



NATIONAL
OSTEOPOROSIS
FOUNDATION

Fighting Osteoporosis & Promoting Bone Health

MEMORANDUM

TO: Food and Drug Administration Endocrinologic and Metabolic Drugs Advisory Committee

CC: Commissioner Mark McClellan
Assistant Commissioner for Women's Health Susan Wood

FROM: Ethel S. Siris, MD
Chair, National Osteoporosis Foundation Science and Research Committee

DATE: September 30, 2003

RE: National Osteoporosis Foundation Statement: Women's Health Initiative Study Results: Implications for the use of hormone therapy with estrogen/progestin, as a second-line drug, in the prevention and treatment of postmenopausal osteoporosis in women

Introduction and Background on Osteoporosis:

On behalf of the National Osteoporosis Foundation (NOF), I appreciate the opportunity to present a statement before the FDA Endocrinologic and Metabolic Drugs Advisory Committee on osteoporosis and the implications resulting from the Women's Health Initiative (WHI) study results for the use of hormone therapy with estrogen/progestin.

The NOF is the leading national voluntary health organization solely dedicated to promoting lifelong bone health in order to reduce the widespread prevalence of osteoporosis and associated fractures, while working to find a cure for the disease through programs of research, education and advocacy.

Osteoporosis is a silent disease, until it is complicated by fractures. Osteoporosis is defined as a bone disease characterized by low bone mass, structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. Osteoporosis is a risk factor for fracture just as hypertension is for stroke.

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Bone loss often occurs without any symptoms. People may not know that they have osteoporosis until their bones become so weak that a sudden strain, bump, or fall causes a fracture or a vertebra to collapse. Vertebral fractures also may occur without symptoms or a collapsed vertebra may be felt as severe back pain or seen as the loss of height, or spinal deformities, such as stooped posture.

These fractures cause a tremendous medical and personal toll on individuals. Osteoporosis affects an enormous number of people, and its prevalence will increase as the population ages. Osteoporosis and low bone density pose a major public health threat for an estimated 44 million Americans. In the US today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis. While osteoporosis is most prevalent in Caucasian and Asian women, significant risk has been reported in people of all ethnic backgrounds.

The consequences of osteoporosis can be devastating. Eighty percent of those affected by osteoporosis are women. One in two women over age 50 will have an osteoporosis-related fracture in their lifetime. Osteoporosis is responsible for more than 1.5 million fractures annually. These include 300,000 hip fractures, and approximately 700,000 vertebral fractures, 250,000 wrist fractures, and 300,000 fractures at other sites.

The estimated national direct expenditures (hospitals and nursing homes) for osteoporotic fractures were \$17 billion in 2001 (\$47 million each day) – and the cost is rising.

Overall Views:

NOF encourages physicians to consider the possibility of osteoporosis and fracture risk in all postmenopausal women, based on the presence of risk factors and certain medical conditions. Usually, the more risk factors a woman has, the greater her risk of fracture. Risk factors include: Caucasian or Asian race, personal history of fracture as an adult; history of fragility fracture in close relatives; estrogen deficiency at an early age; use of oral corticosteroids for more than three months; low body weight; recent falls; low calcium intake; and low physical activity.

The National Osteoporosis Foundation advises health professionals to counsel all women on the risk of osteoporosis and related fractures. Universally, several interventions to reduce fracture risk can be recommended to the general population. These include an adequate intake of calcium and vitamin D, lifelong participation in regular weight-bearing and muscle strengthening exercise, treatment of chronic medical conditions known to harm bone health and an awareness of medications that are detrimental to the maintenance of bone health.

Because bone loss accelerates around the time of menopause, NOF recommends that all patients, including those considered for drug treatment of osteoporosis, should be counseled on risk factor reduction. Prior to a physician's initiating treatment, NOF advises that patients should be evaluated for secondary causes of osteoporosis and have dual x-ray absorptiometry (DXA) measurements, when available. NOF recommends bone mass density (BMD) testing for all women aged 65 and older. It also recommends BMD testing for younger postmenopausal women who have one or more risk factors (other than being white, postmenopausal, and female).

It advises initiating therapy to reduce fracture risk in postmenopausal women with BMD T-scores by DXA below -2 in the absence of risk factors and in women with T-scores below -1.5 if one or more risk factors is present. It urges consideration of postmenopausal women with vertebral or hip fractures as candidates for osteoporosis treatment.

Views on Hormone Therapy:

The Food and Drug Administration has approved six pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis. Estrogen/hormone therapy (available in several brands) is approved for the prevention of postmenopausal osteoporosis. Women who have not had a hysterectomy require hormone therapy that contains progestin to protect the lining of the uterus. The Women's Health Initiative study found that five years of one hormone therapy (Prempro) reduced the risk of clinical fractures, vertebral fractures and hip fractures by 23-34 percent. However, the findings also showed that its use resulted in increased risk for breast cancer, heart attack, stroke, and venous thromboembolism. Because of these risks, the NOF has advised that when hormone therapy use is considered solely for prevention of osteoporosis, approved non-estrogen treatments should first be carefully considered, and if hormone therapy is selected, it should be used in the lowest possible dose for the shortest duration to meet treatment goals. It should be noted, however, that when hormone therapy is discontinued, its benefit to bone is quickly lost, making long-term hormone therapy with estrogen necessary.

This month a new study that reevaluates the WHI Estrogen Plus Progestin Clinical Trial was released. Its conclusions support the positive effects of estrogen plus progestin on BMD and the decreased risk of fracture. However, it concludes that "given [the] overall unfavorable risk benefit ratio [and the] availability of other agents for the prevention and treatment of osteoporosis, estrogen plus progestin cannot be recommended for the prevention of fractures or for the treatment of osteoporosis."¹

The NOF is aware that sound science dictates caution in generalizing the findings of any single clinical study. The NOF also is mindful that not all women are the same and that response to any medication may vary from woman to woman. Therefore, the NOF supports continued basic and clinical research to alleviate and eradicate osteoporosis. The NOF also supports the continued availability of options for the prevention and treatment of osteoporosis. Because there are other effective drug therapies for prevention and treatment of osteoporosis, non-hormone therapies should be fully considered first. In some cases, however, hormone therapy may need to be considered as an alternative. The NOF supports continued availability of hormone therapy for the prevention of osteoporosis in such women. In these cases, it should be used in the lowest doses possible for the shortest period of time to meet treatment goals. In all cases, decisions should be made on an individual basis, with the patient understanding that her benefits should outweigh her potential risks for any medical treatment.

¹ Cauley, Jane A. "Estrogen and Bone: What have we learned from the Women's Health Initiative Estrogen Plus Progestin Clinical Trial?" ASBMR 25th Annual Meeting, September 2003, Minneapolis, MN