Call for FDA to withdraw preterm birth drug divides doctors and insurers

January 28 2020, by Emmarie Huetteman

Credit: CC0 Public Domain

Doctors fear that the only drug approved to prevent preterm birth, the nation's leading cause of infant mortality and disability, will no longer be available to expectant mothers.

The drug, sold under the brand name Makena, has been in limbo since

October, when an expert panel convened by the Food and Drug Administration reviewed the accumulated evidence and concluded that Makena is not effective in preventing preterm birth.

In a close vote, the panel recommended the FDA withdraw approval and pull the drug off the market.

That recommendation has sparked a fierce debate within the health care community. Doctors are torn between two clinical studies of the drug that had differing results: An older trial of American patients at high risk of having a preterm delivery showed Makena's active ingredient seemed to be effective. But, more recently, a larger trial of lower-risk, international patients—a study conducted by the drug's manufacturer after the FDA's request—suggested that the medicine did not work.

Complicating matters is the possibility that even if the FDA decides to let Makena remain for sale, or permits pharmacies to create their own versions of the drug for use, insurers might well refuse to pay.

Insurers are generally under no obligation to cover drugs just because the FDA approves them. And Cathryn Donaldson, a spokesperson for America's Health Insurance Plans, said AHIP is convinced by the larger, more recent trial. "Now it is clear it is not effective," she said.

This puts the FDA in a bind.

Many practicing obstetricians have been prescribing some form of the drug as standard treatment since around 2003, when the smaller clinical trial—a National Institutes of Health study—showed that the synthetic hormone 17-hydroxyprogesterone caproate, or "17P," was effective in preventing preterm delivery in women with a history of preterm labor.

In 2011, sensing a market opportunity, a drug manufacturer jumped in to

offer Makena—the only branded, FDA-approved version of 17P.

Makena has since effectively cornered the market. And if the FDA complies with the recommendation of its advisory panel to order Makena off the market, the action might remove all options for treating premature labor. By law, if the FDA withdraws its approval for Makena, generic versions of 17P must be pulled, too, and the FDA could decide to also stop specialty pharmacies from compounding Makena's active ingredient.

That's why seven of the 16 members of the FDA panel have argued that removing Makena's FDA approval could do more damage than simply leaving a drug on the market that may, or may not, work.

Cutting off all access to the drug, whether it is Makena or its compounded versions, would be "a big disaster," especially for women in disadvantaged communities who are at a higher risk of preterm birth, said Dr. George Saade, the director of maternal-fetal medicine and chief of obstetrics at the University of Texas Medical Branch at Galveston. (Saade has chaired panels awarding research grants from Makena's manufacturer.)

"It's not like, Oh, they're going to be fine," he said. "No, they're not."

If Makena stays on the market, doctors and insurers will be left to haggle over prescribing a drug that can cost an average of more than $10,000 per pregnancy. If the FDA blocks further sales, a treatment that many doctors and patients rely on will disappear overnight.

Giving Infants Their Best Start

Babies born prematurely can have problems breathing or digesting food or experience bleeding in their brains, among other life-threatening

risks. Some of the children who survive struggle with lifelong disabilities. Giving them an extra few days or weeks in the womb can be transformative.

So it was considered a major breakthrough when the NIH released the results of its study in 2003, showing 17P was effective at preventing delivery before 37 weeks' gestation for many women who had previously experienced preterm birth and were carrying a single baby.

That clinical trial, which studied more than 450 women in the United States, showed that about 37% of participants who received 17P had given birth before 37 weeks—contrasted with about 55% of participants who received the placebo. Researchers found no major safety concerns.

The drug seemed so clearly effective that researchers ended the study early. And the American College of Obstetricians and Gynecologists recommended that all pregnant women who fit that criteria be given 17P.

"The only problem was, no one was making it," said Dr. Alan Peaceman, the chief of maternal-fetal medicine at Northwestern University's Feinberg School of Medicine and a researcher on the 2003 study.

Thus, for more than a decade, compounding pharmacies—specialty pharmacies that typically make prescription drugs for patients who have allergies or other conditions—created cheap injections of 17P for use by pregnant women.

At the time, a weekly dose of the compounded drug cost about $10-$20. For the same dose, Makena, the branded version that emerged in 2011 and cornered the market, cost about $1,500 from the get-go.

In 2017, a study of the drug's cost by researchers from Harvard

University found no notable difference between the outcomes of women who took Makena and women who took compounded 17P—even though the mean per-pregnancy cost of Makena was $10,711 more than that of 17P.

How Makena Cornered The Market

In less than 10 years, the makers of Makena pushed its competition, particularly low-cost compounding pharmacies, out of the market.

Many of the women at risk of preterm birth, and the babies they have, are on Medicaid. Compounding facilities can be difficult to find. The drug was rendered inaccessible to many of the women who doctors thought needed it most.

