. Monitoring .....</b>	<b>6</b>
<b>E. Primary Endpoints.....</b>	<b>8</b>
<b>APPENDIX: HISTOLOGIC DESCRIPTIONS RECOMMENDED FOR USE WHEN READING ENDOMETRIAL BIOPSY SLIDES .....</b>	<b>9</b>

## Guidance for Industry<sup>1</sup>

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.<sup>2</sup>

## 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

<sup>1</sup> 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).

<sup>2</sup> Drugs for the prevention or treatment of osteoporosis are reviewed by the Division of Metabolic and Endocrine Drug Products, Office of New Drugs, CDER.

39 reduce the risk of estrogen-induced endometrial hyperplasia without compromising the positive  
40 effects of estrogen on vasomotor symptoms, vulvar and vaginal atrophy symptoms, or bone  
41 mineral density.  
42

43 Although adding progestins to estrogens decreases the risk of endometrial hyperplasia in  
44 postmenopausal women, the addition of progestins to estrogen therapy may be associated with  
45 increases in the risk of a variety of serious adverse events, such as breast cancer,  
46 thromboembolic events, and myocardial infarction. Therefore, this guidance encourages  
47 sponsors to develop the lowest doses and exposures for both estrogens and progestins for  
48 indications sought, even though specific relationships between dose, exposure, and risk of  
49 adverse events may not be known. Sponsors are encouraged to investigate dosing schedules and  
50 drug delivery systems that can achieve efficacy with lowest possible exposures.  
51

52

### 53 **III. DRUG PRODUCTS CONTAINING ESTROGEN ALONE**

54

#### 55 **A. Indications**

56

57 There are two symptomatic indications for estrogen alone therapy.

58

##### 59 *1. Moderate to severe vasomotor symptoms associated with the menopause*

60

61 Vasomotor symptoms in postmenopausal women are commonly known as *hot flushes or*  
62 *hot flashes*. The severity of vasomotor symptoms are defined clinically as follows:  
63

64

64 Mild: sensation of heat without sweating

65

65 Moderate: sensation of heat with sweating, able to continue activity

66

66 Severe: sensation of heat with sweating, causing cessation of activity  
67

67

##### 68 *2. Moderate to severe symptoms of vulvar and vaginal atrophy associated with the* 69 *menopause*

70

71 Patient self-assessed symptoms of vulvar and vaginal atrophy include:  
72

73

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

78

#### 79 **B. Study Considerations**

80

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

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

88  
89 If the drug product is considered to be a new molecular entity or poses an unexpected safety  
90 concern, two placebo-controlled phase 3 clinical trials are recommended to establish safety and  
91 efficacy.

92

### 93 C. Inclusion and Exclusion Criteria

94

95 We recommend that:

96

97 • Only postmenopausal women be included in studies. We define *postmenopausal* as 12  
98 months of spontaneous amenorrhea or 6 months of spontaneous amenorrhea with serum  
99 FSH levels > 40 mIU/ml or 6 weeks postsurgical bilateral oophorectomy with or without  
100 hysterectomy.

101 • For the indication of treatment of moderate to severe vasomotor symptoms, study  
102 participants be enrolled who have a minimum of 7 to 8 moderate to severe hot flushes per  
103 day, or 50 to 60 per week at baseline.

104 • For the indication of treatment of moderate to severe symptoms of vulvar and vaginal  
105 atrophy, study participants be enrolled who have self-identified at least one moderate to  
106 severe symptom (see Section III.A.2) that is the most bothersome to her, have no greater  
107 than 5 percent superficial cells on a vaginal smear, and have a vaginal pH > 5.0.

108 • Study participants not be taking estrogen alone or estrogen/progestin containing drug  
109 products. The following washout periods are recommended before baseline assessments  
110 are made for subjects previously on estrogen alone or estrogen/progestin containing  
111 products:

112 — 1 week or longer for prior vaginal hormonal products (rings, creams, gels)

113 — 4 weeks or longer for prior transdermal estrogen alone or estrogen/progestin products

114 — 8 weeks or longer for prior oral estrogen and/or progestin therapy

115 — 8 weeks or longer for prior intrauterine progestin therapy

116 — 3 months or longer for prior progestin implants and estrogen alone injectable drug  
117 therapy

118 — 6 months or longer for prior estrogen pellet therapy or progestin injectable drug  
119 therapy

120 • Women >40 years have documentation of a negative screening mammogram (obtained at  
121 screening or within 9 months of study enrollment) and normal clinical breast examination  
122 prior to enrollment in clinical studies. Findings indicating any suspicion of breast  
123 malignancy would result in exclusion from enrollment.

