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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Ln.
Rockville, MD 20852

Citizen Petition to the U.S. Food and Drug Administration

The Physicians Committee for Responsible Medicine (Petitioner) submits this petition under Section **352(f)** of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 352(f), and Section 10.30 of Title 21 of the Code of Federal Regulations, 21 C.F.R. § 10.30, to request that the U.S. Food and Drug Administration (FDA) mandate the inclusion of new advisories in product labeling and labeling intended for patients for all **products** containing estrogens intended for oral use, indicating that (1) oral estrogens are not approved for **the purpose** of suppressing growth in tall girls and (2) the safety of their use in that context has not been **established**.

Statement of Grounds

Estrogens are approved for treatment of vasomotor symptoms of menopause, atrophic vaginitis, and **hypoestrogenism**; osteoporosis prevention; and palliation of appropriately selected cases of breast or **prostate** cancer.

The use of estrogens as a growth-suppressant therapy for tall adolescent girls was first suggested in **the 1940s**, based on the observation that, when used in high doses, they stimulate cartilage maturation without accelerating growth and thus lead to epiphyseal closure.¹ In 1956, Goldzieher published the first report of estrogen use for growth suppression in 14 girls aged 9 to 16 who were at least 168 centimeters tall or 10 centimeters above mean height for **age**.² Since then, numerous other reports of estrogen use in this context have been published and were recently reviewed.³

The treatment has no medical indication. Rather, it **is** used solely to prevent social or psychological problems presumed to result from tall stature. The effect of treatment, based on final compared to predicted height, varies depending on the height-prediction method and treatment regimen used, but ranges from -2.6 to **6.4** centimeters, with a greater effect seen when treatment begins at earlier skeletal **ages**.³ Psychological and **social** benefits have never been established.

A 1978 survey revealed that 50 percent of responding pediatric endocrinologists had treated girls **for tall** stature.* The *Journal of Pediatric* and *Adolescent Gynecology* of February 2002 reports the findings of a new survey of prescribing practices of U.S. pediatric **endocrinologists**.⁵ A questionnaire was mailed on **November 12, 1999**, to all U.S. members of the Lawson Wilkins Pediatric Endocrine Society, whose **membership** includes approximately 80 percent of U.S. pediatric endocrinologists. Follow-up mailings were sent to **nonresponders**

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in February and May 2000. Of the 715 clinicians who were mailed questionnaires, responses were received from 501 (70 percent). Of this number, 90 were excluded from analysis, including 51 who were no longer in practice and 39 whose responses provided insufficient information for scoring.

Of the 411 remaining respondents, 23 percent had treated at least one such case in the preceding five years. Four had treated more than five cases. As in 1978, conjugated estrogens were the most frequently used formulation (55 percent of respondents). Typical doses ranged up to 10 milligrams per day. Ethinyl estradiol was the next most commonly used product (40 percent of respondents). Typical doses ranged up to 0.5 milligrams per day.

Treatment was generally continued until closure of the epiphyses. Typical treatment duration of less than one year was reported by 5 percent of respondents, 1 to 2 years by 40 percent, and 2 to 5 years by 29 percent. At the time of the survey, estrogen treatment for excessively tall stature was still offered by 33 percent of respondents. Among those who declined to offer such treatment, concerns about the possibility of long-term adverse effects were frequently cited.

The use of estrogens for growth suppression contrasts sharply with their use for approved indications. When estrogens are prescribed for approved, non-palliative purposes, the lowest effective dose is normally selected. However, when estrogens are used for growth suppression, they are used in much higher doses, usually for a few years, in order to close the epiphyses. Because estrogens used for growth suppression are prescribed at higher doses than for approved indications and are used during the time when breast tissue and other organ systems are undergoing the growth and maturation of adolescence, the likelihood of long-term side effects may be greater than when estrogens are prescribed for approved indications at lower doses later in life.

Commonly reported side effects of estrogens include weight gain, headache, nausea, night leg cramps, increased pigmentation of the areola and nipples, and vaginal discharge. Rare potential effects of long-term use may include thrombosis, hypertension, liver disorders, and gallbladder disease.⁶ Of particular concern is their potential contribution to the progression of hormone-related malignancies. Studies of oral contraceptive use indicate increased breast cancer risk among younger, nulliparous women.^{6,7} Regrettably, no study has examined the potential side effects of growth suppressant therapy for more than ten years after treatment, although many investigators have called for such a study.¹ To the Petitioner's knowledge, no study has been proposed to monitor cancer rates among treated individuals. Because estrogen treatments induce early menarche as well as an initial increase in height, it is possible that this early change may have adverse psychological effects, although such effects have not been systematically studied.⁸

The current labeling intended for patients for conjugated estrogens (Premarin) is uninterpretable for adolescent patients and their parents considering treatment for growth suppression. It states, "You must decide, with your doctor, whether the risks of estrogens are acceptable in view of their benefits." The absence of studies establishing the benefits and long-term risks of estrogens used for growth suppression renders this section unhelpful and confusing in this context.

The current labeling further states, "If you decide to start taking estrogens, check with your doctor to make sure you are using the lowest possible effective dose." Since estrogens used for growth suppression are often prescribed in intentionally high doses, this section is also potentially confusing.

Requested Action

1. The Petitioner requests that the FDA mandate the following addition to the product labeling for all estrogen-containing products intended for oral use:

Estrogens are not approved for suppression of growth in adolescents, and, because no studies have monitored adverse effects in treated cases for more than ten years post-treatment, the safety of such use has not been established.

2. We also request that a notice be sent by certified mail to all pediatric endocrinologists practicing in the United States to notify them of this change.
3. The Petitioner further requests that the FDA mandate the following advisory in the labeling intended for patients:

Although estrogens are sometimes prescribed for tall adolescent girls in an attempt to limit their growth, the safety of this practice has not been established, particularly since estrogens may have significant side effects when used at high doses for long periods of time.

Conclusion

One-third of surveyed U.S. pediatric endocrinologists currently offer estrogen treatment for tall stature, despite the absence of studies establishing its benefits or elucidating its long-term risks. Modification of product information for practitioners and patients is justified.

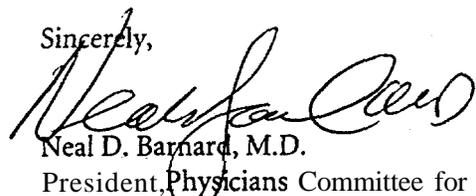
Environmental Impact Statement

Nothing requested in this petition **will have** an impact on the environment.

Certification

I certify that, to my best knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the petition.

Sincerely,



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