# FDA Briefing Document

# Pharmacy Compounding Advisory Committee (PCAC) Meeting

# October 29, 2024

The attached package contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

# Hydroxyprogesterone Caproate

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# FDA Evaluation of Hydroxyprogesterone Caproate

DATE: July 30, 2024

FROM: Mariestela Buhay, JD
Regulatory Counsel, Office of Compounding Quality and Compliance (OCQC)
Office of Compliance (OC)

Dorcas (Ann) Taylor, PharmD, JD
Team Lead, Regulatory Counsel, OCQC, OC

Emily Kneeream, PharmD
Clinical Analyst, Pharmacy Compounding Review Team (PCRT),
Office of Specialty Medicine (OSM), Office of New Drugs (OND)

Lolita Lopez, MD
Lead Physician, PCRT, OSM, OND

Daiva Shetty, MD
Associate Director, PCRT, OSM, OND

THROUGH: Charles Ganley, MD
Office Director, OSM, OND

Frances Gail Bormel, RPh, JD
Office Director, OCQC, OC

TO: Pharmacy Compounding Advisory Committee

SUBJECT: Evaluation of Certain Drug Products Containing Hydroxyprogesterone Caproate for the Withdrawn or Removed List

## I. INTRODUCTION

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) 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 three sections of the FD&C Act: sections 505 (concerning the approval of new drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)), 502(f)(1) (concerning the labeling of drugs with adequate directions for use), and 501(a)(2)(B) (concerning current good manufacturing practice requirements). One of the conditions that must be satisfied for a

compounded drug product to qualify for the exemptions under section 503A is that the licensed pharmacist or licensed physician "does not compound a drug product that appears on a list published by the Secretary 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."[1]

Section 503B of the FD&C Act describes the conditions that must be satisfied for a drug compounded for human use by or under the direct supervision of a licensed pharmacist in an outsourcing facility to be exempt from three sections of the FD&C Act: sections 502(f)(1), 505, and 582 (concerning drug supply chain security requirements). One of the conditions in section 503B of the FD&C Act that must be satisfied for a compounded drug product to qualify for the exemptions is that "[t]he drug does not appear on a list published by the Secretary 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."[2]

FDA has established a list of drug products that were 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, and which are not eligible for the exemptions provided by section 503A(a) or section 503B(a) of the FD&C Act (the Withdrawn or Removed List).[3]

## II. BACKGROUND AND REGULATORY HISTORY

On February 3, 2011, FDA approved Makena (hydroxyprogesterone caproate) injection, 250 milligrams (mg) per milliliter (mL), NDA 021945, under the accelerated approval pathway[4] to reduce the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth (sPTB).[5,6] As a condition of Makena's approval, the sponsor[7] was required to conduct a postmarketing confirmatory trial to verify and describe the clinical benefit of Makena on reducing the risk of neonatal morbidity or mortality from complications of PTB among babies born to women with a singleton pregnancy who had a

[1] Section 503A(b)(1)(C).
[2] Section 503B(a)(4).
[3] See 21 CFR 216.24.
[4] Section 506(c) of the FD&C Act; 21 CFR part 314, subpart H. Under the accelerated approval pathway, FDA approves a drug based on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict the drug's clinical benefit, rather than based on a direct measurement of clinical benefit or on a surrogate endpoint that is validated (i.e., known) to predict clinical benefit. Sponsors of drugs approved under the accelerated approval pathway have been required to conduct a postmarket confirmatory trial designed to verify the predicted clinical benefit. If the clinical benefit is not verified, or if certain other grounds for withdrawal are satisfied, FDA can withdraw approval of the drug under expedited withdrawal procedures described in section 506(c) of the FD&C Act.
[5] The February 2011 original approval letter for Makena is included in the action package for NDA 021945, which is available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945_makena_toc.cfm
[6] Makena (hydroxyprogesterone caproate injection) Information, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information
[7] At the time of approval, the sponsor of NDA 021945 was Hologic, Inc. Thereafter, ownership of this application was transferred to KV Pharmaceuticals Company, and then it was transferred to Lumara Health, Inc., which was later purchased by AMAG Pharma. Covis Pharma GmbH, the sponsor of NDA 021945 before it was withdrawn, acquired AMAG Pharma and NDA 021945 in March 2021.

previous singleton sPTB. The confirmatory trial, referred to as "Trial 003", failed to show that Makena reduced the risk of neonatal morbidity and mortality from the complications of PTB. Trial 003 also failed to show that Makena had any effect on reduction in the proportion of women delivering prior to 37 weeks' gestation, the intermediate clinical endpoint that was the basis of Makena's accelerated approval. In sum, the available evidence post-approval demonstrated that Makena was no longer shown to be effective under its approved conditions of use.