124 • All subjects who have a uterus have endometrial biopsy performed at screening.  
125 Findings indicating endometrial hyperplasia or cancer would result in exclusion from  
126 enrollment.

127  
128 **D. Monitoring**  
129

130 We recommend that:

- 131
- 132 • All subjects who have a uterus undergo an endometrial biopsy at end-of-study.
  - 133 • Any new findings noted during the conduct of the study or during the end-of-study  
134 physical examination (including findings related to the breast) receive careful and  
135 appropriate evaluation and be monitored until there is complete clinical resolution of any  
136 diagnosed condition.
  - 137 • Sponsors provide plans for monitoring and/or reducing the risk of adverse endometrial  
138 effects in women who have a uterus.
  - 139 • Safety assessments of lipids and of carbohydrate and coagulation parameters  
140 (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
  - 141 • Serum levels of the parent compounds and metabolites be measured.

142 **E. Primary Endpoints**  
143

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

- 146
- 147 • Mean change in frequency of moderate to severe vasomotor symptoms from baseline to  
148 week 4
  - 149 • Mean change in frequency of moderate to severe vasomotor symptoms from baseline to  
150 week 12
  - 151 • Mean change in severity of moderate to severe vasomotor symptoms from baseline to  
152 week 4
  - 153 • Mean change in severity of moderate to severe vasomotor symptoms from baseline to  
154 week 12

155

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

- 158
- 159 • Mean change from baseline to week 12 in the moderate to severe symptom that has been  
160 identified by the patient as being the most bothersome to her
  - 161 • Mean change from baseline to week 12 in vaginal pH
  - 162 • Mean change from baseline to week 12 in vaginal maturation index (parabasal and  
163 superficial cells)

164 **F. Study Analysis**  
165

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

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

175  
176 For estrogen alone drug products intended to treat moderate to severe symptoms of vulvar and  
177 vaginal atrophy, we recommend that the primary efficacy analyses demonstrate a statistically  
178 significant improvement versus placebo from baseline to week 12 of treatment in all three of the  
179 following parameters:

- 180
- 181 1. Maturation Index (decrease of parabasal vaginal cells and increase in superficial
- 182 vaginal cells)
- 183 2. Lowering of the vaginal pH
- 184 3. The moderate to severe symptom identified by the subject as being most bothersome
- 185 to her
- 186
- 187

#### 188 **IV. DRUG PRODUCTS CONTAINING ESTROGEN PLUS PROGESTIN**

189

190 The approval of specific fixed dose estrogen/progestin drug products for estrogen class labeling  
191 indications in women who have a uterus will be based on two criteria: (1) that each component  
192 contribute to the efficacy and safety as defined in the combination drug policy (see 21 CFR  
193 300.50) and (2) the determination that a combination drug contains the lowest effective dose of  
194 each of its active components for their respective labeled indications.

##### 195 **A. Indications**

###### 196 *1. Estrogen Component*

197

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

###### 200 *2. Progestin Component*

201

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

##### 206 **B. Study Considerations**

207 To support the indication of the treatment of moderate to severe vasomotor symptoms or the  
208 treatment of moderate to severe symptoms of vulvar and vaginal atrophy, see Section III.B in  
209 this guidance.  
210  
211  
212  
213  
214



215  
216 To demonstrate protection of the endometrium, we recommend that a single, 12-month,  
217 randomized, double-blind, dose-ranging phase 3 clinical trial be conducted and include two or  
218 more progestin drug treatment arms for each estrogen dose studied. However, the indications in  
219 Section III.A can be studied as part of the 12-month endometrial protection study, provided all  
220 entrance criteria for each indication are met and the study is powered adequately for each  
221 endpoint. We recommend that study results clearly identify the lowest effective dose of estrogen  
222 (as described in Section III.B) and the lowest effective dose of progestin to support endometrial  
223 safety by demonstrating an ineffective lower dose on the endometrium.

224  
225 If the drug to be studied is considered to be a new molecular entity or if it poses unique safety  
226 concerns, two placebo-controlled phase 3 clinical trials are recommended to establish safety and  
227 efficacy.

### 228 **C. Inclusion and Exclusion Criteria**

229  
230 Please refer to the criteria set out in Section III.C., except as specified below.  
231  
232

233 We recommend that:

- 234  
235 • All subjects have a uterus and have an evaluable screening endometrial biopsy (i.e.,  
236 endometrial tissue sufficient for diagnosis). Findings indicating endometrial hyperplasia  
237 or cancer would result in exclusion from enrollment and subjects would be referred for  
238 *standard of care* clinical management.
- 239 • A negative screening mammogram (obtained at screening or within 3 months of study  
240 enrollment) and normal clinical breast examination be documented prior to enrollment in  
241 clinical studies for women > 40 years old. Findings indicating any suspicion of breast  
242 malignancy would result in exclusion from enrollment.

