PUBLICCITIZEN
1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Citizen Petition

Date: April 27, 2023

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide; Public Citizen's Health Research Group; and Adam C. Urato, M.D., Chief, Maternal-Fetal Medicine, MetroWest Medical Center in Framingham, Massachusetts, the undersigned submit this petition under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §§ 353a and 353b) and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs promptly initiate the regulatory process to amend FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and therefore may not be compounded under the exemptions provided by sections 503A(a) or section 503B(a) of the FDCA — to include hydroxyprogesterone caproate injection for prevention of preterm birth.

A. ACTION REQUESTED

Promptly initiate the regulatory process to amend, through notice and comment rulemaking, FDA regulations at 21 C.F.R. § 216.24 — the list of drug products that were withdrawn or removed from the market for reasons of safety or effectiveness and that therefore may not be compounded under the exemptions provided by section 503A(a) or section 503B(a) of the FDCA — to include hydroxyprogesterone caproate injection for prevention of preterm birth.

B. STATEMENT OF GROUNDS

1. Background

Statutory requirements

Section 503A of the FDCA describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the requirements of the following three sections of the FDCA: section 505 (concerning the approval of drugs under new drug applications or abbreviated new drug applications), section 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and section 501(a)(2)(B) (concerning current good manufacturing

practice requirements). One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503A is that a licensed pharmacist or licensed physician may not compound a drug product that appears on a list published by the Secretary of Health and Human Services in the Federal Register of drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (section 503A(b)(1)(c)).

Section 503B of the FDCA describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the requirements of the following three sections of the FDCA: section 505, section 502(f)(1), and 21 U.S.C. § 360eee-1 (concerning pharmaceutical distribution supply chain requirements). One of the conditions that must be met for a compounded drug product to qualify for the exemptions under section 503B is that a registered outsourcing facility may not compound a drug product that appears on a list published by the Secretary of Health and Human Services of drugs that have been withdrawn or removed from the market because such drugs or components of such drugs have been found to be unsafe or not effective (section 503B(a)(4)).

21 C.F.R. § 216.24 – Drug products withdrawn or removed from the market for reasons of safety or effectiveness

FDA regulations at 21 C.F.R. § 216.24 currently list 85 drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness.

Notably, 21 C.F.R. § 216.24 includes all drug products containing bromocriptine mesylate for prevention of physiological lactation, whereas there are prescription drug products containing bromocriptine mesylate marketed under the brand names Cycloset[1] and Parlodel[2] and in generic versions that are approved by the FDA for indications other than the prevention of physiological lactation.

Hydroxyprogesterone caproate

On February 3, 2011, the FDA approved the new drug application (NDA) for Makena (hydroxyprogesterone caproate injection) under the accelerated approval pathway to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (recurrent sPTB).[3]

Importantly, from 2000 when the FDA announced the withdrawal of the approval of the NDA for hydroxyprogesterone caproate under the brand name Delalutin — which was approved for the prevention of habitual and threatened abortion, among other things —[4] until the FDA approved Makena in 2011, hydroxyprogesterone caproate was widely prescribed by obstetricians

[1] VeroScience, LLC. Drug label: bromocriptine mesylate tablets (CYCLOSET) August 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020866s012lbl.pdf. Accessed April 14, 2023.
[2] Validus Pharmaceuticals LLC. Drug label: bromocriptine mesylate (PALODEL). July 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017962s083lbl.pdf. Accessed April 14, 2023.
[3] Food and Drug Administration. Final decision on the proposal to withdraw approval of Makena. April 5, 2023. https://www.regulations.gov/document/FDA-2020-N-2029-0385. Accessed April 14, 2023.
[4] 65 FR 55264-55265.

for prevention of preterm birth exclusively through pharmacy compounding. Moreover, one utilization study published in 2017 found that from 2012 to 2015, following FDA approval of Makena, most women who were treated with hydroxyprogesterone caproate for prevention of preterm birth were prescribed much less expensive compounded versions of the drug.[5]

On October 5, 2020, the FDA's Center for Drug Evaluation and Research (CDER) proposed withdrawing accelerated approval of Makena and provided Covis, the sponsor of the Makena NDA, with an opportunity to request a hearing on the proposal.

