

November 9, 2004

Dockets Management Branch, Food and Drug Administration, Department of Health and Human Services, Room 1-23, 12420 Parklawn Dr., Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under 21CFR Part 10.30 of the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs (under 21CFR, 5.10) to request the Commissioner of Food and Drugs to amend a regulation.

A. ACTION REQUESTED

Request 1.

Update "ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER" section of the prescribing information of all strengths of Premarin tablets (.3mg, .45mg, .625mg, 1.25mg, 2.5mg) to recognize significant prolonged levels of equilin after withdrawal of estrogen therapy. The following wording would be appropriate:

Replace:

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. 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. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

With:

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER

Close clinical surveillance of all women taking estrogens is important. 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. There is evidence that the use of equine estrogens results in a different endometrial risk profile than human estrogens of equivalent estrogen dose.

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Request 2.

Add the following to the WARNINGS section

**PROLONGED EXPOSURE TO EQUINE ESTROGENS CONTINUES FOLLOWING CESSATION OF ESTROGEN THERAPY**

Equine estrogens can accumulate during Premarin™ therapy. It has been shown that equine estrogens have a prolonged presence after estrogen therapy has stopped. Premarin™ contains estrogens which can accumulate. Significant amounts of equilin and its metabolites may be present for at least 3-6 months after estrogen therapy has ended.

**B. STATEMENT OF GROUNDS**

Grounds for Request 1 and 2:

Recently, while researching hormone replacement products, I found discrepancies in the prescribing information of Premarin™. It is important to make the prescribing information as accurate as possible to avoid deleterious outcomes.

The goal of estrogen therapy is to restore estrogen levels to a therapeutic level. When estrogen therapy is stopped it is expected that estrogen levels fall to pre-treatment levels within 48-72 hours. If the pharmacokinetics of a hormone product shows that this is not the case then the expected timeline should be indicated.

Premarin™, an oral hormone product, has been shown to accumulate equilin, an equine estrogen native to the pregnant horse and not to human females in the circulation of women as equilin sulfate and its metabolites after just 1 month of use<sup>1</sup>. Studies have verified that equilin and its metabolites are present at least 3-6 months and perhaps longer after ending estrogen therapy with Premarin™ (see Table 1 and Table 2)<sup>1,2,3</sup>. Equilin sulfate is bound to albumin and continues to be in equilibrium with its metabolites, which all have estrogenic activity, until it is finally cleared from the blood (see Figure 1)<sup>4</sup>. This is important as one of the metabolites of equilin sulfate is 17β-dihydroequilin. It is accepted that 17β-dihydroequilin sulfate is an extremely potent oral uterotrophic agent, being over 8 more potent than a uterotrophic agent than equilin sulfate and estrone sulfate and in its unconjugated form 17β-dihydroequilin has the highest affinity for estrogen receptors in the human endometrium<sup>5,6</sup>. Furthermore, 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<sup>4,5</sup>.

It is very important to advise women and their doctors of the prolonged presence of equilin after cessation of estrogen therapy with Premarin™. It is of particular importance should a woman be diagnosed with an estrogen receptor positive tumor. Being aware of



**Plasma Equilin Concentrations**

| Patient                                   | 1 months therapy |   | 3 months therapy |        |
|---|------------------|---|------------------|--------|
|   | pg/ml (nmol/l)   |   | pg/ml (nmol/l)   |        |
| 1   | 810              | ( 3.0)                                  | 3,380            | (12.6) |
| 2   | 2,760            | (14.9)                                  | 2,000            | ( 7.5) |
| 3   | 1,660            | ( 6.2)                                  | 910              | ( 3.4) |
| 4   | 460              | ( 1.7)                                  | ND               |        |
| 5   | 1,180            | ( 4.4)                                  | ND               |        |
| 6   | ND               |   | 520              | ( 1.9) |
| 7   | 350              | ( 1.3)                                  | 780              | ( 2.9) |
| 8   | 1,580            | ( 5.9)                                  | 2,140            | ( 7.9) |
| 9   | 1,260            | ( 4.7)                                  | 310              | ( 1.2) |
| 10  | 4,000            | (14.9)                                  | 4,360            | (16.3) |
| 11  | 1,520            | ( 5.7)                                  | ND               |        |
| 12  | 4,900            | (18.3)                                  | 2,820            | (10.5) |
| 13  | 2,240            | ( 8.3)                                  | 4,900            | (18.3) |
| 14  | 1,380            | ( 5.2)                                  | 1,620            | ( 6.0) |
| 15  | 6,620            | (24.7)                                  | ND               |        |
| 16  | 8,520            | (31.8)                                  | 7,600            | (28.3) |
| 17  | 4,160            | (15.5)                                  | ND               |        |
| 18  | 80               | ( 0.3)                                  | 1,860            | ( 6.9) |
| 19  | 7,960            | (29.7)                                  | 2,460            | ( 9.2) |
| 20  | 7,420            | (27.7)                                  | ND               |        |
| 21  | 570              | ( 2.1)                                  | 740              | ( 2.8) |
| <b>mean 2,970 (11.3) +/- 2,730 (10.2)</b> |                  | <b>mean 2,430 (9.0) +/- 1,980 (7.4)</b> |                  |        |

**Table 1: Plasma Equilin Concentrations.** Morgan MR, Whittaker PG, Fuller BP, Dean PD., J Steroid Biochem., May;13(5):551-5., 1980, A radioimmunoassay for equilin in post-menopausal plasma: plasma levels of equilin determined after oral administration of conjugated equine oestrogens (premarin).

