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November 2, 2022

Robert M. Califf M.D.
Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Namandjé N. Bumpus, Ph.D.
Chief Scientist
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Center for Drug Evaluation and Research's Proposal to Withdraw Approval of MAKENA (Hydroxyprogesterone Caproate Injection), New Drug Application 021945, Held by Covis Pharma Group/Covis Pharma GmbH

Dear Dr. Califf and Dr. Bumpus:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing in followup to its October 18, 2022, testimony expressing strong support for the evidence-based proposal from the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research to withdraw approval of the new drug application (NDA) for Makena (hydroxyprogesterone caproate injection) to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

Makena should have been removed from the market soon after the results of the FDA-mandated postmarket PROLONG trial became available. The yearslong delay in the FDA withdrawing approval of the NDA for Makena demonstrates fundamental deficiencies in the current regulatory oversight for drugs approved under the accelerated approval pathway.

Public Citizen urges you to promptly withdraw approval of the NDA for Makena and the abbreviated NDAs for all generic hydroxyprogesterone caproate injection products for which Makena was the reference listed drug. Failure to take such action would further erode FDA's credibility and public confidence in the agency's accelerated approval process.

In addition, as soon as the approval of Makena is withdrawn, the FDA must take prompt regulatory action to prevent the predictable pharmacy compounding of hydroxyprogesterone caproate for prevention of preterm birth. Specifically, when the agency announces its final decision to withdraw approval of the NDA for Makena, it should simultaneously publish in the Federal Register the following:

(1) A notice announcing the agency's determination that hydroxyprogesterone caproate injection for prevention of preterm birth was withdrawn from the market for reasons of effectiveness.

(2) A proposed rule that would amend FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by Section 503A(a) or 503B(a) of the of the Federal Food, Drug, and Cosmetic Act (FDCA) — to include all parenteral drug products containing hydroxyprogesterone caproate for prevention of preterm birth. We note that the FDA took similar regulatory action to prevent pharmacy compounding of bromocriptine mesylate for prevention of physiological lactation.

The FDA should finalize the rule to amend FDA regulations at 21 C.F.R. § 216.24 to include all parenteral drug products containing hydroxyprogesterone caproate for prevention of preterm birth within six months after issuing the proposed rule. Although Section 503A(c)(1) of the FDCA stipulates that the FDA must convene and consult with an advisory committee before implementing changes to FDA regulations at 21 C.F.R. § 216.24, it allows the agency to issue such regulations *before consultation with an advisory committee if it determines that doing so is necessary to protect public health*. Such a determination could reasonably be made in the case of withdrawing approval of Makena once the agency announces that the approval of hydroxyprogesterone caproate was withdrawn because of the lack of evidence that the drug is effective. Nevertheless, if the agency feels it needs to seek advice from its Pharmacy Compounding Advisory Committee before issuing a final rule amending FDA regulations at 21 C.F.R. § 216.24, the agency could schedule a meeting of the advisory committee for shortly after the proposed rule is published in the Federal Register.

Such expeditious regulatory action would minimize the period during which pregnant women could be potentially harmed by exposure to compounded formulations of parenteral hydroxyprogesterone caproate for which there is a lack of evidence of effectiveness but known risks of serious harms.

Thank you for considering our comments regarding this important public health issue.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group