GUIDANCE FOR CLINICAL EVALUATION OF COMBINATION ESTROGEN/PROGESTIN-CONTAINING DRUG PRODUCTS USED FOR HORMONE REPLACEMENT THERAPY OF POSTMENOPAUSAL WOMEN*

Introduction

The increased risk of endometrial cancer associated with estrogen replacement therapy (ERT)[1,2,3] has led to the clinical recommendation that non-hysterectomized women who use ERT should also receive progestin treatment. Although observational data suggest that concomitant progestin treatment for 10 or more days each month substantially reduces the excess risk of endometrial cancer[4,5,12], the overall effect of long term combination estrogen/progestin hormone replacement therapy (HRT) on the health of postmenopausal women remains largely unknown[6]. All progestins have adverse short-term effects on carbohydrate metabolism and on the lipid and lipoprotein profile, lowering the ratio of HDL:LDL cholesterol as compared with the effects of unopposed ERT. Whether these short-term metabolic effects can be taken as surrogates for adverse long term cardiovascular outcomes is not known but is being investigated in several clinical trials, including the ongoing NIH-sponsored Women's Health Initiative Randomized Clinical Trial (WHI/RCT), which will require up to 9 years for completion.

Emerging observational data on the risk of breast cancer with ERT and HRT raise additional concern that added progestins do not reduce, and may even exacerbate, the increased occurrence of breast cancer reported with long term ERT use[6-9]. Further data are needed to resolve this issue, from the WHI/RCT, and from new observational studies that are larger and more thorough than those currently available.

While many uncertainties exist regarding the long-term risks of HRT, the better defined risks and benefits of ERT appear reasonably favorable overall for women without contraindications[6]. Thus, the Division of Metabolism and Endocrine Drug Products (DMEDP) considers it safe and appropriate to require unopposed ERT comparison groups in the recommended development schema for HRT drugs, provided that women with contraindications to these drugs are excluded from these studies.

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*This guidance is an informal communication by the Division of Metabolism and Endocrine Drug Products (DMEDP) containing current recommendations regarding the development of combination estrogen/progestin drug products for postmenopausal HRT indications. These recommendations are based on current data and may require modification as additional data become available. Sponsors are advised that these recommendations are not legally binding on the Center for Drug Evaluation and Research in regulatory approval decisions regarding HRT products.

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Principles of this guidance

Since the only rationale for adding progestin to ERT is to reduce the excess risk of endometrial cancer associated with ERT, and since observational data suggest that progestin drugs as a class are effective for this usage, DMEDP will apply the following principles to the regulatory review of marketing applications for combined estrogen/progestin HRT products:

1. Approvals of specific fixed dose estrogen/progestin HRT products for estrogen class labeling indications will be based on the combination drug policy (see 21 CFR 300.50) and the determination, within reasonable limits, that a combination drug contains the lowest effective dosages of each of its active components for their respective labeled indications.

2. Sponsors are referred to the "Labeling Guidance Text for Non-contraceptive Estrogen Drug Products" (August 1992 revision) for the currently approved indications for estrogen components of HRT products. HRT products must be shown safe and effective for each estrogen indication proposed for labeling. Because a dose-dependent increased risk of breast cancer has been reported in long term ERT users[6-10], the lowest effective estrogen dose for each proposed indication must be demonstrated.

3. Approvals of progestin components will be based on evidence of safety and efficacy derived from a single adequate and well-controlled clinical trial documenting the lowest effective progestin dose which prevents the excess risk of endometrial cancer associated with a specific ERT regimen. Since progestins in HRT are intended to reduce the estrogen-associated excess risk of endometrial cancer, the progestin component must be shown safe and effective in reducing this risk compared to the estrogen component alone. To minimize the possible adverse long-term effects of progestin treatment, the lowest effective progestin dosage regimen, which reduces the risk of endometrial cancer induced by the unopposed estrogen component, must be shown.

   In clinical trials, induction of a reversible precursor lesion as a surrogate for malignancy is considered reasonably safe and ethical, provided study subjects are monitored and treated for developing pre-malignant lesions. Sponsors are expected to design Phase III clinical trials of HRT products with endometrial hyperplasia as the primary progestin efficacy endpoint. The histopathologic diagnosis of endometrial hyperplasia encompasses a spectrum of pre-malignant lesions, most of which resolve spontaneously after the inciting estrogen stimulation is withdrawn, or with simple medical treatment. As the only clinical condition clearly shown to predict the development of endometrial cancer (albeit in only a small minority of

untreated cases), endometrial hyperplasia is the only accepted surrogate endpoint for endometrial cancer.

