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Democracy Dies in Darkness

FDA wants to yank pregnancy drug. Firm argues Black women will suffer.

WITH NO ALTERNATIVE TREATMENTS, SOME WORRY THE MOVE COULD DEEPEN MATERNAL AND INFANT HEALTH INEQUITIES

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"Help give your baby more time." The eye-catching bright pink ads for the drug Makena tout its ability to reduce the risk of preterm birth. Introduced in 2011, it has been seen as a potential miracle drug for women at high risk.

The problem: The Food and Drug Administration contends it does not work.

In a highly unusual move, the agency has indicated it will make the case to withdraw Makena from the market during several advisory committee meetings in Washington that began Monday morning. Covis Pharma, the company that owns the patent, is fighting to continue sales, making arguments about racial equity.

The company's CEO, Michael Porter, has argued that there is evidence to suggest the drug may work in a narrow population that includes Black women, who have historically been at higher risk of maternal complications. That claim is brd on a 2003 study that was used to grant the treatment accelerated approval in the first place. Several Black health groups support keeping Makena on the market for further testing, and the NAACP said it worries pulling the drug may "deepen profound existing maternal and infant health inequities in the U.S." given the lack of alternatives.

Preterm birth is one of the most devastating and costly health issues facing the United States. About 1 in 10 babies is born too soon, risking lifelong complications and death. Black newborns are more than twice as likely to die as White newborns.

Patrizia Cavazzoni, director of the FDA's Center for Drug Evaluation and Research (CDER), said the agency once hoped Makena would offer a solution to this problem. "We no longer do," she said at the hearing, adding that its analyses of data on Makena were "disappointing" and "unexpected."

The situation has confounded doctors who are divided about whether to continue prescribing the medication — which is indicated for women who have already experienced a preterm birth — and it raises thorny questions about the confluence of race, clinical trials and capitalism.

Adriane Fugh-Berman, a Georgetown University Medical Center professor who studies pharmaceutical marketing practices, accuses Covis of exploiting racial sensitivities to maximize profits. The Luxembourg-brd company is owned by private equity firm Apollo Global Management, which purchased it in 2020 in a deal estimated to have been worth $700 million, in large part because of optimism about Makena's blockbuster sales potential. The drug has already been used by an estimated 350,000 women across the country. Fugh-Berman said the drug is not only expensive for women — costing upward of $10,000 in some cases — but that it carries risks.

"There's no scientific debate here," Fugh-Berman said. "The debate is between science and profit."

Adam C. Urato, a maternal-fetal medicine specialist in Framingham, Mass., who has filed testimony for the FDA advisory meeting, said experts inside and outside the agency have repeatedly analyzed clinical trials looking for evidence of Makena's efficacy but have found none.

He recently tweeted: "No one should be fooled by the racial equity spin for Makena." In his prepared remarks, he called Covis "unethical" for using "high-risk, Black pregnant women as 'props' to make a racial equity argument."

"How does keeping Makena on the market — so pregnant Black women can disproportionally be injected with an ineffective drug — improve racial equity in any way?" he argued.

No one should be fooled by the racial equity spin for Makena.

Keeping Makena on the market does nothing to help racial equity – it just puts Black moms & their babies at risk.

FDA: Ignore a pharma company's deceptive racial equity argument for Makena https://t.co/PyBwQKS5Qb
— Adam Urato, MD (@AdamUrato1) September 26, 2022

A promising beginning

The story of how Makena came to be was somewhat serendipitous.

As Alan Peaceman, professor emeritus of maternal-fetal medicine at Northwestern University's Feinberg School of Medicine, recalls, back in the 1970s and 1980s, there were studies showing that animals given the hormone progesterone could have prolonged pregnancies. He remembers thinking that was a bit "weird" because the amount of the medication being given was "a drop in the ocean given how much progesterone is circulating in the body already."

But as a researcher who was part of a National Institutes of Health maternal-fetal network that ran a clinical trial of 17P, a synthetic form of progesterone given by injection, he was happy and surprised to find that it appeared to reduce the risk of recurrent preterm birth.

The study's results were published in 2003, and Peaceman and many other physicians began to use the drug, which at that point was being made in special pharmacies that mix medicines in-house. It cost about $50 for five doses. The price was reasonable, but due to the lack of oversight of these often-small operations, the treatments could be inconsistent, and in 2011, the FDA granted approval for a company to make the drug and sell it for reducing the risk of preterm birth in women who had a history of spontaneous preterm birth with a singleton pregnancy (as opposed to twins or higher-order multiples).

The price immediately skyrocketed, Peaceman remembers, to $7,500 for the same amount of medication, "which upset a lot of people." But the FDA's stamp of approval also paved the way to insurance coverage that allowed many more women, including those on Medicaid, to get the drug. Pharmacies could still continue to produce less expensive versions of the drug, but the market largely shifted to Makena.

Conflicting data

Makena was authorized in 2011 under a fast-tracked process intended to speed the availability of drugs that treat serious or life-threatening conditions, but which requires follow-up data that confirms or refutes the drug's benefits. The FDA typically likes to see multiple studies before approving drugs, and the original trial, with 310 women in the progesterone group and 153 women getting a placebo, was considered well-designed and promising but not definitive.

The larger confirmatory trial, as it is known, out in 2019, was universally disappointing, showing no effect of Makena in 1,130 women who received the drug vs. 578 who got a placebo.