There is one marketed generic product containing hydroxyprogesterone caproate that is approved by the FDA for nonpregnant women for the following indications: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; as a test for endogenous estrogen production; and for the production of secretory endometrium and desquamation.[6]

2. FDA determination regarding Makena (hydroxyprogesterone caproate injection)

On April 6, 2023, the FDA announced its final decision to withdraw approval of Makena, which was approved in 2011 to reduce the risk of preterm birth in women pregnant with one baby who have a history of spontaneous preterm birth, and of all abbreviated new drug applications (ANDAs) that reference Makena.[7] The primary basis for this decision was the agency's determination that there was a lack of evidence that hydroxyprogesterone caproate is effective. The following are excerpts from the agency's decision,[8] which was issued jointly by FDA Commissioner Robert Califf and Chief Scientist Namandjé Bumpus and effective immediately:

> Fundamentally, however, the touchstone of FDA drug approval is a favorable benefit-risk assessment; without that favorable assessment, the drug should not have the status of being FDA-approved. After thoroughly reviewing the record for this matter, we have determined that there is an insufficient demonstration of effectiveness to balance any level of risk. Accordingly, as further explained below and in the referenced attachment, FDA hereby withdraws approval of Makena. We also hereby withdraw the approvals for the abbreviated new drug applications (ANDAs) that reference Makena pursuant to 21 CFR 314.151(b)(3)…
>
> After reviewing the record for this matter, including the submissions by the parties, comments to the docket, the transcript of the hearing, and the PO

[5] Fried I, Beam AL, Kohane IS, Palmer NP. Utilization, cost, and outcome of branded vs compounded 17-alpha hydroxyprogesterone caproate in prevention of preterm birth. *JAMA Intern Med.* 2017;177(11):1689-1690.
[6] McGuff Pharmaceuticals, Inc. Drug label: hydroxyprogesterone caproate injection. August 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/200271lbl.pdf. Accessed April 14, 2023.
[7] Food and Drug Administration. FDA news release: FDA Commissioner and Chief Scientist announce decision to withdraw approval of Makena. April 6, 2023. https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena. Accessed April 14, 2023.
[8] Food and Drug Administration. Final decision on the proposal to withdraw approval of Makena. April 5, 2023. https://www.regulations.gov/document/FDA-2020-N-2029-0385. Accessed April 14, 2023.

> [Presiding Officer for the FDA's hearing on Makena] for the Report, we have determined that FDA must withdraw approval of Makena and generic versions of Makena. The PO Report provided a detailed and thoughtful presentation and analysis of the evidence and the issues relevant to this matter, and we agree with the findings and conclusions of that report. Rather than repeat that analysis here, we are incorporating the PO Report by reference as part of this final decision. We offer a few comments below to highlight the key considerations and address certain questions raised in the post-hearing submissions.
>
> There is no dispute that FDA has grounds under the statute for withdrawing approval of Makena and its generic versions. Indeed, Covis [the sponsor of Makena] conceded that the [postmarketing] PROLONG trial failed to demonstrate clinical benefit. Accordingly, the remaining question is whether FDA should withdraw approval, as was the focus for most of the hearing itself. We agree with the Presiding Officer's analysis of the various arguments presented. The bottom line is that, based on current studies, there is an insufficient demonstration of effectiveness to balance any level of risk. Without a favorable benefit-risk assessment, there is no justification for keeping the product on the market, even where there is an unmet need…
>
> We have also considered Covis's arguments relating to compounding hydroxyprogesterone caproate (17-OHPC) (the active ingredient in Makena). The current lack of adequate data supporting effectiveness implicates compounded products as well as Makena and its generic versions. However, as a procedural matter, compounded products are not within the scope of this withdrawal proceeding, and the agency must address them through a separate regulatory process.
>
> Covis requests that we delay the effective date of the withdrawal so that current patients can complete their courses of treatment and for remaining in-channel inventory to be exhausted. We decline to do so. Given our conclusions regarding the unfavorable benefit-risk assessment for Makena as discussed above, FDA's continued approval of Makena and its generic versions is unwarranted and inappropriate.

Attached to the April 5, 2023, decision document from the FDA Commissioner and Chief Scientist was the January 19, 2023, written report summarizing the agency's public hearing and providing recommendations on CDER's proposal to withdraw approval of Makena that was written by Celia Witten, the Deputy Director of the FDA's Center for Biologics Evaluation and Research and the Presiding Officer for the agency's public hearing regarding CDER's proposal to withdraw approval of Makena.[9] The following are excerpts from the Presiding Officer's report:

[9] *Ibid*.

