United States Senate
WASHINGTON, DC 20510

September 22, 2022

The Honorable Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Commissioner Califf:

We write in connection with the Food and Drug Administration's (FDA) recent decision to add a warning regarding incidents of pseudotumor cerebri to the labeling of gonadotropin-releasing hormone (GnRH) agonists approved for the treatment of central precocious puberty (CPP). [1]

The FDA stated that its decision was based on six instances involving female patients between the ages of 5 and 12, of which "Five were undergoing treatment for central precocious puberty and one for transgender care." We note that while CPP is an approved indication for GnRH agonists, their use in connection with diagnoses of gender dysphoria or the provision of transgender care are not.

Congress and the Agency have long recognized that, when evaluating the safety and efficacy of drugs and other therapies, the biological processes associated with the growth and development of children entail additional concerns and potential risks beyond those associated with adult patients.

With respect to GnRH agonists, their approved use for treating patients with CPP is intended to address instances of developmental imbalance by delaying puberty until the normal age of onset, to align the natural processes of physical development with normal chronological development.

However, the off-label use of GnRH agonists in connection with diagnoses of gender dysphoria or the provision of transgender care is, by definition, intended to suppress the normal biological processes of puberty beyond the normal age of onset.

Given that such off-label use deliberately delays and alters normal development, we are deeply concerned that it could result in significant short-term and long-term risks and adverse effects on adolescent patients. In fact, the Mayo Clinic notes that the use of GnRH agonists could have long-term negative effects on children's bone growth and density and future fertility.[2]

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[1] "Risk of Pseudotumor Cerebri Added to Labeling for Gonadotropin-Releasing Hormone Agonists," FOOD AND DRUG ADMINISTRATION (July 1, 2022), available at https://publications.aap.org/aapnews/news/20636/Risk-of-pseudotumor-cerebri-added-to-labeling-for?_ga=2.105816391.550249189.1662732525-824563572.1662491082.
[2] "Pubertal Blockers for Transgender and Gender-Diverse Youth," MAYO CLINIC (June 18, 2022), available at https://www.mayoclinic.org/diseases-conditions/gender-dysphoria/in-depth/pubertal-blockers/art-20459075.

Our concern has been heightened by reports of increased off-label use of GnRH agonists in connection with transgender care.

In light of these concerns, please respond to the following questions by October 7, 2022:

1. What clinical trials or other studies have been conducted, including in other countries, to evaluate the safety and long-term effects of administering GnRH agonists in connection with diagnoses of gender dysphoria or the provision of transgender care?

2. How many reports of adverse effects associated with the administration of GnRH agonists to adolescent patients has the FDA received?

3. Will the FDA commit to conducting pharmacoepidemiologic studies using electronic health data to assess the long-term effects on pediatric patients who were administered GnRH agonists in connection with diagnoses of gender dysphoria or the provision of transgender care? If not, why not?

Sincerely,

Marsha Blackburn
United States Senator

Cynthia M. Lummis
United States Senator