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NIH Asks Participants in Women's Health Initiative Estrogen-Alone Study to Stop Study Pills, Begin Follow-up Phase

Statement from Barbara Alving, M.D., Director of the Women's Health Initiative and Acting Director of the National Heart, Lung, and Blood Institute

The National Institutes of Health (NIH) has instructed participants in the estrogen-alone study of the Women's Health Initiative (WHI), a large multi-center trial, to stop taking their study pills and to begin the follow-up phase of the study.

Letters have been sent to all participants in the estrogen-alone study, 11,000 healthy postmenopausal women who have had a hysterectomy, informing them of a recent NIH review of the study data. After careful consideration of the data, NIH has concluded that with an average of nearly 7 years of follow-up completed, estrogen alone does not appear to affect (either increase or decrease) heart disease, a key question of the study. At the same time, estrogen alone appears to increase the risk of stroke and decrease the risk of hip fracture. It has not increased the risk of breast cancer during the time period of the study.

The increased risk of stroke in the estrogen-alone study is similar to what was found in the WHI study of estrogen plus progestin when that trial was stopped in July 2002. In that study, women taking estrogen plus progestin had 8 more strokes per year for every 10,000 women than those taking the placebo. The NIH believes that an increased risk of stroke is not acceptable in healthy women in a research study. This is especially true if estrogen alone does not affect (either increase or decrease) heart disease, as appears to be the case in the current study.

The NIH has determined that the results would not likely change if the estrogen trial continued to its planned completion in 2005. Furthermore, enough data have been obtained to assess the overall risks and benefits of the use of estrogen in this trial. WHI researchers have begun a detailed analysis of the data from the estrogen-alone study and expect to

report full results in the next two months. The report, to be published in a peer-reviewed journal, will include additional data collected through the end of February 2004.

A separate report will contain information on probable dementia and/or mild cognitive impairment in the women age 65 and older who participated in the estrogen-alone WHI-Memory Study (WHIMS), an ancillary study of the WHI Hormone Trials. Preliminary data suggest that for the WHIMS participants who were on estrogen alone when compared to the women who were taking the placebo, there was a trend toward increased risk of probable dementia and/or mild cognitive impairment.

The WHI estrogen study was designed to assess the effect of long-term use of hormone therapy in healthy postmenopausal women on the prevention of heart disease and hip fractures, and any associated change in risk for breast cancer. It was not designed to evaluate the short-term risks and benefits of hormones for the treatment of moderate to severe menopausal symptoms.

The estrogen-alone study involved women ages 50 to 79 years. Study participants were randomly assigned to a daily dose of estrogen-- 0.625 mg/day of conjugated equine estrogen (Premarin™)--or a placebo.

The NIH decision to stop the estrogen-alone trial was made on February 2, 2004. In November and December 2003, the WHI Data and Safety Monitoring Board (DSMB), an independent advisory committee which regularly reviews study data and oversees the safety of study participants, reviewed the latest data from the estrogen-alone study. The DSMB was split as to whether the study pills should be stopped or whether the pills should be continued, provided that a letter would be sent to the participants clearly informing them of the stroke risks and other findings. After careful review, the NIH decided that women in the estrogen-alone study should stop taking their study pills.

The NIH advises women to continue to follow the FDA guidance regarding hormone therapy. Currently the FDA advises postmenopausal women who use or are considering using estrogen or estrogen with progestin to discuss the benefits and risks with their physicians. These products are approved therapies for relief from moderate to severe hot flashes and symptoms of vulvar and vaginal atrophy. Although hormone therapy is effective for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis who cannot take non-estrogen medications. The FDA recommends that estrogens and progestins should be used at the lowest doses for the shortest duration needed to achieve treatment goals.

The WHI involves over 161,000 women who are either participating in a set of clinical trials to test preventive measures for heart disease, fractures, breast and colorectal cancer, or in a large observational study. In addition to the trials of estrogen alone and estrogen

plus progestin, other WHI trials are studying a low-fat eating pattern and calcium/Vitamin D supplementation. These trials are continuing.

Participants in all of the WHI studies will be informed about the detailed results of the estrogen-alone study at the time of their publication in the next two months.

The estrogen-plus-progestin trial was stopped after 5.6 years of follow-up because of an increased risk of breast cancer and because the risk of breast cancer, coronary heart disease, stroke, and blood clots outweighed the benefits on hip fracture and colorectal cancer. Participants in the combined hormone therapy study were assigned to either estrogen plus progestin (0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate) or to a placebo. Since these women had a uterus, they were given progestin in combination with estrogen, a practice known to prevent endometrial cancer. Women who were enrolled in the active phase of the estrogen-plus-progestin study are currently in a follow-up phase and, like participants in the estrogen-alone study, will be monitored to assess long-term effects of hormone use.

WHI is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, and the Office of Research on Women's Health. Note: Wyeth Ayerst Research provided the active hormone for the estrogen-alone study and funded the WHIMS study.

NHLBI is part of the National Institutes of Health (NIH), the Federal Government's primary agency for biomedical and behavioral research. NIH is a component of the U.S. Department of Health and Human Services. Additional information on menopausal hormone therapy, including the WHI estrogen-plus-progestin study, can be found on the NIH Website: www.nih.gov, on the NHLBI Website: www.nhlbi.nih.gov, and on the FDA Website: www.fda.gov.

Additional information:

Women's Health Initiative (www.nhlbi.nih.gov/whi)
Questions and Answers About the Estrogen-Alone Study (www.nhlbi.nih.gov/whi/e-a_faq.htm)

- Sample Letter to Estrogen-Alone Participants (www.nhlbi.nih.gov/whi/e-a_letter.htm)
- Advisory for Physicians (www.nhlbi.nih.gov/whi/e-a_advisory.htm)
- WHI Estrogen-Plus-Progestin Study (www.nhlbi.nih.gov/whi)

Women's Health Initiative Memory Study (WHIMS) (www.wfubmc.edu/whims/)
FDA Statement on Postmenopausal Hormone Therapy (www.fda.gov/cder/drug/infopage/

estrogens_progestins/default.htm)
Postmenopausal Hormone Therapy (NHLBI) (www.nhlbi.nih.gov/health/women/index.htm)
Menopausal Hormone Therapy Information (NIH) (www.nih.gov/PHTindex.htm)

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