5. Presiding Officer's Advice and Recommendations

This part of the report conveys my views on the matters discussed at [the] hearing. First, I will review CDER's proposed grounds for withdrawing approval of Makena. Second, I will provide my recommendation regarding whether FDA should withdraw approval.

a. Grounds for withdrawal: CDER proposed to withdraw approval of Makena on two grounds: (1) the confirmatory study (Trial 003) failed to verify clinical benefit of the drug, and (2) the evidence does not establish that the drug is effective under its conditions of use.

(1) The confirmatory study (Trial 003) failed to verify clinical benefit of the drug.

This proposed ground for withdrawing approval of Makena has been met. Trial 003 failed to meet its coprimary endpoints, one of which was a neonatal morbidity/mortality composite index to evaluate clinical benefit. CDER and the sponsor, as well as the ORUDAC [Obstetrics, Reproductive and Urologic Drugs Advisory Committee], agreed that the study failed to verify clinical benefit of the drug.

(2) The evidence does not establish that the drug is effective under its conditions of use.

This proposed ground for withdrawing approval has also been met. The basis for accelerated approval of Makena was the effect on gestational age seen in Trial 002. Trial 003 [the postmarketing PROLONG trial] had a coprimary endpoint of gestational age at delivery. Trial 003 failed to meet this endpoint. Covis provided an extensive discussion of additional analyses to explain the difference in results between Trials 002 and 003 with respect to Makena's effectiveness for its intended use. While it is true that there are differences in where the trials were conducted and in the baseline characteristics of the population, the analyses provided by CDER that evaluated the effect of Makena in various subpopulations, and the analyses that evaluated whether risk factors such as race were effect modifiers, did not support Covis's attempts to explain the failure of Trial 003 to demonstrate an effect of the drug on recurrent sPTB. As one of the committee members noted, the argument that Trial 003 was underpowered due to the low rate of sPTB in the placebo arm is not supported by the results of the trial. Trial 003 was a large, randomized trial, with 1708 patients. It was almost four times as large as Trial 002, and it is not possible to dismiss the results of this trial. As several members of the committee noted, Trial 003 did not prove that Makena is ineffective for its labeled indication, but the trial did call into question the results of Trial 002 with respect to Makena's effect on reducing the risk of recurrent sPTB.

b. Recommendations regarding whether FDA should allow Makena to remain on the market while a new confirmatory study is performed.

Both the statute and the regulation provide that FDA "may" withdraw approval based on those grounds, but withdrawal is not mandatory. During the three-day hearing and in submissions to the docket, CDER, Covis, and members of the public raised several issues for consideration in evaluating whether FDA should withdraw approval of Makena, many of which the advisory committee members discussed. Below I provide my views on each significant factor discussed at the hearing.

(1) Benefit-risk in the overall population

The first two grounds for withdrawing approval speak to the question of benefit of the drug in the indicated population. I believe, as explained above, that the existing evidence for Makena does not establish either a clinical benefit or a treatment effect on the intermediate endpoint that was the original basis for accelerated approval. On the other hand, there are established risks, as listed in the product label and described by CDER at the hearing. In addition, various speakers raised the potential intergenerational risks, such as cancer in individuals exposed in utero. (As CDER acknowledged, the data on this potential risk are currently indeterminate, but several speakers advocated for further study.) Absent a benefit to patients, the benefit-risk balance is not favorable for Makena.

(2) Benefit-risk in a narrowed population

The sponsor proposed retaining the product on the market with a narrowed indication. Covis itself characterized the analyses provided to arrive at their conclusion as "hypothesis generating." The subset identified comprises 87 out of 1708 subjects in Trial 003. Covis proposed conducting a new randomized controlled trial to confirm Makena's effect on reducing the risk of recurrent sPTB in that population.6 However, in Trial 002, it did not appear that the treatment effect of Makena relative to sPTB was any different in Black or non-Black women or for women with a history of a qualifying sPTB of less than 34 weeks, as compared to those without that history. In the analyses of Trial 003 presented by CDER, there was no benefit suggested in any prespecified subgroup. I agree with Covis and CDER that the analysis of the 87-subject subset used to identify a high-risk group, which is fewer than five percent of the patients in the overall study, is hypothesis generating. I agree with the committee member who commented that there is not good evidence that Makena is effective in reducing the risk of recurrent sPTB in any subgroup. See Hearing Transcript (Oct. 19, 2022) at 121 (comment by Dr. Caughey). For this reason, I do not feel that the benefit-risk profile is favorable in a narrowed indication…