4. For osteoporosis prevention, see "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", April 1994.

Requirements for symptomatic indications

The symptomatic indications for estrogen class labeling are treatment of: a) moderate to severe vasomotor symptoms associated with the menopause, b) vulvar and vaginal atrophy associated with menopause, c) hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and, d) abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology and only when associated with a hypoplastic or atrophic endometrium.

In order to obtain approval for symptomatic indications, the sponsor must conduct two Phase III clinical trials showing safety and efficacy of the estrogen component, one of which should be placebo-controlled. The studies should be at least 3 months in duration, should evaluate dosage levels which include the lowest effective dose, and should be conducted under double blind conditions.

In regard specifically to treatment of vasomotor symptoms, the primary efficacy analysis must show a clinically and statistically significant reduction in both the frequency and severity of hot flushes in the treated group(s) compared with the control groups. Entry criteria should require enrolled subjects to have a minimum of 7 to 8 moderate to severe hot flushes per day or 60 per week, at baseline. Subjective endpoint measures are acceptable (i.e., patient diaries), provided the protocol contains adequate blinding and placebo controls; however, objective measurements (i.e., thermography) are preferable to validate the subjective endpoints.

Hot flushes are defined clinically as follows:

Mild – Sensation of heat without perspiration.
Moderate – Sensation of heat with perspiration, able to continue activity.
Severe – Sensation of heat with sweating, causing the woman to stop activity.

The onset and frequency of hot flushes are determined by thermography as the occurrence of subjective symptoms (moderate-to-severe hot flushes) followed within 5 minutes of onset by a recorded increase in skin temperature, characterized by a steady, continuous pattern and a peak within 20 minutes of baseline at least 1° C higher than baseline temperature. The onset of this temperature increase is considered the onset of the hot flush.

In regard to symptomatic indications b), c), and d), above, the lowest effective dose of the estrogen component must be shown to support labeled dosage recommendations for each requested indication.

Requirements for endometrial protection indication

1. One 12-month dose-ranging pivotal trial is required to demonstrate the lowest effective dose of the progestin component to protect the endometrium from the development of estrogen-induced endometrial hyperplasia or cancer.

2. The protocol design must include a comparison of unopposed estrogen treatment (i.e., estrogen plus placebo progestin, which is needed to ensure blinded treatment assignment) to treatment with the equivalent estrogen dose in combination with at least 2 different progestin doses. Thus, at least 3 treatment arms are required for each estrogen dose studied.

   The primary efficacy analysis must show a clinically and statistically significant reduction in the one-year incidence of endometrial hyperplasia or cancer in at least one combination estrogen/progestin treatment group compared with the equivalent dose level unopposed estrogen group.

3. Endometrial biopsies should be conducted at a minimum of baseline and study end, and subjects with hyperplasia at baseline should be excluded and referred for treatment. Uterine ultrasound in lieu of biopsy is not acceptable for the evaluation of endometrial hyperplasia except when insufficient tissue is obtained on biopsy. However, sponsors are encouraged to perform routine transvaginal ultrasound (TVS) immediately preceding biopsies in order to generate a prospective data base correlating ultrasound and histological findings.

4. The biopsy slides should be read by 2 independent pathologists, blinded to treatment group assignment and to each other's readings, using standardized criteria for the diagnosis of endometrial hyperplasia, based on the Blaustein's pathology text[11]. If diagnostic differences between the first and second readers occur (i.e., the same biopsy read as hyperplasia by one and non-hyperplasia by the second), then a third independent, blinded pathologist should re-read those slides to adjudicate the differences. In the event that a third pathologist is needed, the slide set for re-evaluation should include a random sample of biopsies whose diagnoses (both hyperplasia and non-hyperplasia) were not previously in dispute, as an additional quality control. Data analysis should utilize the best 2 of 3 competing diagnoses as the histology endpoint.

Quantitative analyses of the variability between readers in pathology diagnoses should be provided, to validate the diagnostic classification scheme for endometrial hyperplasia.

