Drug Safety Revisions: FDA Update

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Conjugated Estrogens/Medroxyprogesterone Acetate Tablets (Prempro™, Premphase®)
Conjugated Equine Estrogen Tablets, USP (Premarin®)

Manufacturer: Wyeth Pharmaceuticals

Rationale for Labeling Review: The new boxed warning, the highest level of warning information in labeling, highlights the increased risks of these drugs for heart disease, heart attacks, strokes, and breast cancer as the result of the Women’s Health Initiative (WHI) study. This warning also emphasizes that these products are not approved for the prevention of heart disease. The Food and Drug Administration (FDA) has modified the approved indications for these conjugated estrogens to clarify that they should be used only when the benefits clearly outweigh the risks.

Indications: Conjugated estrogens are intended for (1) the relief of moderate to severe vasomotor symptoms, such as “hot flashes,” associated with menopause (the primary reason women seek treatment), (2) the alleviation of moderate to severe menopausal symptoms of vulvovaginal atrophy (dryness and irritation), and (3) the prevention of postmenopausal osteoporosis (weak or thinning bones) in women for whom non-estrogen therapies have been carefully considered.

When these products are prescribed solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered. Estrogens and combined estrogen–progestin (any group of steroid hormones that have the effect of progesterone) products should be considered only for women with a significant risk of osteoporosis that outweighs the potential dangers of the drug.

To minimize the potential risks and to accomplish the desired treatment goals, the new labeling also advises health care providers to prescribe the estrogen and the combined estrogen–progestin drug products at the lowest possible doses and for the shortest duration appropriate for individual patients.

Women who choose to take estrogens or combined estrogen and progestin therapies, after discussing treatment with their doctors, should have yearly breast examinations by a health care provider, should perform monthly breast self-examinations, and should receive periodic mammography evaluations based on their age and risk factors. Women should also talk to their health care providers about other ways to reduce their risk factors for heart disease (e.g., high blood pressure, poor diet, tobacco use) and about measures to prevent osteoporosis (e.g., an appropriate diet, the use of vitamin D and calcium supplements, and weight-bearing exercise).

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Label Change
Boxed Warning (Prempro™ and Premphase®)

Estrogens and estrogens plus medroxyprogesterone acetate therapies should not be used for the prevention of cardiovascular disease. The WHI study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during five years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.

Other doses of conjugated estrogens and medroxyprogesterone acetate and other combinations of estrogens and progestins were not included in the WHI study; in the absence of comparable data, however, the risks should be assumed to be similar. Because of these risks, estrogens and progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for individual patients.

Boxed Warning (Premarin®)

Estrogens and the Increased Risk of Endometrial Cancer: Close surveillance of all women taking estrogen is essential. Adequate diagnostic measures, including endometrial sampling when indicated, should be taken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of “natural” estrogens results in an endometrial risk profile differing from that of synthetic estrogens with an equivalent estrogen dose.

Cardiovascular and Other Risks: Estrogens with or without progestins should not be used for the prevention of cardiovascular disease. The WHI study reported an increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during five years of treatment with conjugated equine estrogens (0.625 mg) in combination with medroxyprogesterone acetate (2.5 mg).

Other combinations and doses of estrogens and progestins were not studied in the WHI, but in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for each patient.

Warnings for Prempro™, Premphase®, and Premarin®

Cardiovascular Disorders: Estrogen/medroxyprogesterone therapy has been associated with an increased risk of cardiovascular events. Should any cardiovascular event (myocardial infarction, stroke, pulmonary embolism) occur or be suspected, drug usage should be discontinued immediately. Risk
factors for cardiovascular disease (hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) should be managed appropriately.

