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Dr Steve K. Galson, MD, MPH
Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD, 20852

Re: Docket Number 2004P-0513

Dear Dr. Galson,

The purpose of this letter is to formally appeal the denial of my citizen petition, docket number 2004P-0513. My petition requested a change to the black box warning and to the warnings section of the prescribing information for Premarin™. Your letter dated January 30, 2006 documents your reasons for the denial. This letter examines in detail the points you raised and explains why the decision should be reversed and the petition approved.

The core issue in my citizen petition is that the elevated levels of equine estrogens and their prolonged presence after cessation of therapy has sufficient clinical significance to warrant special attention in the black box warning of the prescribing information of Premarin™. The issues that were raised to refute the importance of my request did not address the clinical significance in the following ways.

1) On page 5, you state "The use of equine estrogen does not, as your petition argues, result in a different endometrial risk profile than the use of human estrogens of an equivalent estrogen dose." I disagree with this conclusion for the following reasons:

- The stimulation of the human endometrium is different both from other forms of estrogen while on Premarin™ and for months following discontinuation of Premarin™. The difference is how Premarin™ and other forms of estrogen are bound in the blood and how quickly they are metabolized.

- Typically, only about 1-2% of estrogen remains unbound and biologically active in the blood. The rest is bound by SHBG (sex hormone binding globulin) or

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albumin. For an average level of 100 pg/ml of total estradiol this means that about 2 pg/ml of estradiol is in a free state. Treatment with Premarin™ 1.25 mg per diem, creates mean total equilin levels of 2172 pg/ml after 15 weeks[1]. Assuming there is a similar distribution of free and bound hormones, for this level of total equilin, the free equilin level would be about 43 pg/ml. This assumption, as well as free equilin levels as high as 454 pg/ml, is confirmed by ID Cooke for this dosage and timeframe.[2] The level of free equilin after just 3 months on Premarin™ would then be 22-227 times higher than a level of 2 pg/ml of free estradiol. We know equilin to be about ½ the potency of estradiol. This would work out to be an 'estradiol equivalent' of 11-113 times that of the stimulation of 100 pg/ml or a normal menstrual cycle.

- Elevated levels of equine estrogens from Premarin™ continue for months following cessation of therapy, creating a continual source of unopposed estrogen stimulation to the endometrium many fold higher than a normal menstrual cycle. Other forms of estrogen products are no longer detectable in the blood 24-48 hours after cessation of therapy.

2) On page 7 you state, "In light of our review, we find that you have not provided reasonable evidence of an association of a serious hazard with a drug that would warrant adding specific warnings on the accumulation of equine estrogens." I disagree for the following reason:

- While Premarin is used, the accumulated levels of free equilin and its potent metabolites present excessive estrogen stimulation not only to the uterus but throughout the body. This excessive stimulation continues for many months past the time that Premarin™ is stopped. The free levels of equilin present, after just 3 months on Premarin™, result in stimulation 11-113 times higher than the stimulation the uterus would receive during a normal menstrual cycle. This demonstrates that Premarin™ -- equilin being just one component of it -- creates a different, more aggressive, endometrial profile than other estrogen products which contain other forms of estrogens. Excessive endometrial stimulation is considered to be a significant risk factor for endometrial cancer.

3) In your footnote on page 6, you state, "While a health care practitioner's decision on how to treat a woman's breast cancer is made by taking into account all relevant factors, our understanding is that the levels of equilin does not generally dictate the decision as to which type of treatment for breast cancer is optimal in any particular situation." I disagree for the following reasons:

- Equilin presence after stopping Premarin™ is equivalent to a non-suppressible source of estrogen, akin to ovarian function in a pre-menopausal woman. Clinically, this information is of paramount importance, as the decision to use either an aromatase inhibitor or estrogen competitor is based on the levels of free and biologically active estrogen present when a decision for cancer treatment is

made.

- Without adequate warnings, a healthcare practitioner would not know about circulating elevated or prolonged levels of equilin after stopping Premarin™.