Requirements for osteoporosis prevention

In order to demonstrate the safety and efficacy of the combination product in preserving bone mineral density at the lowest effective doses of both estrogen and progestin, the following conditions must be fulfilled:

1. One 24-month placebo-controlled, dose ranging trial is required to demonstrate the lowest effective dose of estrogen that will maintain bone mineral density. (Refer to Guidelines for Anti-Osteoporotic Agents, April 1994.)

2. The study design should include a comparison of 3 doses of estrogen (including one expected to be subtherapeutic) to determine the lowest effective dose.

3. All women entering the protocol, including those on placebo, should maintain a total daily intake of 1.0-1.5 g of elemental calcium. Dietary supplementation to achieve these levels is acceptable.

4. No combination estrogen-progestin product will be approved for this indication until both the lowest effective estrogen dose (for bone density preservation) and the lowest effective progestin dose (for endometrial protection) have been demonstrated adequately.

Patient population

1. All enrolled subjects should have an intact uterus.

2. Menopausal status is recognized as 12 months spontaneous amenorrhea or 6 months amenorrhea with serum levels of FSH > 50 mIU/ml and estradiol < 20 pg/ml.

3. For subjects on previous estrogen and/or progestin hormone replacement therapy, the following washout periods are required before baseline assessments are made: for studies of osteoporosis prevention, at least 6 months; and for studies of menopausal symptoms and/or endometrial protection, at least 8 weeks for prior oral estrogen and/or progestin therapy, and at least 4 weeks for prior transdermal hormone therapy.

Treatment arms for HRT studies

Although it may appear that time could be saved and patient numbers reduced by combining studies of menopausal symptoms or osteoporosis prevention with studies of endometrial hyperplasia, DMEDP does not recommend this practice. Combining trials of symptomatic and non-symptomatic indications may result in significant logistical difficulties because the necessary study duration, appropriate control groups, and ideal patient populations for these three types of studies differ. For example, highly symptomatic women needed for studies of vasomotor symptoms and/or vulvovaginal atrophy may not tolerate placebo treatment for longer than 3 month periods. If they are enrolled in prolonged trials of endometrial protection or osteoporosis prevention, their high dropout rate from the placebo or other groups may compromise study results. On the other hand, asymptomatic or mildly symptomatic women eligible for trials of endometrial protection or osteoporosis prevention would not meet eligibility criteria for studies of vasomotor symptoms.

If a single combined HRT study of menopausal symptoms and endometrial protection is contemplated (i.e., for a HRT regimen with an approved estrogen component), its design -- to adequately evaluate a single estrogen dose level -- would need to include at least 4 treatment arms; for example:

E placebo + P placebo	(placebo group)
E drug + P placebo	(unopposed E group)
E drug + P dose-1	(HRT/low dose P group)
E drug + P dose-2	(HRT/high dose P group)

To evaluate 2 estrogen dose levels, the study would need at least 7 treatment arms:

E placebo + P placebo	(placebo group)
E dose-1 + P placebo	(unopposed low dose E group)
E dose-1 + P dose-1	(HRT/low dose E/low dose P group)
E dose-1 + P dose-2	(HRT/low dose E/high dose P group)
E dose-2 + P placebo	(unopposed high dose E group)
E dose-2 + P dose-1A	(HRT/high dose E/low dose P group)
E dose-2 + P dose-2A	(HRT/high dose E/high dose P group)

To evaluate 3 estrogen dose levels (as required for osteoporosis studies, refer to "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", April 1994), at least 10 treatment arms would be needed:

E placebo + P placebo	(placebo group)
E dose-1 + P placebo	(unopposed low dose E group)
E dose-1 + P dose-1	(HRT/low dose E/low dose P group)
E dose-1 + P dose-2	(HRT/low dose E/high dose P group)
E dose-2 + P placebo	(unopposed mid-dose E group)
E dose-2 + P dose-1A	(HRT/mid-dose E/low dose P group)
E dose-2 + P dose-2A	(HRT/mid-dose E/high dose P group)
E dose-3 + P placebo	(unopposed high dose E group)
E dose-3 + P dose-1B	(HRT/high dose E/low dose P group)
E dose-3 + P dose-2B	(HRT/high dose E/high dose P group)

Sequence of studies

To minimize logistical difficulties, DMEDP recommends the following sequence for the required HRT studies:

1. Select the primary estrogen indication for proposed marketing (e.g., treatment of vasomotor symptoms, vulvovaginal atrophy, and/or prevention of osteoporosis).