The WHI study revealed a higher risk of coronary heart disease (CHD) events and stroke in women receiving Prempro™ than in women receiving placebo. The increased risk, observed in year one of the study, persisted. There was no cardiovascular benefit or secondary prevention of cardiovascular disease in postmenopausal women with documented heart disease who were receiving Prempro™ (0.625 mg). High doses of conjugated estrogens (5 mg daily), comparable to those doses used to treat cancer of the prostate and breast, have been shown, in a large prospective clinical trial in men, to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

In the WHI study, there was a two times greater rate of venous thromboembolism, including deep venous thrombosis and pulmonary embolism, in women receiving Prempro™ than in women receiving placebo.

Malignant Neoplasms

Breast Cancer. Estrogen/medroxyprogesterone therapy in postmenopausal women has been associated with an increased risk of breast cancer. In the WHI study, a 26% increase in invasive breast cancer after an average of 5.2 years of treatment was observed in women receiving Prempro™ compared with women receiving placebo. The increased risk of breast cancer became apparent after four years of Prempro™ therapy. Women who reported prior postmenopausal use of estrogen and/or estrogen with medroxyprogesterone had a higher relative risk for breast cancer associated with Prempro™ than women who had never used these hormones.

Endometrial Cancer. The reported endometrial cancer risk among users of unopposed estrogen was approximately two-fold to 12-fold greater than in nonusers and appears to be dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than one year. The greatest risk appears to be associated with prolonged use, with an increased risk of 15-fold to 24-fold for five years or more, and this risk has been shown to persist for at least eight to 15 years after estrogen therapy has been discontinued.

It is important to perform clinical surveillance of all women taking estrogen/medroxyprogesterone combinations. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1% or less with Prempro™ or Premphase®.

Gallbladder Disease: In postmenopausal women taking estrogens, a two-fold to four-fold increase in the risk of gallbladder disease necessitating surgery has been reported.

Hypercalcemia: Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, the drug must be discontinued.

Visual Abnormalities: Retinal vascular thrombosis has been reported in patients receiving estrogens. Medication should be discontinued if a partial or complete loss of vision occurs.

Conclusion: Overall health risks exceeded the benefits from the use of combined estrogen plus medroxyprogesterone acetate (progestin) for an average 5.2-year follow-up among healthy postmenopausal women in the U.S. All-cause mortality was not affected during the WHI trial. The risk–benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that an estrogen-plus-medroxyprogesterone acetate regimen should not be initiated or continued for the primary prevention of coronary heart disease.

Reference


Sertraline HCl (Zoloft®)

Manufacturer: Roergig, Division of Pfizer

Rationale for Labeling Revision: The FDA has required the manufacturer of this selective serotonin reuptake inhibitor (SSRI) antidepressant to add a warning to the drug’s professional product labeling or package insert, alerting physicians that sertraline should not be used in combination with the antipsychotic drug pimozide (Ora®). The basis of the new warning was the result of a controlled study of a single dose of pimozide (2 mg) given to subjects who had been taking 200 mg of sertraline daily. The co-administration of the two drugs was associated with an average increase in pimozide absorption of about 40%. No changes in heart function were seen, as measured by an electrocardiogram (ECG); however, because the highest recommended pimozide dose of 10 mg has not been evaluated in combination with sertraline, the effect on the heart at doses higher than 2 mg is not known at this time.

Indications: Sertraline is used to treat the following conditions:

Major Depression. The efficacy of sertraline in the treatment of a major depressive episode was established in short-term and long-term clinical trials of outpatients whose diagnoses corresponded most closely to the category of Major Depressive Disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

Obsessive-Compulsive Disorder (OCD). As defined in DSM-III-R, OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions). The obsessions and compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning. They are ego-dystonic or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Panic Disorder. Patients with this medical condition have
repeated “panic attacks”—sudden, unexpected periods of intense fear—that often arise “out of the blue.” Not every person who has a panic attack develops Panic Disorder. The signs and symptoms of a panic attack usually occur abruptly and are often at their worst within 10 minutes.

**Premenstrual Dysphoric Mood Disorder.** This disorder is an important cause of symptoms and functional impairment in menstruating women. Improvement in psychosocial functioning with sertraline treatment is similar to that found in studies of major depression.

