rienced a somewhat increased risk of heart attack, stroke, breast cancer, pulmonary emboli, and deep vein thrombosis. Shortly after the study was published, Prempro’s manufacturer, Wyeth Pharmaceuticals, added a warning about these risks in boldfaced type on the label and sent a letter to a half million physicians to inform them of the study’s findings.

**WARNING FOR ALL ESTROGEN HRT**

Now, however, the FDA is requiring Wyeth and all other companies making drugs that contain estrogen with or without progestin to carry a boxed warning—the highest level of caution in label warning information. In addition to noting the increased risk for heart attacks, strokes, blood clots, and breast cancer, the warning also stressed that these products are not approved for preventing heart disease. While estrogen and progestin had never been approved by the FDA for heart disease prevention, physicians have prescribed them “off-label” for this purpose.

The WHI study found that of every 10000 women taking Prempro, there would be 8 more cases of breast cancer, 7 more cases of heart attacks, 8 more cases of stroke, and 18 more cases of blood clots in the lungs or legs.

The FDA said that although other doses of Prempro and other estrogens and estrogen-progestin combinations were not studied in the WHI trial, in the absence of data, all estrogen products should be assumed to carry similar risks and will be required to have warning labels similar to those used for Prempro.

“A woman who is using or considering estrogen or estrogen-progestin treatment should consult with her health care provider about the implications of the new information on risks and benefits in her case,” noted FDA Commissioner Mark McClellan, MD, PhD. In many cases, women will still want to use such products for relief of menopausal symptoms, while alternative treatments will be appropriate for others, he said.

**ALTERED INDICATIONS**

Approved indications of estrogen-based HRT have included treatment of moderate-to-severe vasomotor symptoms such as hot flashes and night sweats; symptoms of vulvar and vaginal atrophy, such as vaginal dryness and itching; and the prevention of postmenopausal osteoporosis. Because there are few alternatives to HRT for the first two indicated conditions, estrogen-based drugs are still expected to play an important role for women with severe symptoms.

Weighing risks and benefits, the FDA has now decided that the indication for vasomotor symptoms should remain unchanged, but that the other two indications for HRT use should be revised. The agency says that in the case of symptoms of vulvar and vaginal atrophy, estrogen products are indicated for women with moderate-to-severe symptoms associated with menopause, although women taking estrogen solely for such symptoms should consider using topical products such as vaginal creams. And while prevention of postmenopausal osteoporosis remains an indicated use of the products, revised labels will state that consideration should be given to approved nonestrogen products and that estrogen products should only be considered for women with a significant risk of osteoporosis that outweighs the risks of the drugs.

The new labels also advise physicians to minimize potential risks when they prescribe estrogen products by prescribing the lowest effective doses for the shortest duration, weighing the potential benefits and risks for the individual woman.

**OTHER RECOMMENDATIONS**

The FDA recommends that women who choose estrogen-based therapy should have yearly breast examinations, perform monthly breast self-examinations, and receive periodic mammograms (to be scheduled based on their age and risk factors). Clinical surveillance for endometrial abnormalities is also important for women who have not had a hysterectomy.

In addition, women should consult with their clinician about other measures to reduce their risk for heart disease (such as treating hypertension and avoiding tobacco use) and to prevent osteoporosis (such as taking vitamin D and calcium supplements, changing her diet, and performing weight-bearing exercise).

The agency said it intends to work with researchers, sponsors, and product manufacturers to encourage further research to determine whether smaller doses of estrogen and progestin will have lower risks and whether other types of estrogen and progestins and patches or other ways of delivering the drugs pose different risks.