2. If the estrogen component is not the subject of an approved NDA or ANDA for this indication, conduct placebo-controlled, dose-ranging studies to evaluate the estrogen component alone (e.g., for vasomotor symptoms) and to identify the dose or doses to be marketed.

   a. For symptomatic indications, see requirements above.

   b. For osteoporosis prevention, a single 24-month study is required and the following treatment arms are needed: a placebo group plus 3 estrogen dose level groups (refer to "Guidelines for Preclinical and Clinical Evaluation of Agents Used in the Prevention or Treatment of Postmenopausal Osteoporosis", April 1994).

   If the estrogen component is the subject of an approved NDA or ANDA for the proposed indication(s), this step may be omitted. The DMEDP should be consulted to determine appropriate study designs.

3. Using the estrogen dose(s) identified for marketing, conduct a dose-ranging study of the progestin component, to identify the lowest effective progestin dosage for each estrogen dose selected.

For pivotal trials of the progestin component (for endometrial protective efficacy in combination with a specific estrogen dosage regimen) the following treatment arms are needed:

E dose-1 + P placebo	(unopposed E group)
E dose-1 + P dose-1	(E dose/P fixed dose-1)
E dose-1 + P dose-2	(E dose/P fixed dose-2)

Thus, for 2 estrogen dose levels, a 6-arm study is needed; for 3 estrogen doses,1 9-arm study is needed.

4. As discussed above, for osteoporosis prevention trials of HRT drugs containing an estrogen component which is not approved for osteoporosis prevention, steps (2) and (3) may be combined, but the combined study will require at least 10 treatment arms, and may have logistical difficulties. Sponsors who wish to conduct combined studies of HRT products for osteoporosis prevention and/or vasomotor symptoms, combined with endometrial protection, should consult with the DMEDP for guidance in study design prior to submitting the IND.

Summary of recommendations for HRT trials

Symptomatic Indications	Endometrial Protection	Postmenopausal Osteoporosis
Two controlled clinical trials ■1 placebo-and 1 active-controlled or 2 placebo-controlled groups ■At least 3-month study duration ■Subjects with 7-8 moderate to severe hot flushes/day or 60/week ■Primary efficacy endpoint: significant decrease in frequency and severity of hot flushes	**One 12-month placebo-controlled trial** ■Includes unopposed E group(s) ■Two P doses for each E dose ■To demonstrate the minimum effective dose of P for each proposed E dose ■Endometrial biopsy at baseline and at end of study ■Independent, replicated, blinded assessment of biopsy slides	**One 24-month placebo-controlled trial** ■To demonstrate the lowest effective dose of E to prevent bone loss (See Osteoporosis Guidelines)

Other requirements

In all clinical studies of HRT products, sponsors should note the following safety requirements:

1. All safety and efficacy studies of HRT products must be conducted in non-hysterectomized women, the target population for drug marketing.

2. All subjects must be screened with mammography prior to enrollment in HRT studies and subjects aged 50 or older should have annual follow-up mammograms during study participation. Abnormal findings should result in prompt exclusion from enrollment or further drug treatment and referral for clinical management as indicated. Subjects who have received study treatment should be monitored by the sponsor until clinical resolution is complete.

3. Endometrial safety monitoring should include annual endometrial biopsies during study participation, or, for studies of less than 6 months, single endometrial biopsies at study exit. Subjects with endometrial hyperplasia or cancer should be excluded from enrollment or further drug treatment and referred for clinical management as indicated. Subjects who receive study treatment should be monitored by the sponsor until clinical resolution is complete.

4. The effects of treatment on lipid/lipoprotein profiles as well as on carbohydrate metabolism and coagulation functions should be assessed.

5. Levels of circulating drug estrogens and/or progestins and their metabolites should be ascertained.

6. Sponsors should consult with the Division of Biopharmaceutics for guidance in study design prior to submitting clinical pharamcokinetics protocols.

7. Sponsors are encouraged to contact the DMEDP for further clarification and/or discussion of modifications in this guidance as needed.

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