DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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Neal D. Barnard, M.D.
President, Physicians Committee for Responsible Medicine
5100 Wisconsin Ave., N.W.
Suite 400
Washington, DC 20016

Re: Docket No. 02P-0067/CP1

Dear Dr. Barnard:

This letter responds to your citizen petition (petition) dated February 5, 2002, requesting that the Food and Drug Administration (FDA) mandate the inclusion of new advisories in the product labeling and labeling intended for patients for all products containing estrogens intended for oral use. The advisories would indicate that oral estrogens are not approved for the purpose of suppressing growth in tall girls, and the safety of oral estrogens used in that context has not been established. Specifically, you request that FDA take the following actions.

1. Mandate the addition of the following statement to the product labeling:

   > 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. Send a notice by certified mail to all pediatric endocrinologists practicing in the United States to notify them of the change.

3. 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.

FDA has considered information submitted in your petition. For the reasons explained below, your petition is denied.

No estrogen-containing drug product has been granted an indication of treatment for constitutional tall stature (CTS) by FDA. However, estrogens have been prescribed by

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physicians as a growth-suppressant to decrease final height by accelerating epiphyseal closure since at least the mid-1950s and numerous reports have been published in the literature on this subject. Thus, the use of estrogens as growth-suppressant therapy is an unapproved off-label use. Off-label use of a drug product occurs when a physician, in his or her practice of medicine, prescribes a drug product for a use not granted an FDA-approved indication in the labeling of the drug product. Prescribing a drug product for an off-label use in the course of the practice of medicine is not a violation of the law. FDA does not restrict such usage when the use is within the practice of medicine. However, physicians prescribing drug products for off-label use in the course of their practice of medicine have a responsibility to do so ethically.[1]

FDA recognizes that there may be physicians prescribing estrogens for off-label use as treatment for CTS. Your survey of the Lawson Wilkin Pediatric Endocrine Society (the Endocrine Society) indicates that of 411 respondents, 92 (22%) reported having treated 1 to 5 girls for CTS during a recent 5-year period. In a recent article in the lay press,[2] you are quoted as estimating that "more than 100 girls" are currently receiving this therapy. Your survey data indicates that the use of estrogens as a growth-suppressant has decreased dramatically over the past two decades, and you attribute this decrease to greater acceptance of tall stature as well as concerns about potential risks of hormone use in the population.

FDA understands that your concern is with the safety of this treatment. However, the data you present focuses on the number of members of your survey population engaging in this off-label use. While your data may inform the medical community and public about the practice of prescribing estrogens for treatment of CTS, any labeling changes to estrogen drug products would be based on consideration of issues of safety and efficacy.[3]

FDA reviewed the eight articles referenced in your petition and conducted its own review of other scientific and medical literature for safety and efficacy issues.[4] The reviewed scientific literature fails to identify any unique or previously unreported adverse events in adolescent females treated with estrogen to reduce final height when compared with the adverse events reported in patients treated with estrogens for approved indications. Your survey states that commonly reported side effects were weight gain, headache, nausea, night leg cramps, increased pigmentation of areolae and nipples, and vaginal discharge.

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[1] FDA notes that neither the American Medical Association, the American College of Obstetrics and Gynecology, nor the Endocrine Society have adopted a formal position or written policy on using or banning the use of estrogen to control height.

[2] Dally, M, 2003, Stunted Growth [investigative report], Health, p. 52-56.

[3] To support your petition, you indicate that such treatment is done solely to prevent social or psychological problems and not to treat an underlying disease. FDA notes that with the recent approval of Humatrope (synthetic human growth hormone) for the long-term treatment of idiopathic short stature, there is a precedent for the Agency to approve drugs for growth disorders that are not the result of underlying disease.

[4] In addition to the articles you submitted, FDA reviewed 38 articles derived from its own review of the scientific literature.

A survey conducted in 1978 lists the most common side effects as accelerated pubertal development, weight gain, transient nausea, irregular menses, improvement of acne, and leg cramps at night.[5] The 1978 survey also stated that one subject had a thromboembolic episode after a crushing foot injury, hypertension was noted in a small number of patients, three patients reported ovarian cysts, five patients had transient galactorhea, and three patients report endometrial polyps and hyperplasia. These adverse reactions are listed as having been reported with estrogen use in the current draft guidance for industry on *Labeling for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling* (the current draft estrogen labeling guidance),[6] and the draft guidance for industry on *Combined Oral Contraceptives-Labeling for Healthcare Providers and Patients* (the current draft oral contraceptive guidance), or are an expected consequence of the administration of estrogen (e.g., accelerated pubertal development). Reassuringly, the 1978 survey noted no cases of cholestatic jaundice or neoplasms of the breast, uterus, or liver.

Section 310.515(c) (21 CFR 310.515(c)) of the current regulations lists the requirements for patient labeling for estrogens. The current draft estrogen labeling guidance, used by manufacturers in complying with the requirements of the regulations, discusses the adverse events associated with estrogen usage regardless of the indication. Section 310.501 addresses the requirements for patient labeling for oral contraceptives, and the current draft oral contraceptive guidance discusses adverse events associated with their use. Unless data becomes available showing new and previously unreported adverse events or that a significantly higher rate of known adverse events occurs in adolescent females treated with estrogen to reduce final height, FDA believes the labeling for these products adequately addresses safety concerns for physicians and patients. Therefore, FDA does not anticipate adding the statements you suggest to the physician or patient labeling for estrogen drug products.[7]

Only limited conclusions about efficacy can be drawn from the published literature regarding the use of estrogens for final height reduction. Further study would be needed to resolve issues of efficacy. Since, as you and others note, the use of estrogen treatment for CTS has declined dramatically over the past two decades, it is unlikely that additional studies will be conducted on this issue or that a sponsor will apply for the indication.

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[5] Conte, FA, Grumbach MM, 1978, Estrogen Use in Children and Adolescents: A Survey, Pediatrics 62:1091-7.

[6] In the Federal Register of September 27, 1999 (64 FR 52100), FDA first published a draft of this guidance. However on September 10, 2002, the Agency withdrew the draft guidance pending consideration of the results from the National Institutes of Health (NIH) Women's Health Initiative (WHI). The current draft estrogen labeling guidance addresses concerns raised by the findings of the WHI.

[7] The statement you suggest adding to the physician labeling seems to imply that because no study has monitored adverse effects post-treatment for more than 10 years, the safety of such use has not been established. FDA notes that the 10-year standard you suggest is higher than that for most safety trials conducted for approved drug products and their indications.

The Agency has concerns about adding statements to the physician labeling for oral estrogen drug products and mentioning the off-label use at a time when this practice appears to be in decline. Also, FDA is concerned that mention of the potential growth-suppressive effects of estrogen in oral contraceptive labels may result in adolescents discontinuing their use of prescribed oral contraceptives because of misinterpretation that the use of such products may reduce their adult height. As you note, there is a greater acceptance of tall stature in girls, and any stigma associated with height in young girls appears to be on the decline.

As previously stated, FDA would consider data showing new and previously unreported adverse events or a significantly higher rate of known adverse events in adolescent females treated with estrogen to reduce final height. The articles in your petition and the other available literature do not identify such data. For the reasons discussed above, your petition is denied.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Acting Director
Center for Drug Evaluation and Research