

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

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TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 7 October 2003 Advisory Committee meeting on the Women's Health Initiative randomized clinical trial of estrogen plus progestin in healthy postmenopausal women

1. Type of meeting: Open Public Hearing.

2. Purpose

2.1 Review results from the Women's Health Initiative (WHI) randomized clinical trial of estrogen plus progestin in healthy postmenopausal women (hereafter, "the WHI trial").

2.2 Consider implications of results from the WHI trial for FDA regulation of estrogen plus progestin drug products, specifically regarding long-term use of these products for the prevention and/or treatment of postmenopausal osteoporosis.

3. Issues for the Committee

The drug product used in the estrogen plus progestin arm of the WHI trial was Prempro™ [conjugated estrogens(CEE)/medroxyprogesterone acetate(MPA)]. The dose was 0.625 mg CEE/2.5 mg MPA. The Prempro™ Prescribing Information refers to all approved doses (0.625/5.0, 0.625/2.5, 0.45/1.5, and 0.3/1.5).

Results from the estrogen plus progestin arm of the WHI trial were first published in July 2002. Since then, the FDA-approved Prescribing Information for Prempro™ has been revised, and the FDA has asked for similar changes in the Prescribing Information for other estrogen plus progestin products that are approved or

pending approval for the prevention of postmenopausal osteoporosis. This revision provides a description of the main benefits and harms, from treatment with estrogen plus progestin, as reported from the WHI trial.

At the Advisory Committee meeting, data and analyses from the WHI trial will be presented and discussed by WHI investigators and FDA staff.

Considering the indication for long-term use of estrogen plus progestin for the prevention of postmenopausal osteoporosis, DMEDP requests that the Committee, in their deliberations:

3.1 Comment on the revisions to the Prempro™ Prescribing Information¹ referred to above. (Attachment 1: copy of current Prempro™ Prescribing Information).

3.2 Discuss implications of the WHI trial results for the future development, testing, and potential approval of estrogen plus progestin drug products for the prevention and/or treatment of postmenopausal osteoporosis.

3.3 Provide DMEDP with other comments or recommendations related to the WHI trial, or to regulation of estrogen plus progestin products for the prevention and/or treatment of postmenopausal osteoporosis.

4. Background

4.1 Women's Health Initiative

In the first publication from the WHI trial, in July 2002, the authors concluded that the "overall health risks exceeded benefits from use of combined estrogen plus progestin for an average of 5.2-year follow-up among healthy postmenopausal US women²." Specifically, the rates of coronary heart disease, stroke, breast cancer, and pulmonary embolism were higher in women on estrogen plus progestin compared to placebo. The benefits of estrogen plus progestin included lower rates of colon cancer and fractures.² Although the WHI did not specifically recruit postmenopausal women with or at risk for osteoporosis, the study confirmed decades of evidence, from observational studies and smaller randomized trials, that estrogen plus progestin significantly reduces risk for osteoporotic fractures, including those at the hip.²

In publications since the first one, detailed results regarding breast cancer, stroke, dementia, mild cognitive impairment, & global cognitive function, quality of life, and fractures. (add colorectal cancer if published in time) have been presented.² Of the benefits had harms reported thus far, the benefits are a reduced risk of fractures and colorectal cancer, and the most important harm is an increased risk of breast cancer.²

(Attachment 2: NHLBI/WHI Briefing Document)

4.2 Regulatory history of estrogen and estrogen plus progestin products used for the prevention of postmenopausal osteoporosis

4.2.1 Approval of Premarin[®] and Prempro[™]

In 1942, the Food and Drug Administration (FDA) approved the 1.25 mg dose of Premarin[®] [conjugated equine estrogens (CEE)] for the treatment of “menopausal symptoms,” based on safety considerations alone, under the Food, Drug, and Cosmetic Act of 1938 (hereafter, “the Act.”) Doses approved since then range from 0.3 to 2.5 mg.

In 1962 the Act was amended to require that all drugs be shown to be effective, in addition to safe, prior to marketing. In response, the FDA contracted with the National Academy of Sciences (NAS), to evaluate the efficacy of all drugs approved between 1938 and 1962, including estrogens. This work was done by the NAS Drug Efficacy Study Implementation (DESI) Group. After reviewing the DESI reports, the FDA concluded, in 1972, that estrogens were “probably effective” in selected cases of postmenopausal osteoporosis, and labeled the products as such.

In 1986, the FDA concluded that estrogens at doses equivalent to 0.625 mg or higher of CEE were “effective” for postmenopausal osteoporosis. This conclusion was based on input from two FDA Advisory Committees and a review of published literature. The literature review included a 2-year dose-ranging study, in which doses of CEE lower than 0.625 mg per day were found to be ineffective for the prevention of postmenopausal bone loss. The Prescribing Information for estrogen products was changed to include postmenopausal osteoporosis as an indication, saying: “There is evidence that the rate of bone loss can be reduced in postmenopausal women by taking estrogens, but substantial evidence is lacking that estrogens decrease the incidence of osteoporotic bone fractures.” Thus, the postmenopausal osteoporosis indication for estrogens was established on the basis of changes in bone mass, not in fracture incidence.