SERUM ESTROGEN LEVELS OF WOMEN ON PREMARIN™ THERAPY\*

| Steroid                 | Weeks on Therapy |             |             |             |             |            |             |                        |
|-------------------------|------------------|-------------|-------------|-------------|-------------|------------|-------------|------------------------|
|                         | 0†               | 3           | 7           | 11          | 15          | 19         | 23          | 13 wk after withdrawal |
| EQ (pmol/l)             | 0                | 9130 ± 7670 | 7880 ± 3160 | 4380 ± 1310 | 8040 ± 7520 | 4010 ± 610 | 5620 ± 2680 | 532 ± 267              |
| E <sub>2</sub> (pmol/l) | 180 ± 133        | 314 ± 109   | 304 ± 61    | 633 ± 334   | 420 ± 228   | 397 ± 200  | 330 ± 68    | 287 ± 389              |
| E <sub>1</sub> (pmol/l) | 167 ± 78         | 569 ± 140   | 633 ± 192   | 655 ± 216   | 730 ± 218   | 480 ± 71   | 465 ± 140   | 175 ± 163              |
| No. of patients         | 7                | 6           | 5           | 4           | 5           | 4          | 3           | 3                      |

\*Results are mean ± SD. †Mean of 3 weekly visits. 100 pmol/l is equivalent to 27 pg/ml.

TABLE II -- SERUM ESTROGEN LEVELS OF WOMEN ON PREMARIN THERAPY AND NORETHISTERONE\*

| Steroid                 | Weeks on Therapy |             |             |             |             |             |             |                        |
|-------------------------|------------------|-------------|-------------|-------------|-------------|-------------|-------------|------------------------|
|                         | 0†               | 3           | 7           | 11          | 15          | 19          | 23          | 13 wk after withdrawal |
| EQ (pmol/l)             | 0                | 7620 ± 3760 | 9350 ± 4390 | 8380 ± 2870 | 9400 ± 6740 | 9140 ± 4320 | 9540 ± 2670 | 584 ± 841              |
| E <sub>2</sub> (pmol/l) | 142 ± 144        | 402 ± 138   | 349 ± 103   | 287 ± 92    | 347 ± 76    | 316 ± 142   | 347 ± 126   | 77 ± 38                |
| E <sub>1</sub> (pmol/l) | 145 ± 72         | 492 ± 322   | 501 ± 276   | 455 ± 155   | 712 ± 367   | 650 ± 230   | 638 ± 340   | 140 ± 28               |
| No. of patients         | 6                | 6           | 6           | 6           | 5           | 5           | 4           | 4                      |

\*Results are mean ± SD. †Mean of 3 weekly visits.

**Table 2: Serum Estrogen Levels of Women on Premarin™ Therapy.** Whittaker PG, Morgan MR, Dean PD, Cameron EH, Lind T., Lancet. Jan 5;1(8158):14-6., 1980, Serum equilin, oestrone, and oestradiol levels in postmenopausal women receiving conjugated equine oestrogens ('Premarin').

Therefore, in accordance with 21 CFR 201.57 subsection (e), these changes to the warning section must be included on the labeling.

C. ENVIRONMENTAL IMPACT STATEMENT

No environmental impact statement is required for this petition under 21 CFR 25.30 subsection k. The proposal is for a labeling change that does not change the level of use or the intended use of the product.

D. ECONOMIC IMPACT STATEMENT

No economic impact statement has been requested.

E. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Signature

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Encl:

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<sup>1</sup> Morgan MR, Whittaker PG, Fuller BP, Dean PD., J Steroid Biochem., May;13(5):551-5., 1980, A radioimmunoassay for equilin in post-menopausal plasma: plasma levels of equilin determined after oral administration of conjugated equine oestrogens (premarin).

<sup>2</sup> Morgan MR, Whittaker PG, Dean PD, Lenton EA, Sexton L, Cooke ID., Eur J Clin Invest. Dec;9(6):473-4, 1979, Plasma equilin concentrations in an oophorectomized woman following ingestion of conjugated equine oestrogens (Premarin).

<sup>3</sup> Whittaker PG, Morgan MR, Dean PD, Cameron EH, Lind T., Lancet. Jan 5;1(8158):14-6., 1980, Serum equilin, oestrone, and oestradiol levels in postmenopausal women receiving conjugated equine oestrogens ('Premarin').

<sup>4</sup> Bhavnani BR., Proc Soc Exp Biol Med. 1998 Jan;217(1):6-16., Pharmacokinetics and pharmacodynamics of conjugated equine estrogens: chemistry and metabolism.

<sup>5</sup> Bhavnani BR, Cecutti A., J Clin Endocrinol Metab. Nov;77(5):1269-74., 1993, Metabolic clearance rate of equilin sulfate and its conversion to plasma equilin, conjugated and unconjugated equilenin, 17 beta-dihydroequilin, and 17 beta-dihydroequilenin in normal postmenopausal women and men under steady state conditions.

<sup>6</sup> Bhavnani BR, Cecutti A, Gerulath A., J Soc Gynecol Investig. Mar-Apr;9(2):102-10, 2002, Pharmacokinetics of 17 beta-dihydroequilin sulfate in normal postmenopausal women under steady state conditions.

<sup>7</sup> Woolever CA, Bhavnani BR., Lancet. Mar 8;1(8167):547-8., 1980, Serum equilin and conjugated equine oestrogens.

<sup>8</sup> Whittaker PG, Lind T, Morgan MRA, Dean PDG, Lancet. Mar 8;1(8167):548-9., 1980, Serum equilin and conjugated equine oestrogens.