- Even if a healthcare practitioner wanted to know equilin levels, a commercially available blood test does not exist and so the practitioner would be and is unable to check equilin levels.

- In the current prescribing information for Premarin™ the levels of equilin are only indicated after 1 pill is taken, which is clinically irrelevant given daily usage, and the daily accumulation and prolonged presence of Premarin™.

In response to your comments about my references, see the following:

Ref 1) Equilin is not a hormone normally produced by the human female. Following ingestion of Premarin™ all of the women had elevated equilin levels. The clinical significance of increased levels of equilin lies in the elevated levels themselves and not the mechanism by which the equilin sulphate is converted to equilin. The increased equilin level is important and is positively correlated with ingestion of Premarin™.

Ref 2) Yes, it is a case study of one person. This study, however, is representative and consistent with documentation of the accumulation of equilin.

Ref 3) Equilin has been shown to be 4-8 times more potent than estrone. Equilin is in equilibrium with 17β-dihydroequilin which has been shown to be more than 8 times more potent than estradiol, the most potent human estrogen. So long as equilin is present, there will be 17β-dihydroequilin because they are in equilibrium. After three months of use, free equilin levels are high enough to cause 11-113 times the stimulation of a normal menstrual cycle. As you stated, "The critical issue is whether a given woman is predisposed to have an exaggerated response to estrogen stimulation." Anyone predisposed to endometrial cancer needs to be aware of the more aggressive profile of Premarin™ via its components.

Ref 4) This reference documents that as long as equilin remains in the bloodstream so do its metabolites. As I state in my petition, "equilin can be metabolized by normal and malignant tissue into equilenin, 17β-dihydroequilin and 17β-dihydroequilenin, all estrogens with at least the same or greater affinity for estrogen receptors than human estrogens." This is critical information to know if excessive stimulation of the endometrium is to be avoided for those predisposed to endometrial cancer.

Ref 5 and 6) Premarin™ creates an estrogen environment which is the sum total of all the estrogenic activity of all of its components. Equilin, accumulating to very high levels, and identified as being in equilibrium with even more potent components, is representative of the excessive estrogen environment which Premarin™ creates. Equilin and its

metabolites all possess strong affinities for estrogen receptors. Equilin, in its free state, provides this stimulation like any other estrogen. As noted above, the presence of equilin is positively correlated with usage of Premarin™. Therefore, it is Premarin™ that causes excessive stimulation of the endometrium via its components, equilin being one of them.

Ref 7 and 8) To clarify, it is my 3rd reference, *Serum equilin, oestrone, and oestradiol levels in postmenopausal women receiving equine conjugated equine estrogens ('Premarin')* by Whittaker, *et al.* that is being discussed in these letters. Reference 7 was a letter to the editor, and simply stated the opinion of two doctors who do not want to accept that Premarin™ presents this estrogenic profile. They use pharmacokinetic studies based on very low levels of equilin from single dose studies, not studies on the elevated levels of equilin found by Whittaker, *et al.* The fact that these letters are over 25 years old is not the issue, the veracity of the RIA technique used should be. The assay used was verified by Morgan, *et al.*[1] The citizen petition process requests that I submit opposing views of what I am requesting. This was the only opposing view I could find. Therefore, this letter to the editor was submitted as part of the citizen petition process.

For these reasons, the FDA should change the black box warnings on the prescribing information of Premarin™. Making these changes would help women and their doctors avoid the potentially adverse and aggravating effects of Premarin in specific situations, and, as a result, make better healthcare decisions.

Thank you.

Beth Rosenshein

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[1] Morgan MR, Whittaker PG, Fuller BP, Dean PD, *A radioimmunoassay for equilin in post-menopausal plasma: plasma levels of equilin determined after oral administration of conjugated equine oestrogens (premarin).*, J Steroid Biochem. 1980 May;13(5):551-5.
[2] ID Cooke, *The Role of Estrogens/Progestogen in the Management of the Menopause*,, University Park Press, Baltimore, Maryland, 1978