In 1994, DMEDP approved Prempro[™] 0.625/2.5 (0.625 mg CEE plus 2.5 mg MPA) and Premphase[®] (0.625 mg CEE for 14 days followed by 0.625 mg CEE plus 5.0 mg MPA for 14 days) for the prevention of osteoporosis, the treatment of moderate to severe vasomotor symptoms associated with menopause, and the treatment of vulvar and vaginal atrophy. In 1998, approval was expanded to include Prempro[™] 0.625/5.0 (0.625 mg CEE plus 5.0 mg MPA). These approvals were based on reference to Premarin[®]'s postmenopausal osteoporosis indication, coupled with evidence that the doses of MPA were unlikely to attenuate the effect of the CEE dose on bone mineral density. The approval was also contingent on the Sponsor, Wyeth-Ayerst, agreeing to conduct a randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of lower doses of CEE/MPA on bone mineral density, in recently postmenopausal women. That study has since been completed, resulting in the approval, in 2003 of Prempro[™] 0.45/1.5, and 0.3/1.5 for the prevention of postmenopausal osteoporosis, the treatment of moderate to

severe vasomotor symptoms associated with menopause, and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. (In 2003, a 0.45 mg dose of Premarin® was also approved.) The results of the study have been published.³

4.2.2 Approval of other estrogen and estrogen plus progestin products

In 1994, DMEDP updated the “Guidelines for preclinical and clinical evaluation of agents used in the prevention or treatment of postmenopausal osteoporosis.” (The current term is “Guidance.”) Significant changes included:

- (1) a statement that: “Epidemiological studies have demonstrated that estrogen therapy reduces the risk of vertebral and non-vertebral (femoral neck and distal radius) fractures. Therefore, fracture evaluation for estrogen preparations is not required...,” and
- (2) guidance that an indication for the prevention of postmenopausal osteoporosis could be approved, for estrogen or estrogen plus progestin products, if randomized, double-blind, placebo-controlled clinical trials showed superiority, for the drug(s) tested compared to placebo, in maintaining or increasing lumbar spine bone mineral density (BMD), over a 2-year period, in women 45 years of age or older, and recently (1-3 years) postmenopausal

By 2000, several other estrogen and estrogen plus progestin products were FDA-approved for the prevention of postmenopausal osteoporosis, in addition to Premarin® and Prempro,TM (Table 1). These other approvals were based either on designation as DESI products, or on data from 2-year clinical trials with lumbar spine BMD as the outcome, as described above.

5. Approval of non-estrogen products

Since 1995, the Agency has approved 4 non-estrogen products for the prevention of postmenopausal osteoporosis, including 3 bisphosphonates [Fosamax® (alendronate), Actonel® (risedronate), and Boniva® (ibandronate)] and 1 selective estrogen receptor modulator [Evista® (raloxifene)]. These approvals were based on 2-year, randomized, double-blind, placebo-controlled clinical trials. The participants were recently postmenopausal, non-osteoporotic women, in whom active treatment increased lumbar spine bone mineral density by a statistically significant amount compared to placebo. Because these drugs were also shown to reduce the 3-year incidence of morphometric vertebral fractures, by a statistically significant relative risk reduction of 0.3 to 0.5 compared to placebo, they were approved for the treatment of postmenopausal osteoporosis, in addition to prevention.

Forteo (teriparatide), representing the first 34 amino acids of human parathyroid hormone, has also demonstrated fracture efficacy and has been approved for the treatment of postmenopausal osteoporosis, in particular for the treatment of severe disease.

Regarding the comparative efficacy of estrogen or estrogen plus progestin, alendronate, risedronate, and raloxifene, for a vertebral fracture outcome, some information is available, from a meta-analysis that was published in by the Osteoporosis Methodology Group in 2002, before the first publication from the WHI trial (Table 2).⁴

REFERENCES

1. ATTACHMENT 1: Current Prescribing Information for Prempro™ and Premphase.®
2. ATTACHMENT 2: National Heart, Lung, and Blood Institute, and Women's Health Initiative Briefing document for 7 October 2003 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, Food and Drug Administration.
3. Lindsay R, et al. Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women. *JAMA*. 2002;287:2668-2676.
4. Cranney A, et al. Summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocrine Reviews*. 2002;23:570-578.

Table 1

FDA-Approved Estrogen and Estrogen Plus Progestin Products for the Prevention of Postmenopausal Osteoporosis		
Product	Active Ingredients	Doses (mg)
	Estrogen	
Premarin®	conjugated estrogens	0.3, 0.45, 0.625, 0.9, 1.25, 2.5
Estrace®	estradiol	0.5, 1.0, 2.0
Climara® (transdermal)	estradiol	0.025, 0.05, 0.075, 0.1
Ogen®	estropipate	0.75, 1.5, 3.0
Ortho-Est®	estropipate	0.75
Vivelle-Dot® (transdermal)	estradiol	0.025, 0.0375, 0.05, 0.075, 0.1
	Estrogen/Progestin	
Prempro™	conjugated estrogens/ medroxyprogesterone	0.625/2.5 0.625/5.0 0.45/1.5 0.3/1.5
Premphase®		0.625 x 14 days; 0.625/5.0 x 14 days
Activella®	estradiol/norethindrone	1.0/0.5
Femhrt®	ethinyl estradiol/norethindrone	0.005/1.0
Ortho-Prefest™	estradiol/norgestimate	1.0/0.09

Table 2⁴

Effect of various osteoporosis drugs compared to placebo, on risk of vertebral fractures (Prior to WHI trial)			
Drug	Number of Trials/Patients	RR (95% CI)**	p-value
Estrogen/ Progestin*	5/3117	0.66 (0.41, 1.07)	0.12
Alendronate	8/9360	0.52 (0.43, 0.65)	<0.01
Risedronate	5/2604	0.64 (0.54, 0.77)	0.01
Raloxifene	1/6828	0.60 (0.50, 0.70)	0.01

*Includes various estrogen plus progestin products/doses

**RR= relative risk, CI = confidence interval