**Agitation and Post-traumatic Stress Disorder (PTSD).** Patients with PTSD have experienced, witnessed, or heard about a life-threatening or serious event and have felt intense fear, helplessness, or horror as a result.

**Boxed Warning Label:** Cases of serious, and sometimes fatal, reactions have been reported in patients receiving sertraline, an SSRI, when it has been combined with a monoamine oxidase (MAO)–inhibitor. Manifestations of a drug interaction between an SSRI and an MAO-inhibitor can include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include confusion, irritability, and extreme agitation, progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued an SSRI medication and have started MAO-inhibitor therapy. Some patients have presented with features resembling neuroleptic malignant syndrome. Therefore, sertraline should not be used in combination with an MAO-inhibitor or within 14 days of discontinuing treatment with an MAO-inhibitor. Similarly, at least 14 days should be allowed after sertraline is discontinued before an MAO-inhibitor is started.

**Label Change**

**Contraindications:** Sertraline should not be used in combination with MAO-inhibitors or with pimozide.

**Precautions:** In a controlled study of a single dose (2 mg) of pimozide, a 200-mg sertraline (once-a-day) co-administration to the steady state was associated with a mean increase in pimozide area-under-the-curve concentration and a maximum concentration ($C_{max}$) of about 40%, but not with any changes in the ECG. Because the highest recommended pimozide dose (10 mg) has not been evaluated in combination with sertraline, the effects on the QT interval and pharmacokinetic parameters at doses higher than 2 mg are not known. Although the mechanism of this interaction is unclear, because of the narrow therapeutic index of pimozide and the interaction noted at a low dose of pimozide, concomitant administration of sertraline and pimozide is contraindicated.

**Palivizumab (Synagis®)**

**Manufacturer:** Medimmune, Inc.

**Rationale for Labeling Revision:** When palivizumab was licensed, there were no observable cases of anaphylaxis resulting from the use of this drug. Post-licensure information, based on four seasons of worldwide post-marketing experience representing more than 400,000 patients and two million doses administered, revealed anaphylactic reactions in two patients. Both patients fully recovered with appropriate therapy. Because the risk of anaphylaxis has now changed from a theoretical to an actual—although rare—occurrence, a portion of the section covering adverse reactions has been adjusted.

**Indications:** Palivizumab, a humanized monoclonal antibody (IgG-1κ), is produced by recombinant DNA technology. It is a composite of human (95%) and murine (5%) antibody sequences and is directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV).

Palivizumab has been developed to combat infectious respiratory disease and to prevent serious lower respiratory tract disease caused by RSV in children who are at high risk for RSV infection. The safety and efficacy of the drug have been established in infants with bronchopulmonary dysplasia and in infants with a history of prematurity (less than 35 weeks of gestation).

**Label Change**

**Warnings:** Extremely rare cases of anaphylaxis (fewer than one case per 100,000 patients) have been reported following re-exposure to palivizumab. Rare severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to drug therapy. If a severe hypersensitivity reaction occurs, palivizumab therapy should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on re-administration of palivizumab. If anaphylaxis or severe allergic reactions occur after palivizumab therapy, appropriate medication (e.g., epinephrine) should be given and supportive care provided as required.

**Overdosage:** No data are available from humans who have received more than five monthly doses of palivizumab during a single RSV season.

**Adverse Reactions, Post-Marketing Experience:** Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of palivizumab are similar in character and frequency to adverse events after the initial five doses.

**Conclusion:** Palivizumab belongs to a group of drugs known as immunizing agents. Palivizumab works by giving the body the antibodies it needs to protect it against RSV infection, which can cause serious problems affecting the lungs, such as pneumonia and bronchitis, and in severe cases can even cause death. These problems are more likely to occur in infants and children younger than six months of age with chronic lung disease and breathing problems and in babies who were premature.

No cases of anaphylaxis were observed at the time of licensing; however, because of the protein nature of the product, such reactions might be anticipated. The new labeling changes reflect the recognized risks of anaphylaxis with palivizumab therapy.