

[U.S. Food and Drug Administration](#)
[FDA Consumer magazine](#)
[March-April 2003](#)
[Table of Contents](#)

[Email this Page](#) 
[To a Friend](#)

The Estrogen and Progestin Dilemma: New Advice, Labeling Guidelines

By Linda Bren

The Food and Drug Administration is giving important new safety advice to postmenopausal women and their health-care providers concerning drug products that contain estrogen. The updated advice, which includes product label revisions, reflects the agency's review of data from the Women's Health Initiative (WHI) study, sponsored by the National Institutes of Health.

The landmark WHI study has raised concern about the risks associated with the use of estrogen and estrogen with progestin products, including increased risks for cardiovascular disease and breast cancer.

One arm of the WHI study found that after one year of treatment with estrogen with progestin, for every 10,000 women, there may be seven more cases of heart disease, eight more strokes, eight more instances of blood clots in the lungs, 13 more cases of blood clots in the limbs, and eight more cases of breast cancer. This part of the study was stopped in July 2002 after five years because the risks from taking the drug exceeded the benefits of reduced instances of colon cancer and bone fracture.

The WHI study included 16,000 postmenopausal women who still had a uterus and were taking either a combination estrogen-progestin drug or a placebo. The results are published in the July 17, 2002, issue of the *Journal of the American Medical Association*.

To help women and their health-care providers better understand this new information and make appropriate treatment decisions, the FDA has asked all manufacturers of estrogen-containing products to revise their physician prescribing information and patient information leaflets, also referred to as the labeling. The new labeling is one of several actions the agency has taken to help clarify the risks, benefits, and appropriate indications for using

estrogen and estrogen-progestin products. Other actions include issuing revised guidances to manufacturers of these products and pursuing research on questions involving the safety and effectiveness of the products.

Labeling Changes

The WHI has several components, one of which was designed to assess the effects of Prempro, a combination of estrogens plus a progestin, on the risk of developing heart disease. Prempro's manufacturer, Wyeth Pharmaceuticals of St. Davids, Pa., made labeling changes to Prempro and two other estrogen-containing products, Premphase and Premarin, shortly after the release of the WHI findings. The FDA has worked with Wyeth to build on these changes and develop the new labeling currently approved for these products.

The FDA is asking all manufacturers of estrogen and estrogen-progestin products for postmenopausal use to make similar changes to their product labeling because it is believed these products have risks similar to those of Prempro, the drug used in the WHI study. "We don't want women to think these other products don't have any risk or are less risky--we simply don't have the data yet because we haven't studied them in the manner Prempro was studied," says Florence Houn, M.D., director of the FDA office that reviews reproductive drugs. "However, from what limited information we do have, we know that blood clots, heart attacks, and other side effects may also happen with other estrogen and estrogen-progestin products." These products include estrogen-containing tablets, gels, transdermal (skin) patches, and vaginal creams and rings. About 10 million postmenopausal women in the United States are taking some form of estrogen, according to Wyeth.

The FDA is requiring the physician's labeling to include a boxed warning--the highest level of warning information in labeling--that highlights the increased risks found in the WHI study and emphasizes that estrogen and estrogen-progestin products are not approved for heart disease prevention. "For over 20 years, many medical experts thought estrogens protected women from heart disease," says Houn. "These thoughts were based on less rigorous studies."

New Treatment Advice

Prior to the WHI study findings, the FDA had approved three indications for

the use of estrogen and estrogen-progestin products in postmenopausal women. Two of the three indications have now changed to include consideration of alternative treatments:

- Treatment of moderate to severe symptoms of vulvar and vaginal atrophy (such as dryness, itching, and burning) associated with menopause. When these products are being prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
- Prevention of postmenopausal osteoporosis (weak bones). When these products are being prescribed solely for the prevention of postmenopausal osteoporosis, approved non-estrogen treatments should be carefully considered. Estrogens and combined estrogen-progestin products should only be considered for women with significant risk of osteoporosis that outweighs the risks of the drug.
- Treatment of moderate to severe vasomotor symptoms (such as hot flashes and night sweats) associated with menopause. This indication has not changed. Estrogen-containing products are the most effective approved therapies for these symptoms.

If a woman and her health-care provider decide that estrogen-containing products are appropriate, they should be used at the lowest doses for the shortest duration to reach treatment goals. It is not yet known what dose is less risky, says Houn. "We hope new studies will tell us this, and as we learn more, we'll tell the public." Women who are already taking these products should talk to their physicians before stopping their medication.

Women also should talk with a health-care provider periodically about whether estrogens should be continued and how to monitor for side effects. To minimize potential risks, the new labeling advises that women do a monthly breast self-examination and have a breast exam by a health-care provider and mammogram (breast X-ray) regularly. In addition, women should talk to a health-care provider about other ways to lower their chances for getting heart disease and osteoporosis.

More Study Needed

In addition to giving the industry advice on labeling, FDA-issued guidances also will provide recommendations on conducting studies to develop better information on the lowest effective doses of estrogen-containing drugs.

The FDA's review of the WHI study findings leads to some important research questions for the medical community. These questions include:

- Will lower doses of estrogen and progestin have lower risks?
- Do other types of estrogens and progestins or other ways of administering these drugs, such as through patches, have different risks?
- What is the best method to stop taking estrogens and progestins?

The FDA plans to work with researchers, sponsors, and product manufacturers to encourage this further research.

For more information, visit FDA's Drug Information Page: [Estrogen and Estrogen with Progestin Therapies for Postmenopausal Women](#).

Estrogen and Birth Control

The FDA's new advice and labeling changes on products that contain estrogen or estrogen and progestin apply to those prescribed for postmenopausal women. Oral contraceptives also contain estrogen and progestin, but different types and doses. All estrogens have similar side effects; however, the risks of particular side effects may differ since oral contraceptives are used in younger women with different health status compared to postmenopausal women.

As with all estrogens, the use of oral contraceptives is also associated with increased risks of some serious conditions, including heart attack, blood clots, stroke, liver tumors, and gallbladder disease. These risks are higher in women with underlying risk factors such as high blood pressure, high cholesterol and diabetes, and in those who smoke cigarettes.

--L.B.

[Table of Contents](#) | [How to Subscribe](#) | [Back Issues](#) | [Editorial Questions](#)

FDA/Office of Public Affairs
Web page created by [clb](#) 2003-FEB-23.