When Makena first arrived, doctors, advocates and, eventually, members of Congress objected to its high price. Insurers, including government programs like Medicaid, refused to cover it.

At the time, Makena's manufacturer struggled to compete with the cheaper, compounded 17P. In 2012, it sued the FDA in an unsuccessful attempt to stop compounding—gaining some ground later that year when a meningitis outbreak caused by a different compounded drug drew federal scrutiny of specialty pharmacies.

In 2014, the manufacturer went bankrupt and sold Makena to AMAG Pharmaceuticals, which owns the drug today.

But compounding of 17P continued until 2016, when the FDA approved a preservative-free version of Makena and, in doing so, handed AMAG Pharmaceuticals the exclusive right to make the drug, ending the compounding of 17P.

In a press release noting its victory, AMAG said at the time that about 38% of patients were taking compounded 17P instead of Makena.

"Ultimately, we felt pressured into prescribing the Makena because it was FDA-approved," Peaceman said. "And especially in big systems, you are discouraged from using non-FDA-approved medicines when there is an FDA-approved medicine available."

A Second Clinical Trial Muddies the Waters

For years, the results of the NIH's 2003 study reassured many doctors, insurers, health officials and patients: 17P, Makena's active ingredient, had been proven to prevent preterm birth.

When Makena's original manufacturer sought FDA approval, it cited the NIH's results to vouch for the drug's safety and effectiveness. But while the FDA granted it approval to market Makena, the agency also ordered the company to conduct its own trial to confirm it was safe and effective, though with stricter requirements: Among other things, the company would have to prove the drug was effective at preventing preterm birth before 35 weeks, rather than 37.

Nearly a decade later, AMAG released the long-awaited findings of that nine-year scientific study: Although the company also turned up no major safety issues, researchers said last fall they could not prove Makena is effective at preventing preterm birth.

With more than 1,700 women participating, AMAG's study was much larger than the NIH's. But, critics said, for a clinical trial ultimately intended to prove whether Makena works for American women at high risk of preterm birth, AMAG's trial was deeply flawed.

For one thing, 35% of participants in the NIH trial had experienced

preterm birth more than once, putting them at higher risk, compared with just 15% in AMAG's trial.

Also, the majority of participants in the NIH trial—about 59% - were black, while the vast majority in AMAG's trial—about 89% - were white. According to the Centers for Disease Control and Prevention, preterm birth is more common among babies born to black mothers.

AMAG told the FDA that it had had difficulty enrolling enough women who fit its criteria in the United States—because if a woman was already taking 17P, generally speaking, then she was not eligible for the study. And because the drug was already considered the standard of care, a lot of American women were taking it.

Instead, 61% of women involved in the trial were from Russia and Ukraine—countries that have notably different demographics than those of the United States. Patients from the United States made up just 23% of participants in the study.

Based largely on AMAG's findings, the FDA's expert panel recommended in October, in a 9-7 vote, that the FDA withdraw its approval of Makena. The seven dissenting members recommended keeping the drug on the market while conducting further study.

So far, pending a final FDA decision, Makena is still on the market. The FDA does not have to accept the recommendations of its expert panels, though typically it does. Amanda Turney, a spokesperson of the agency, said there is no established timeline for when the FDA will announce whether it will withdraw its approval of Makena.

But the about-face from the expert panel about the drug's usefulness has left all sides trying to figure out their next steps.

On Jan. 9, AMAG announced that because of "uncertainty" over Makena, it would divest itself of two of its other drugs, including one that was approved by the FDA last summer. In a statement in which the drugmaker also announced plans for its chief executive, William Heiden, to step down, Heiden was quoted as saying that the ambiguity about Makena's future revenue "makes it challenging to invest in both our promising pipeline and in the physician and consumer marketing required to support these two new products."

The American College of Obstetricians and Gynecologists has said it will continue to monitor the issue but has not changed its guidance to doctors in the meantime. Makena remains the standard of care for many pregnant women who have given birth prematurely in the past.

As doctors stand by for the FDA's decision on withdrawing Makena from the market, many have suggested they will turn to compounding again if Makena disappears.

However, many withdrawn drugs are added to a federal list of drugs that may not be compounded due to failures of safety or efficacy—and if Makena is withdrawn, 17P could end up on that list, too.

That decision would also be made by the FDA, after receiving the recommendation of a different panel of experts on compounding, said Jeremy Kahn, an FDA spokesperson.

Dr. Kimberly Hickey, chief of maternal-fetal medicine at Walter Reed National Military Medical Center in Bethesda, Md., and a member of the FDA panel that voted for Makena to be withdrawn, said even if the drug is pulled from the market, obstetricians will seek out whatever version of its active ingredient remains for sale.

"People will look for progesterone wherever they can find it," she said

during the panel's meeting, referring to the hormone 17P mimics. "They're not just going to say, 'I'm not going to treat you.'"