

IN THE CIRCUIT COURT OF LOGAN COUNTY, WEST VIRGINIA

CLINTON VANCE, as EXECUTOR of the
ESTATE OF DOROTHY VANCE,

Plaintiff,

vs.

RITE AID OF WEST VIRGINIA, INC.,
FIRST DATABANK, INC., WYETH a/k/a
WYETH, INC., AMERICAN HOME
PRODUCTS, INC., AHP SUBSIDIARY
HOLDING CORPORATION, WYETH-
AYERST LABORATORIES COMPANY
WYETH PHARMACEUTICALS, INC.
WYETH-AYERST PHARMACEUTICALS,
INC., BARR LABORATORIES, INC.,
BARR PHARMACEUTICALS, INC.,

CIVIL ACTION NO. 06-C-351P

Defendants

SUPPLEMENTAL DISCLOSURE OF DONALD AUSTIN, MD, MPH OPINIONS

Dr. Austin is expected to testify as follows:

A further hypothetical question is posed regarding the hypothetical woman born in November 1944, and diagnosed with lobular breast cancer in September 2002 at age 57 years. The question is: Had she been prescribed conjugated equine estrogen (CEE) and micronized progesterone (mP4) as the CHRT instead of CEE+ medroxyprogesterone acetate (MPA), would the risk have been different? More specifically, would she still have been in the group of exposed women with a greater than two-fold risk of lobular breast cancer?

There is evidence from several sources that lead to an answer of "Yes" to the first question and "No" to the second question.

MPA is associated with elevated breast cancer risk when given alone or with an estrogen. The current evidence indicates that while estrogens cause proliferation of the ductal and lobular breast tissue, MPA induces even more proliferation. In contrast, progesterone, whether taken orally in the micronized form or by some other route, almost completely prevents the breast tissue proliferation produced by estrogen. Proliferation is an intermediate step in the

development of breast cancer. Animal and human studies of cancer outcomes support the findings regarding proliferation.

Animal studies:

A. The use of MPA in beagles in a long-term industry study completed in 1982 demonstrated that beagles with 7 years of exposure to MPA alone had a very much higher risk of breast tumors. While the control animals had 0% incidence, the MPA animals had 25% or 40% incidence, depending upon the dose.

In addition, other histologic studies in both mice and monkeys have demonstrated that compared to estrogen alone, estrogen + MPA causes significantly more cellular proliferation in breast duct tissue. Increased cellular proliferation is a risk factor for malignancy of the breast.

B. Wood et al, in 2006, addressed the question of whether the increased risk of breast cancer produced by the addition of MPA to estrogen therapy was specific to MPA or was a general characteristic of all progestogens. In short term clinical studies in postmenopausal cynomolgous monkeys, an established primate model for human breast studies, they examined breast cancer risk biomarkers in four groups: (1) no hormone supplements, (2) estrogen with no progestogen, (3) estrogen with MPA, or (4) estrogen with micronized progesterone (mP4). They demonstrated that compared to controls, estrogen, estrogen + MPA, and estrogen + mP4 had different effects on the proliferation of ductal and lobular breast tissue, as measured several ways. While the group receiving the combination with MPA resulted in significantly greater cellular proliferation in ductal and lobular cells, the group receiving mP4 did not. The investigators also documented a similar effect for gene expressions of cellular proliferation, (e.g., Ki-67).

Animal studies are consistent in their findings of elevated breast cancer risk with MPA use, either using tumors as a long term marker, or using cellular proliferation as a short term marker but fail to find similar findings using mP4.

Human studies: Human studies provide similar results.

Clinical studies:

Foidart, in 1998, showed that while E2 alone produced proliferation of human breast ductal tissue, the addition of transdermal P4 significantly curtailed this proliferation. (This is the human counterpart of the Wood et al experiment in cynomolgous monkeys.)

Hofseth, in 1999, demonstrated that among postmenopausal women receiving breast biopsies that were diagnosed as benign, women taking estrogen alone (27/32 were CEE) compared to those not taking HRT, had proliferation of the breast ductal tissue, and those taking estrogen with MPA (19/25 were CEE) had similar ductal proliferation but also had significantly increased proliferation in the terminal ductal lobular units, the site of origin for most breast cancers. They were also able to demonstrate that the density of ductal cells, per microscopic field, was

approximately doubled in women receiving estrogen alone, and tripled in those receiving estrogen plus MPA.

The animal findings and human clinical studies of breast cell proliferation are consistent with human randomized controlled trials and observational studies of breast cancer.

The Women's Health Initiative is a randomized controlled trial that demonstrated that with extended duration of CEE+MPA use, the risk of all breast cancers combined significantly increased beyond that of placebo controls, while that of women receiving CEE alone showed a slightly different risk from that of the controls, but not significantly so. The estimate of risk of estrogen sensitive cancers from CEE+MPA in this study is markedly understated (because of several reasons I have discussed previously, including the lack of subject compliance, the lack of focus on ER+ cancers, and other effects).