(4) Safety issues related to drug product compounding

Covis argues that, if Makena is removed from the market, patients will be at risk for safety issues related to drug-product compounding because compounding might increase to fill in the gap and the safety concerns surrounding compounding are greater than the safety concerns regarding the marketed product. I think it is difficult to predict whether the compounding will be more or less than it is currently. For example, we have heard from the sponsor that the utilization of this treatment has decreased by 45 percent since Trial 003 was published, and it is possible that market withdrawal of Makena will decrease compounding rather than increase it. But, in any case, I don't think the potential effect on compounding should be the key factor in making this decision. Maintaining Makena's approval is not the right tool to address a concern about a potential increase in compounding.

c. Summary and conclusion

The advisory committee recommended, by their vote of 14 to 1 on question 3, that Makena should not remain on the market while a new study was being performed. The principal reason that the committee members cited was that Makena was not shown to be effective for its labeled indication. The one member who voted in favor of retaining Makena on the market believed that Trial 003 did not undercut the effectiveness with respect to reducing the risk recurrent sPTB shown in Trial 002.

I do not believe that Makena has been shown to be effective, either in the currently indicated population, or in the more limited population proposed by Covis. In addition, there are known risks, and a potential for other risks, including intergenerational safety risks. For these reasons, I do not think there is a favorable benefit-risk profile to support Makena's remaining on the market and recommend approval be withdrawn. There is equipoise for a new study, which I hope will be feasible to conduct.

3. Conclusions

Given the FDA's April 6, 2023, decision to withdraw approval of Makena and of all ANDAs that reference Makena based on the determination that there is a lack of evidence that Makena is effective for its labeled indication, there is a strong basis for the agency to quickly take regulatory action to prevent pharmacy compounding of hydroxyprogesterone caproate injection for prevention of preterm birth.

FDA Commissioner Califf and Chief Scientist Bumpus themselves acknowledged in their final decision on the proposal to withdraw the approval of Makena that the current lack of adequate data supporting effectiveness of the drug implicates compounded products as well as Makena and its generic versions.

Moreover, given that numerous obstetricians and fetal-medicine physicians submitted comments to the FDA docket or testified at the October 2022 open public hearing in opposition to the agency's October 2020 proposal to withdraw accelerated approval of Makena,[10] it is highly likely that many such physicians will continue to prescribe compounded versions of hydroxyprogesterone caproate to prevent preterm birth until the agency takes the necessary regulatory action to prohibit such pharmacy compounding.

Importantly, the inclusion of all drug products containing bromocriptine mesylate for prevention of physiological lactation on the list of drug products withdrawn or removed from the market for reasons of safety or effectiveness at 21 C.F.R. § 216.24 when there are other marketed drug products containing bromocriptine mesylate that are approved by the FDA for other indications provides ample precedent for the agency to add hydroxyprogesterone caproate injection for prevention of preterm birth to this list even though there is another marketed drug product containing hydroxyprogesterone that is approved by the FDA for other indications.

Therefore, for the reasons stated above, we hereby petition the FDA, pursuant to Sections 503A and 503B of the FDCA and FDA regulations at 21 C.F.R. § 10.30, to take the following action:

> Promptly initiate the regulatory process to amend, through notice and comment rulemaking, 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 that therefore may not be compounded under the exemptions provided by Section 503A(a) or Section 503B(a) of the FDCA — to include hydroxyprogesterone caproate injection for prevention of preterm birth.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

[10] Regulations.gov. Proposal to withdraw marketing approval; opportunity for notice of a hearing. https://www.regulations.gov/docket/FDA-2020-N-2029. Accessed April 18, 2023.

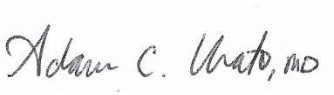
E. CERTIFICATION

We certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
202-588-1000
mcarome@citizen.org

Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group
202-588-1000
swolfe@citizen.org



Adam C. Urato, M.D.
Chief, Maternal-Fetal Medicine
MetroWest Medical Center
Framingham, Massachusetts