4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2020-N-2029]

Final Decision on Withdrawal of MAKENA (Hydroxyprogesterone Caproate) and Eight Abbreviated New Drug Applications Following Public Hearing; Availability of Final Decision

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of the final decision withdrawing approval of MAKENA (hydroxyprogesterone caproate injection, 250 milligrams (mg) per milliliter (mL), once weekly), under the new drug application (NDA) 021945, held by Covis Pharma Group/Covis Pharma GmbH (Covis), and the eight abbreviated new drug applications (ANDAs) from multiple ANDA holders that reference NDA 021945. The Commissioner of Food and Drugs (the Commissioner) and the Chief Scientist jointly issued the decision following an October 2022 public hearing.

DATES: Approval of MAKENA and the ANDAs that reference MAKENA is withdrawn as of April 6, 2023.

FOR FURTHER INFORMATION CONTACT: Patrick Raulerson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6260, Silver Spring, MD 20993-0002, 301-796-3522, Patrick.Raulerson@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

On February 3, 2011, FDA's Center for Drug Evaluation and Research (CDER) approved NDA 021945 for MAKENA (hydroxyprogesterone caproate) Injection to reduce the risk of preterm birth (PTB) in women with a singleton pregnancy who have a history of singleton

spontaneous PTB (sPTB). FDA approved MAKENA under the accelerated approval pathway, pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(c)) and 21 CFR 314.510, based on evidence of the drug's effect on an intermediate clinical endpoint that was considered reasonably likely to predict the drug's clinical benefit.

As a condition of MAKENA's approval, the sponsor was required to complete a postmarketing trial to verify and describe the clinical benefit of MAKENA in reducing neonatal morbidity and mortality from complications of PTB among babies born to women with a singleton pregnancy who had a previous singleton sPTB. This postmarketing confirmatory trial, Trial 003, failed to show that MAKENA reduced the risk of neonatal morbidity and mortality from complications of PTB and failed to show a treatment effect of MAKENA on the intermediate clinical endpoint that was the basis of MAKENA's approval.

On October 5, 2020, CDER issued a proposal to withdraw approval of MAKENA and a notice of opportunity for hearing (NOOH) on two independent grounds using expedited procedures under section 506(c)(3) of the FD&C Act and 21 CFR 314.530(a): (1) the confirmatory trial failed to verify the clinical benefit of the drug and (2) the evidence demonstrates that the drug is not shown to be effective under its conditions of use. CDER's NOOH and proposal to withdraw approval of MAKENA also provided notice to all holders of approved ANDAs referencing the NDA for MAKENA (NDA 021945) that, if the Agency were to withdraw approval of MAKENA, CDER would withdraw approval of those ANDAs under 21 CFR 314.151(b)(3).

MAKENA's sponsor submitted a hearing request dated October 14, 2020, followed by a submission of data and information in support of the hearing request. The Agency granted the sponsor's hearing request on August 18, 2021, and on August 17, 2022, published a notice of hearing (87 FR 50626). The hearing was held on October 17, 18, and 19, 2022. The Obstetrics, Reproductive and Urologic Drugs Advisory Committee was present at the hearing to review the issues involved and to provide advice and recommendations to the Commissioner. The presiding

officer issued a report, dated January 19, 2023, that summarized the legal and factual background, content of the hearing, and her analysis and recommendations. On April 6, 2023, after considering CDER's and Covis' March 6, 2023, post-hearing submissions, the Commissioner and Chief Scientist jointly issued a final decision withdrawing approval of MAKENA and the ANDAs that referenced MAKENA.

FDA has withdrawn approvals of the following NDA and eight ANDAs:

Application No.	Drug	Holder/Sponsor
NDA 021945	Makena (hydroxyprogesterone caproate) Injection, 250 mg per mL	Covis Pharma Group/Covis Pharma GmbH
ANDA 208381	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Sun Pharmaceutical Industries, Ltd.
ANDA 210618	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Slayback Pharma LLC
ANDA 210723	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	American Regent, Inc.
ANDA 210724	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Do.
ANDA 210877	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Slayback Pharma LLC
ANDA 211070	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Eugia Pharma Specialities Ltd.
ANDA 211071	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Do.
ANDA 211777	Hydroxyprogesterone Caproate Injection USP, 250 mg/mL	Aspen Pharma USA Inc.

Withdrawal of approval of the applications listed in the table includes all strengths, dosage forms, amendments, and supplements to these applications, effective April 6, 2023. As discussed in the decision of the Commissioner and Chief Scientist, FDA has withdrawn approval of the MAKENA NDA for reasons of safety or effectiveness, as well as approval of the ANDAs that reference MAKENA.

Section 505(j)(7) of the FD&C Act (21 U.S.C. 355(j)(7)) requires FDA to publish a list of all approved drugs. FDA publishes this list as part of the "Approved Drug Products With Therapeutic Equivalence Evaluations," which is known generally as the "Orange Book," available at https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Under FDA regulations,

drugs are removed from the list if the Agency withdraws or suspends approval of the drug's NDA or ANDA for reasons of safety or effectiveness or if FDA determines that the listed drug was withdrawn from sale for reasons of safety or effectiveness 21 CFR 314.162. Accordingly, the Agency has removed the applications listed in the table from the list of drug products published in the Orange Book. FDA will not accept or approve ANDAs that reference MAKENA.

II. Electronic Access

Persons with access to the internet may obtain the final decision at https://downloads.regulations.gov/FDA-2020-N-2029-0385/attachment_1.pdf. The final decision, a transcript of the hearing, and other documents pertaining to the withdrawal of the NDA for MAKENA (NDA 021945) are available at https://www.regulations.gov under the docket number found in brackets in the heading of this document.

Dated: May 8, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

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