Do No Harm

Filed Electronically

February 10, 2026

The Commissioner of Food and Drugs
c/o Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Do No Harm's Comment on the Citizen Petition Pursuant to 21 C.F.R. § 10.30 Requesting the FDA (A) Open a Docket, (B) Hold a Part 15 Public Hearing Regarding the Off-Label Use of Estrogen in Natal Males for Gender Affirmation, and (C) Consider Regulatory Action Including a Boxed Warning Under 21 C.F.R. § 201.80(e) (Docket #FDA-2025-P-7321, filed December 23, 2025)

Dear Commissioner,

Do No Harm is a nationwide organization composed of medical professionals and others dedicated to protecting healthcare from identity politics. We accomplish our mission through education and advocacy about the divisive and discriminatory ideology increasingly embedded within medical education, training, research, practice, and policy.

Consistent with that mission, Do No Harm believes that medicine should follow the evidence, not fashionable political trends. To that end, we are concerned by the sharp rise in recent years in the off-label use of estrogen in natal males, particularly youth, to alter secondary sex characteristics for gender-identity purposes. Yet, as the recent HHS umbrella review showed,[1] these interventions offer no demonstrated benefit for children—and evidence for the risks of harms continues to grow.

As signers of the Citizen Petition we echo our support for a Part 15 hearing to gather testimony from patients, parents, and experts alike regarding the harms of estrogen in natal males. It is critical for regulators to hear these accounts firsthand to understand the gravity of the issue. We likewise hope the FDA will consider the recommendations outlined in the

[1] Department of Health and Human Services. Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices. November 2025. https://opa.hhs.gov/sites/default/files/2025-11/gender-dysphoria-report.pdf

Citizen Petition, particularly as they relate to a boxed warning, comprehensive safety review, and adverse event reporting.

It goes without saying that hormones have powerful effects, especially when taken outside normal physiological levels. While estradiol is the principal endogenous estrogen in females, males normally have levels below 30 pg/ml—one-fifth to one-tenth the level found in premenopausal women.[2, 3] For gender dysphoria in males, the Endocrine Society recommends an estradiol level of 100 to 200 pg/ml, about 5 to 10 times higher than that found in a normal male.[4]

Taken at these levels, estrogen's effects are significant in men. For one, estrogen interferes with testicular function including sperm production, which may cause infertility.[5, 6] Cardiovascular risks are also multiple from venous thromboembolism to increases in triglycerides.[7, 8] An increased risk for stroke is also evident, as are increased risk for testicular cancer, invasive breast cancer, and thyroid cancer.[9, 10, 11, 12, 13] Further, in terms of adolescents, it is not completely understood how opposite sex hormones impact a youth's brain and mental health (including, but not limited to mood swings, emotional changes, and

---

[2] Ohlsson C, Nilsson ME, Tivesten A, et al. Comparisons of immunoassay and mass spectrometry measurements of serum estradiol levels and their influence on clinical association studies in men. J Clin Endocrinol Metab. 2013;98(6):E1097-1102.
[3] https://www.urmc.rochester.edu/encyclopedia/content?ContentID=estradiol&ContentTypeID=167
[4] Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11):3869-3903.
[5] Rodriguez-Wallberg KA, Pfau DR. Effects of feminizing gender-affirming hormone therapy on testicular function and reproductive capacity. Reproduction. 2024.
[6] Roo, C.D., Schneider, F., Stolk, T.H.R., van Vugt, W.L.J., Stoop, D. & van Mello, N.M. (2025). Fertility in transgender and gender diverse people: Systematic review of the effects of gender-affirming hormones on reproductive organs and fertility. Human Reproduction Update, 00(0), 1-35.
[7] Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation. 2019;139(11):1461-1462.
[8] Koehler, Andreas, Rebecca Elisabeth Beyer, Susan Keen, Timo Nieder, Peer Briken, and Ross J Simpson. 2024. "The Effects of Gender-Affirming Hormone Therapy on Dyslipidemia and Cardiovascular Risk: A Meta-Review of Systematic and Non-Systematic Literature Reviews." Journal of the American College of Cardiology 83 (13): 1840–40. https://doi.org/10.1016/s0735-1097(24)03830-0.
[9] Nota NM, Wiepjes CM, de Blok CJM, Gooren LJG, Kreukels BPC, den Heijer M. Occurrence of Acute Cardiovascular Events in Transgender Individuals Receiving Hormone Therapy. Circulation. 2019;139(11):1461-1462.
[10] Shanker EM, Ren Q, Zhao LC, Bluebond-Langner R, Deng FM. Exploring the Incidence of Testicular Neoplasms in the Transgender Population: A Case Series. Arch Pathol Lab Med. 2024.
[11] De-La Riva Morales, I. et al. (2025). Clinicopathologic analysis and digital pathology evaluation of orchiectomy specimens in gender-affirmation surgery. Pathology – Research and Practice, 269.
[12] de Blok CJM, Wiepjes CM, Nota NM, et al. Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands. BMJ. 2019;365:l1652.
[13] Meci A, Lorenz FJ, Goyal N, Goldenberg D. Elevated Risk of Thyroid Malignancy in Biological Males Taking Estrogen Hormone Therapy. Otolaryngol Head Neck Surg. 2025.

depression), particularly in the long term. Longer follow-up studies are needed to better understand adverse cognitive effects of opposite sex hormones.[14]

Advocates of so-called "gender affirming care" also recognize these significant risks. UCLA Health's "Taking Estrogen for Gender Affirmation" lists a series of possible risks due to estrogen, while also stating that "we are still learning about the long-term health of people who take estrogen for gender affirmation."[15] Cornell Health has a similar guide noting a multitude of possible side effects and risks of estrogen use in males.[16] The Mayo Clinic likewise notes a series of risks associated with feminizing hormone therapy.[17]

The evidence from both the literature and clinical practice shows that the risks associated with estrogen use in natal males are well-documented and significant. Physicians prescribing estrogen and males receiving estrogen must be fully informed of these potential adverse effects. Unfortunately, current labeling for estrogen-containing products does not adequately warn clinicians or patients about the dangers associated with this off-label use, undermining informed consent and patient safety. We urge careful attention to this issue of growing magnitude and public health importance.

Respectfully submitted,

Kurt Miceli, MD
Chief Medical Officer
Do No Harm

---

[14] "Gender-Affirming Hormone Treatment and Cognitive Function in Transgender Young Adults: A Systematic Review and Meta-Analysis." 2020. Psychoneuroendocrinology 119 (September): 104721. https://doi.org/10.1016/j.psyneuen.2020.104721.

[15] https://www.uclahealth.org/sites/default/files/documents/86/gender-health-program-estrogen-final.pdf

[16] https://health.cornell.edu/sites/health/files/docs/External%20Weblinks/Guide%20for%20Gender%20Affirming%20Hormones_feminizing_androgen%20blocking.pdf

[17] https://www.mayoclinic.org/tests-procedures/feminizing-hormone-therapy/about/pac-20385096