On October 5, 2020, FDA proposed withdrawing approval of Makena. The sponsor, Covis Pharma Group/Covis Pharma GmbH (Covis), requested a hearing.[8] A hearing was conducted on October 17 to 19, 2022.[9] The Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC) ("advisory committee") was present to review the issues involved and to provide advice and recommendations to the FDA Commissioner and Chief Scientist. FDA and Covis each made presentations followed by an opportunity for questions from each other, the advisory committee, and the Presiding Officer. There were also comments from twenty public commenters, representing a range of backgrounds and perspectives. No ANDA holders elected to make presentations. All advisory committee members agreed that the findings from Trial 003 did not verify the clinical benefit of Makena on neonatal morbidity and mortality from complications of preterm birth (voting Question 1). Almost all of the members agreed that the available evidence does not demonstrate that Makena is effective for its approved indication of reducing the risk of preterm birth in women with a singleton pregnancy who have a history of singleton sPTB (voting Question 2); and FDA should not allow Makena to remain on the market while another confirmatory study is designed and conducted (voting Question 3).[10]

Following the hearing, the Presiding Officer issued a report, dated January 19, 2023, that summarized the legal and factual background, the content of the hearing, and her analysis and recommendations.[11] The Presiding Officer stated that she did "not think there is a favorable benefit-risk profile to support Makena's remaining on the market and recommend[ed] approval be withdrawn." FDA and Covis submitted post-hearing briefs on March 6, 2023.[12]

On April 6, 2023, the FDA Commissioner and Chief Scientist jointly issued the "Final Decision on the Proposal to Withdraw Approval of Makena," concluding that there was "an insufficient

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[8] CDER's Proposal to Withdraw Marketing Approval of Makena (hydroxyprogesterone caproate injection); Notice of Opportunity for a Hearing (NOOH) (October 5, 2020) at 6, available at https://www.regulations.gov/document/FDA-2020-N-2029-0001. See also 87 Fed. Reg. 50626 (Aug 17, 2022). AMAG Pharmaceuticals, Inc. (AMAG), the sponsor of NDA 021945 at the time, received this notice. After AMAG requested a hearing, Covis acquired AMAG, including NDA 021945. This notice refers to AMAG as ''Covis.''

[9] https://www.regulations.gov/document/FDA-2020-N-2029-0375 (transcript for Oct. 17, 2022); https://www.regulations.gov/document/FDA-2020-N-2029-0376 (transcript for Oct. 18, 2022); https://www.regulations.gov/document/FDA-2020-N-2029-0377 (transcript for Oct. 19, 2022).

[10] Hearing Involving the Obstetrics, Reproductive and Urologic Drugs Advisory Committee (ORUDAC) Transcript, (Oct. 19, 2022), available at https://www.fda.gov/media/163687/download.

[11] *See* Presiding Officer's Written Report Summarizing Public Hearing and Providing Recommendations on CDER's Proposal to Withdrawn Approval of Makena, at https://www.regulations.gov/document/FDA-2020-N-2029-0379.

[12] *See* Makena Hearing – Documents, at https://www.regulations.gov/document/FDA-2020-N-2029-0383.

demonstration of effectiveness to balance any level of risk."[13] FDA's decision also withdrew approvals for the ANDAs that referenced Makena, pursuant to 21 CFR 314.151(b)(3).[14] On May 15, 2023, FDA published a notice in the Federal Register announcing the availability of the final decision to withdraw the approval of Makena.[15]

In summary, Makena (hydroxyprogesterone caproate injection, 250 mg/mL) NDA 021945 was approved in 2011 under the accelerated approval pathway to reduce the risk of PTB in women with a singleton pregnancy who have a history of sPTB. However, the postmarketing confirmatory trial failed to verify the clinical benefit of Makena and the available evidence demonstrated that Makena was no longer shown to be effective under its conditions of use. Thus, FDA concluded that the statutory standard in section 506(c) of the FD&C Act for expedited withdrawal was met, and that approval should be withdrawn. On April 6, 2023, the FDA Commissioner and Chief Scientist issued a decision withdrawing the approval of Makena and the ANDAs that referenced Makena.[16]

## III. CDER EVALUATION OF HYDROXYPROGESTERONE CAPROATE FOR THE WITHDRAWN OR REMOVED LIST

The Office of Compounding Quality and Compliance (OCQC) asked the Office of New Drugs (OND) to provide input on whether certain drug products containing hydroxyprogesterone caproate should be included on the Withdrawn or Removed List and, if yes, how the drug should be described on the list. These questions and OND's responses are provided here.