"We as a medical community have been left scratching our heads not knowing what to do because of the two conflicting trials," Peaceman said. The doctors in his practice chose what he described as a middle ground: They let women know about both studies and let them make the decision.

"We are not big cheerleaders," he explained, "but we do offer it to patients."

Covis has said the "inconsistent" outcomes in the two trials may be due to the differing patient populations. The patient population in the original, promising trial was 59 percent Black women, while the participants in the larger one that showed no benefit from the drug were largely Eastern European, with only 7 percent Black participants. In a filing with the FDA, the drug company called the latter trial "flawed," not only because of its racial demographics, but also because the population was low-risk and the women had access to national health-care systems that differ greatly from the complex piecemeal system in the United States.

The representation of people of color in clinical trials has long been an issue in the United States amid concerns that research on one population group might not necessarily apply to others due to differences in risk factors and other variables.

Researchers said the scant participation of Black women in the second trial was largely due to the fact that few patients were willing to face the risk of being given a placebo instead of Makena, when the drug had already been approved in the United States. Everyone wanted the drug, and so researchers had to move the trial overseas.

In a written response to questions, Francesco Tallarico, general counsel and head of government affairs and policy at Covis, elaborated that Makena "has a compelling efficacy profile that merits further study and should remain available to patients who need it while additional research is completed." Tallarico suggested the company would be open to "narrowing the labeling to focus the indication on the most high-risk patients while additional study is undertaken."

Sally Greenberg, executive director of the National Consumers League, leads a coalition of groups that support continued use of Makena and its generic versions. Greenberg's organization receives funding from Covis, but she said that did not influence its views. She said she became involved because she feels the FDA's position to withdraw the drug is "extreme."

"The FDA is under a lot of pressure at times to look like they are being tough on the industry, and I think this is one of those times," she said. "I think it's misdirected and ill-advised and will do harm to a patient population of African American women and their babies."

The FDA's case

The FDA's efforts to withdraw Makena go back as far back as 2019, when an expert advisory panel voted 9-7 that the drug should be pulled. But because of regulatory requirements and the pandemic, the process was delayed.

In a 153-page slide presentation posted in advance of this month's meetings of the Obstetrics, Reproductive and Urologic Drugs Advisory Committee, FDA experts did not hint at a compromise, arguing that the drug exposes women to "serious risks without demonstrated benefit."

"Allowing Makena to remain on the market would expose pregnant women to serious risks … without any assurance that they and their future children are receiving any benefit at all," the FDA's Cavazzoni said at the hearing.

In fact, when regulators sliced the numbers in several other ways — a strategy sometimes used to try to find statistical links — the conclusion remained the same: No evidence of treatment benefit by geographical region. No evidence of treatment benefit by gestational age. No evidence of treatment benefit by other risk factors.

"After multiple analyses, CDER was unable to identify a group of women for whom Makena had an effect," according to the agency's presentation.

Moreover, the FDA's list of Makena's reported side effects is long and unnerving: blood clots, allergic reactions, decreased tolerance of glucose that can exacerbate diabetes, fluid retention that can worsen preeclampsia and depression that led to hospitalization. The FDA also pointed out the possibility of an increased cancer risk for the children treated with the active ingredient in Makena.

Regulators noted that leaving the drug on the market does not address health disparities. On the contrary, they said, it inhibits development of other effective treatments and does the "greatest disservice" to those at greatest risk of preterm birth.

Divisions

As the debate continues, physicians' attitudes about Makena are split.

"I still believe it works," said Patrick S. Ramsey, professor of obstetrics and gynecology at the University of Texas Health Science Center at San Antonio and chief of its division of maternal-fetal medicine, "and maybe there needs to be another study done to confirm that that represents the population like the United States."

However, Andrew Combs, senior adviser for maternal-fetal medicine clinical quality for the Pediatrix Medical Group, said the group's national network of physicians use it only "occasionally for extremely high-risk patients whose prior preterm birth was at a very early gestational age, or for patients who received Makena in a previous pregnancy and had a good outcome."

"But by and large, usage has greatly fallen off," Combs said.

Mary Norton, also a maternal-fetal medicine specialist and a spokesperson for the Society for Maternal-Fetal Medicine, said the organization continues to support use of the drug "in pregnant people with a profile more representative of the very-high-risk population" in the first trial but that other women should discuss known risks and benefits with their doctors. The American College of Obstetricians and Gynecologists already updated its guidance in 2021 after the second trial results were published to reflect a similar approach.

Since the FDA approved Makena in 2011, the March of Dimes has been one of the biggest boosters for it, as well as generic versions of the drug. But in a letter to the agency on Oct. 4, Zsakeba Henderson, interim chief medical officer for the group, acknowledged that the FDA no longer believes the treatment reduces the risk of recurrent preterm births.

Seeming to indicate its support for the FDA's efforts to withdraw the drug, Henderson wrote that "we respect the scientific review process and decisions made by the agency."

The FDA typically follows the recommendations of its expert panels and has previously taken action within a few months of a committee's vote.

In 2011 the FDA commissioner at the time, Margaret A. Hamburg, revoked approval of the use of the drug Avastin for breast cancer, despite objections from drugmaker Genentech and some patient advocates. While doctors claimed that some patients responded well, studies showed the drug was not helping many others live longer and was exposing them to life-threatening complications. Avastin remains on the market for the treatment of several other cancers.

Rachel Roubein contributed to this report.