### 243 **D. Monitoring**

244  
245 We recommend that:  
246  
247

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

- 258 • For the efficacy evaluation, three independent expert pathologists, blinded to treatment  
259 group and to each other's readings, determine the diagnosis for endometrial biopsy slides  
260 during the conduct of the study.
- 261 • Curricula vitae for participating pathologists be provided to the FDA and document  
262 expertise in gynecologic pathology.
- 263 • Participating study pathologists be from different institutions with independent fiduciary  
264 and organizational reporting, and these pathologists not meet to review slides before or  
265 during the conduct of the clinical trial.
- 266 • Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female  
267 Genital Tract) be used for the diagnosis of endometrial hyperplasia (see Appendix for  
268 recommended histologic characteristics of the endometrium).
- 269 • Endometrial polyps be fully characterized as to the glandular proliferation and atypia (see  
270 Appendix for additional histologic characteristics of the specimen).
- 271 • Subjects found to have endometrial hyperplasia or adenocarcinoma of the endometrium  
272 be excluded from further drug treatment (if discovered during study drug treatment  
273 period) and referred for *standard of care* clinical management and followed to complete  
274 resolution, and the report of any medical or surgical procedures and the resultant  
275 pathology be provided to the FDA.
- 276 • If hyperplasia is diagnosed by the single safety reader for a subject who has bled while on  
277 study drug, this diagnosis be maintained for the efficacy evaluation and the slides become  
278 part of the slide set given to the two other pathologists for reading.
- 279 • For the efficacy evaluation, the concurrence of two of the three pathologists be accepted  
280 as the final diagnosis. If there is no agreement among the three pathologists, the most  
281 severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple  
282 hyperplasia > benign endometrium) would be used as the final diagnosis.
- 283 • The slide set distributed to each of the three pathologists for the end-of-study pathology  
284 review incorporate control sides representing a randomly selected 10 percent of the  
285 screening normal slides and all slides from subjects excluded for the diagnosis of  
286 hyperplasia or cancer to insure quality control.
- 287 • Digital recording of diagnostic areas of the slides be maintained by the central laboratory  
288 and be made available upon FDA request.
- 289 • Any new findings noted during the conduct of the study and on end-of-study physical  
290 examination (including findings related to the breast) receive careful and appropriate  
291 evaluation and be monitored until there is complete clinical resolution of any diagnosed  
292 condition.
- 293 • Safety assessments of lipids and of carbohydrate and coagulation parameters  
294 (antithrombin III, factor V Leiden, protein-C and protein-S) be conducted.
- 295 • Serum levels of the parent compounds and metabolites be measured.
- 296

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**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  $\leq 1$  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.

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

319  
320  
321

322 **Histologic Characteristics of the Endometrium**

323

324 0. No tissue

325

326 1. Tissue insufficient for diagnosis

327

328 2. Atrophic

329

330 3. Inactive

331

332 4. Proliferative

333

334 a. Weakly proliferative

335

336 b. Active proliferative

337

338 c. Disordered proliferative

339

340 5. Secretory

341

342 a. Cyclic type

343

344 b. Progestational type (including stromal decidualization)

345

346 6. Menstrual type

347

348 7. Simple hyperplasia without atypia

349

350 8. Simple hyperplasia with atypia

351

352 9. Complex hyperplasia without atypia

353

354 10. Complex hyperplasia with atypia

355

356 11. Carcinoma (specify type)

357

358

359 **Additional Histologic Characteristics**

360

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

362

363       Functional

364       Atrophic

365       Hyperplastic without atypia

366       Hyperplastic with atypia

367       Carcinomatous

368

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

370

371       Smooth muscle tissue, normal

372       Features suggestive of adenomyoma

373       Features suggestive of stromal nodule

374       Sarcoma (specify type)

375

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

377

378       Squamous

379       Papillary

380       Eosinophilic

381       Ciliated

382       Mucinous

383       Syncytial

384       Other type (specify type)

385

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

387

388       Fragments of negative cervical epithelium

389       Endocervical polyp

390       Atypical endocervical glandular epithelium

391       Atypical squamous metaplasia

392       Squamous dysplasia

393       Cervical carcinoma

394

395