DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

F.O.I

JAN 1 1 1999

TRANSMITTED VIA FACSIMILE

Joseph S. Sonk, Ph.D.
Senior Director,
Women's Healthcare Products
U.S. Drug Regulatory Affairs
Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia PA 19101-8299

RE: NDA #4-782
Premarin (conjugated estrogens tablets, USP)
MACMIS #7000

Dear Dr. Sonk:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed promotional materials for Premarin (conjugated estrogens tablets, USP) disseminated by Wyeth-Ayerst Laboratories (Wyeth-Ayerst) that include brochure 61002-00 ("When Prescribing for Prevention of Osteoporosis, Give Your Patients Better Odds for Response") and advertisements 71357-00 & 71357-01 ("Every day they're discovering more about estrogen loss"). DDMAC has examined these materials and has determined that they contain statements and representations that are false or misleading, and promote Premarin for unapproved uses, in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations.

False or Misleading Representations

Wyeth-Ayerst has disseminated a promotional brochure entitled "When Prescribing for Prevention of Osteoporosis, Give Your Patients Better Odds for Response" (61002-00). The foci of the brochure include: (a) study data from a 619 patient postmenopausal osteoporosis prevention clinical trial that included as primary endpoints, change in spinal and hip bone mineral density (BMD): and, (b) the proceedings from the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, Open Session, November 20, 1997. This brochure contains false or misleading representations about

Premarin and a competitor's drug product -- Evista (raloxifene hydrochloride) (Eli Lilly and Company).

One side of the brochure includes two separate pie charts. One provides the BMD "response rates" for Evista and the other provides the BMD "response rates" for Premarin. The information contained in these charts is separated into two categories -- patients who experienced an increase in BMD and patients who either experienced a decrease in BMD or maintained their BMD. Immediately below the charts is the statement "Premarin spinal BMD response rate represents a 57% increase (83% vs. 53%) over Evista." This presentation in juxtaposition with the banner headline stating, "[w]hen Prescribing for Prevention of Osteoporosis, Give Your Patients Better Odds for Response," clearly implies that only therapy that increases BMD from baseline is effective for the prevention of postmenopausal osteoporosis. This presentation is misleading since BMD maintenance alone is evidence of efficacy for the prevention of postmenopausal osteoporosis. By placing patients who maintained their BMD with those whose BMD decreased, Wyeth-Ayerst implies that only an increase in BMD will prevent osteoporosis in postmenopausal women. This is simply untrue.

The other side of the card contains a chart entitled, "[a]verage increase in BMD from baseline among completers after 2 years with Evista or Premarin," that includes BMD data from the lumbar spine and the total hip. This presentation of data is derived from the 619 patient study that was presented at the Advisory Committee Meeting on November 20. However, there is no presentation of data from the placebo arm of the study. This data would show that placebo patients experienced an actual mean decrease in BMD after two years. Without this data, the effect of Evista and Premarin on BMD cannot be placed in proper perspective since this information conveys the important message that maintenance in BMD alone is sufficient to demonstrate efficacy for the prevention of osteoporosis in postmenopausal women. Furthermore, the lumbar spine value provided for Evista in the chart is lower by a factor of two and one half times than the true lumbar spine value for completers as presented at the Advisory Committee.

As indicated above, any statement that implies that maintenance of BMD is tantamount to a decrease in BMD or that an increase in BMD is necessary for the prevention of osteoporosis (implying that maintenance is insufficient) would be false or misleading in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations. Similarly, since both Evista and Premarin are first-line therapy for the prevention of osteoporosis in postmenopausal women, any statement that implies that Evista is second line therapy or that it should only be used in women for whom estrogen use is contraindicated would also be false or misleading.

Unapproved Uses Representation

Wyeth-Ayerst has disseminated advertisements entitled "Every day they're discovering

more about estrogen loss" (71357-00 & 71357-01). These advertisements promote Premarin for unapproved uses by implying or stating that Premarin is useful in a broad range of undefined health problems.

As described in the Indications and Usage section of the Premarin approved product labeling, Premarin is indicated for: moderate to severe vasomotor symptoms associated with the menopause; atrophic vaginitis; osteoporosis; hypoestrogenism due to hypogonadism, castration, or primary ovarian failure; breast cancer palliation in selected patients with metastatic disease; and, palliation of advanced androgen-dependent carcinoma of the prostate. Notwithstanding, Wyeth-Ayerst advertisements for Premarin imply or suggest that Premarin is indicated for use in a broad and far wider range of undefined menopausal or post-menopausal health conditions. This is evidenced by the use of such statements as: "[e]very day they're discovering more about estrogen loss. That's why I'm glad I take my Premarin"; and, "[r]ecently, I heard about new research. It's comforting to know that they're discovering even more about estrogen loss and menopause."

In an untitled letter dated May 20, 1998, DDMAC objected to the use of statements, in a DTC advertisement, that imply that "Premarin can be used for a broader indication than that supported by substantial evidence." DDMAC requested that Wyeth-Ayerst both withdraw the DTC advertisement from use, as well as "any other materials bearing the same or similar information." In its letter dated June 3, 1998, Wyeth-Ayerst responded to DDMAC's concerns and stated that it had withdrawn the DTC advertisement. Yet, despite its receipt of an untitled letter, Wyeth-Ayerst continues to disseminate promotional material that contains the same theme.

DDMAC is concerned that Wyeth-Ayerst continues to promote broad and ambiguous health claims for Premarin that promise yet-to-be substantiated or even identified health benefits from the use of Premarin. This is particularly troublesome in light of the prominent boxed warnings and numerous contraindications to the use of Premarin, and the serious risks, particularly long-term, associated with the use of Premarin.

In order to address these objections, DDMAC suggests that Wyeth-Ayerst take the following actions:

(1) Immediately discontinue the dissemination of these promotional materials and all other promotional materials for Premarin bearing the same or similar violative claims upon receipt of this letter.

(2) Provide to DDMAC, in writing, Wyeth-Ayerst's commitment to comply with number one above.

Wyeth-Ayerst's response should be received no later than January 25, 1999. If Wyeth-Ayerst has any questions or comments, please contact the undersigned or Lesley R.

Frank, Ph.D., J.D., by facsimile at 301-594-6771, or in writing at the Division of Drug, Marketing, Advertising, and Communications, HFD-40, Room 17B-20, 5600 Fishers Lane, Rockville, MD 20857.

In all correspondence related to this matter, please refer to MACMIS #7000, in addition to the NDA number.

Sincerely,

Jayne Peterson, R.Ph., J.D.
Division of Drug Marketing, Advertising,
and Communications