> ***Question 1:***
> Based on the information available, do you agree that drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth was withdrawn or removed from the market for reasons of safety or effectiveness? Please summarize the basis for the withdrawal or removal of the drug from the market, citing available evidence where appropriate.

**OND response**:
Yes, we agree that the only NDA for a drug product containing hydroxyprogesterone caproate to reduce the risk of singleton spontaneous preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth was withdrawn from the market for safety

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[13] See Final Decision on the Proposal to Withdraw Approval of Makena, https://www.regulations.gov/document/FDA-2020-N-2029-0385 [not cite formatted]
[14] *See* Makena Hearing – Documents, at https://www.regulations.gov/document/FDA-2020-N-2029-0385. (1) ANDA 211070, held by Eugia Pharma Specialties Limited; (2) ANDA 211071, held by Eugia Pharma Specialties Limited; (3) ANDA 210618, held by Slayback Pharma LLC; (4) ANDA 210877, held by Slayback Pharma LLC; (5) ANDA 208381, held by Sun Pharmaceuticals Industries Ltd; (6) ANDA 210723, held by American Regent, Inc.; (7) ANDA 210724, held by American Regent, Inc.; and (8) ANDA 211777, held by Aspen Pharma USA Inc.
[15] See Final Decision on Withdrawal of Makena (Hydroxyprogesterone Caproate) and Eight Abbreviated New Drug Applications Following Public Hearing Notice, at https://www.federalregister.gov/d/2023-10264.
[16] See Final Decision on Withdrawal of Makena (Hydroxyprogesterone Caproate) and Eight Abbreviated New Drug Applications Following Public Hearing Notice, at https://www.federalregister.gov/d/2023-10264.

or effectiveness reasons, and that the ANDAs that relied on Makena were withdrawn. The available evidence demonstrates that Makena is no longer shown to be effective under the conditions of use for which it was approved, including for the indication of reducing the risk of PTB in women with a singleton pregnancy who have a history of singleton sPTB, and that the benefit-risk profile of hydroxyprogesterone caproate for this indication is unfavorable.

FDA approved Makena under the accelerated approval pathway based on evidence from a clinical trial known as Trial 002, which demonstrated an effect on an intermediate clinical endpoint[17] (gestational age of delivery < 37 weeks) that FDA determined was reasonably likely to predict clinical benefit. As explained in the approval letter, FDA required the sponsor to complete a postmarketing confirmatory study. Trial 003 was conducted to fulfill this postmarketing requirement. Trial 003 did not verify the clinical benefit of Makena and also demonstrated that the drug was no longer shown to be effective under the conditions of use for which it was approved. These studies are briefly described below.

Trial 002 was a randomized, double-blind, placebo-controlled trial in 463 women with a singleton pregnancy and at least one prior singleton sPTB, in which the treatment arm receiving hydroxyprogesterone caproate 250 mg injection had a statistically significantly lower rate of delivering prior to 37 weeks' gestation than the placebo arm. The primary efficacy endpoint was the proportion of pregnant women delivering < 37 weeks gestation, and secondary endpoints included the proportion of pregnancy women delivering < 35 weeks and < 32 weeks gestations.[18] This study demonstrated a reduction in the proportion of women delivering prior to 37 weeks of gestation; smaller reductions of preterm birth were also observed at 35 and 32 weeks. There was no prespecified efficacy endpoint on neonatal outcomes.

Trial 002 was also the only adequate and well-controlled trial to support the Makena NDA at the time of accelerated approval. Trial 002 did not demonstrate a reduction of fetal/neonatal deaths or neonatal morbidity as measured on a neonatal composite index; the trial was not designed to evaluate this clinical outcome. FDA's approval of Makena under the accelerated approval pathway required the sponsor to complete a postmarketing study to verify and describe the clinical benefit of Makena on reducing the risk of neonatal morbidity or mortality from complications of PTB among babies born to women with a singleton pregnancy who had a previous singleton sPTB.[19] The sponsor conducted the postmarketing confirmatory study, Trial 003.

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[17] Gestational age of delivery was an intermediate clinical endpoint. An intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality that, in the context of accelerated approval, is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit. FDA Guidance for Industry, Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014) (Expedited Programs Guidance), available at https://www.fda.gov/media/86377/download at 18. In the context of accelerated approval, both intermediate clinical endpoints and surrogate endpoints function as predictors of clinical benefit.