Observational studies:

The Million Women Study is a cohort study that at enrollment included over half of all British women aged 50-64. Investigators examined breast cancer risks associated with HRT use, including risks associated with different types of estrogen and progestational agents singly and in combination and, separately, of risks for different histologic types, by duration of use. For example, for lobular cancer, the relative risk associated with use of estrogen only, for less than 5 years (average 3.7 years) was 1.60, and for 5-9 years (average 7.2 years) was 1.65 (both significant). On the other hand, for lobular cancer, the relative risk associated with use of estrogen plus a progestogen for less than 5 years (average 3.7 years) was 2.46, and for 5-9 years (average 6.8 years) was 2.75. In that particular analysis, all estrogens were considered together, as were all progestogens. In a separate analysis, however, the risks for all breast cancers combined were assessed for different combinations of estrogen and progestogen. Estradiol was not one of the estrogens used among this population, but CEE and ethinylestradiol were, and there was little difference in the elevated risk between them, though continuous use (as opposed to cyclic or sequential use) of higher doses consistently was associated with higher risks. For progestational agents, the three preparations separately assessed were MPA, norethisterone and a mixture of norgestrel and levonorgestrel. All three were associated with significantly elevated risks for all breast cancer, and for those with a duration of use greater than 5 years, the highest relative risk was with MPA (2.42).

Fournier et al also studied the effect on breast cancer risk of the progestational agents used in combination hormone replacement therapy in France. Of note, estrogens with MPA had statistically significantly elevated breast cancer risk, while estrogens with progesterone had no statistically elevated risk, even after 6 or more years of use. In that analysis CEE was not separately identified from other oral estrogens.

In summary, both animal and human clinical studies show that estrogens, including conjugated equine estrogens (CEE), cause proliferation of the breast ductal epithelium. This is consistent with clinical human studies that estrogens, including CEE, produce increased breast

radiodensity, a finding associated with increased risk for breast cancer. Also consistent are the epidemiologic findings that continued use of estrogens as hormonal replacement therapy (HRT), including CEE, increase the risk of subsequent breast cancer, though the relative risk is commonly found to be slight compared to the risk from combined therapy. There is not much difference in breast cancer risk among women receiving estrogens of different types, so long as the agent does not have an androgenic effect.

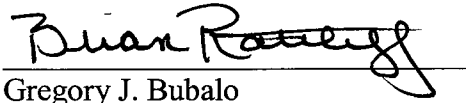
Animal and human clinical studies also show that the addition of MPA to estrogen, including CEE, causes marked increase in cellular proliferation of breast ductal epithelium, particularly that at the ductal-lobular junction, where most breast cancers originate. (This also produces denser breasts in which early diagnosis of breast cancer is more difficult.) In contrast, the use of bioequivalent progesterone by any route, including oral micronized progesterone (mP4), reduces this estrogen-caused cellular proliferation to levels approximately equivalent to those women not receiving HRT. Epidemiologic studies show that while CEE and MPA increase the risk of breast cancer, and especially the lobular and lobular/ductal histologic types of breast cancer, studies of women receiving estrogens and mP4, have little or no elevated risk of breast cancer. In the study of the breast cancer risk from estrogens with different progestational agents, CEE plus mP4 has not examined separately. Other studies demonstrate that estrogens including CEE result in increased breast cancer risk when given with types of progestogens other than mP4, and there is no discernable risk difference among them.

Further, population-based studies of breast cancer risk following exposure to different estrogen and progestational agents provide evidence for the exact same conclusions.

Thus, the preponderance of evidence supports the conclusion that the use of an estrogen, including CEE, together with micronized progesterone continuously (as opposed to sequentially) by postmenopausal women for 5 or more years raises the risk of breast cancer only slightly, if at all, while it is clear that the use of conjugated equine estrogen together with MPA raises the risk of breast cancer, and especially the risk of lobular cancer, well over two-fold.

Dr. Austin is expected to testify that based on the foregoing evidence the hypothetical woman would not have been included in this latter high risk group had she been prescribed CEE and mP4 and she would not have experienced an elevated risk of breast cancer. Based on the evidence reviewed, this is Dr. Austin's opinion, to a reasonable degree of medical certainty.

Respectfully submitted,



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BARR LABORATORIES, INC.
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CERTIFICATE OF SERVICE

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I, **Steven B. Rotman**, counsel for Plaintiff, do hereby certify that I have served the Supplemental Disclosure of Donald Austin, MD, MPH Opinions, upon the following counsel of record via regular U.S. Mail, postage paid, on this the 6th day of October, 2008:

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