[18] Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena. Docket No. FDA-2020-N-2029. Sept. 16, 2022. Available at https://www.fda.gov/media/162246/download. See pp. 23-24/86.

[19] Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena. Docket No. FDA-2020-N-2029. Sept. 16, 2022. Available at https://www.fda.gov/media/162246/download. See p. 9/86.

Trial 003 was an international, randomized, double-blind, placebo-controlled clinical trial in 1,708 women designed to verify Makena's predicted clinical benefit in women with essentially the same eligibility criteria as those of Trial 002. This confirmatory trial evaluated two co-primary endpoints: (a) delivery < 35 weeks gestation and (b) a neonatal morbidity/mortality composite index. The results of the trial failed to demonstrate a statistically significant treatment effect on either endpoint.[20] Also, no differences between Makena and placebo were seen in the secondary outcomes of delivery < 32 or < 37 weeks (< 37 weeks was the primary efficacy endpoint in Trial 002 that formed the basis for accelerated approval). Trial 003 was a rigorous, well-designed, well-conducted trial that was adequately powered to detect efficacy, but despite this, it did not do so.[21]

The confirmatory trial for Makena, Trial 003, failed to verify the predicted clinical benefit of reducing neonatal morbidity and mortality from complications of preterm birth. In addition, the evidence available post-approval demonstrated that Makena was no longer shown to be effective for the indication for which it was approved—reducing the risk of recurrent sPTB in women with a singleton pregnancy who have a history of sPTB.[22]

In summary, the benefit-risk profile for Makena was not favorable. The confirmatory trial, Trial 003, failed to verify the predicted clinical benefit to the neonate and did not even show an effect on the intermediate clinical endpoint of gestational age that was the basis of the accelerated approval.[23] In addition, Makena has known safety risks including thromboembolic events, allergic reactions, decreased glucose tolerance, and injection site reactions. Given the risks of Makena and the absence of demonstrated benefit, the benefit-risk profile was not favorable.[24]

The unfavorable benefit-risk balance, and the withdrawal of approval, was specific to Makena and its generics, which were indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. This did not affect the approval status of drug products containing hydroxyprogesterone caproate that are approved for a different indication. These currently approved indications consist of, in non-pregnant women: 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.

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[20] Post-Hearing Submission Supporting CDER's Proposal to Withdraw Approval of Makena Docket No. FDA-2020-N-2029. March 6, 2023. Available at https://downloads.regulations.gov/FDA-2020-N-2029-0383/attachment_1.pdf See p. 3/20.
[21] Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena. Docket No. FDA-2020-N-2029. Sept. 16, 2022. Available at https://www.fda.gov/media/162246/download. See p. 30/86.
[22] Post-Hearing Submission Supporting CDER's Proposal to Withdraw Approval of Makena Docket No. FDA-2020-N-2029. March 6, 2023. Available at https://downloads.regulations.gov/FDA-2020-N-2029-0383/attachment_1.pdf See p. 4/20.
[23] Final Decision on the Proposal to Withdraw Approval of Makena Docket No. FDA-202-N-2029. April 5, 2023. Available at https://www.regulations.gov/document/FDA-2020-N-2029-0385. See p. 16/26.
[24] Briefing Materials Supporting CDER's Proposal to Withdraw Approval of Makena. Docket No. FDA-2020-N-2029. Sept. 16, 2022. Available at https://www.fda.gov/media/162246/download. See p. 68&74/86.

***Question 2:***
Do you recommend that hydroxyprogesterone caproate be included on the Withdrawn or Removed List and, if so, how should the entry be described? Please include your rationale for your recommendation.

**OND response**:
OND recommends that all drug products containing hydroxyprogesterone caproate for use in reducing the risk of singleton spontaneous preterm birth be included on the Withdrawn or Removed List as proposed below. As noted in the response to question 1, the evidence available post-approval demonstrated that Makena is no longer shown to be effective for the indication for which it was approved, i.e., to reduce the risk of recurrent preterm birth in women with a history of singleton spontaneous preterm birth. The unfavorable benefit-risk determination is limited to hydroxyprogesterone caproate for this indication, and not to other currently approved indications for different drug products containing hydroxyprogesterone caproate.

We recommend that the following entry for hydroxyprogesterone caproate be added to the Withdrawn or Removed List:

*Hydroxyprogesterone caproate:* All drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.