FDA panel says preterm birth drug should be withdrawn

Makena has been given to hundreds of thousands of patients over the past 11 years. Susan Jaffe reports from Washington, DC.

The only treatment in the USA to prevent premature births should be withdrawn from the market because it is ineffective, according to the Food and Drug Administration's (FDA) Obstetrics, Reproductive and Urologic Drug Advisory Committee. The Oct 19 recommendation, which FDA officials support, has renewed scrutiny of a special drug approval process that raises patients' hopes by allowing them to take medications that have not been fully tested for efficacy and safety.

Makena, the brand name in the USA for hydroxyprogesterone caproate, has been prescribed for more than 350 000 patients over the past 11 years after receiving conditional approval. The federal Medicaid health insurance programme has paid an estimated US$700 million to provide the drug to its beneficiaries in just the past 3 years.

"My heart absolutely breaks for women who now have no option available to them, but it is worse to treat women with a drug that is not effective", said Mara McAdams-DeMarco, an Associate Professor of Surgery and Population Health at New York University and an advisory committee member. "It is a travesty that we're at this point in 2022."

"Pregnant people are an understudied population", said Anjali Kaimal, another committee member and Professor and Vice Chair of Clinical Operations in the Department of Obstetrics and Gynecology at the University of South Florida's Morsani College of Medicine. "That leaves both patients and practitioners without evidence regarding what treatments are safe and effective."

Makena received "accelerated approval" from the FDA in 2011, for people at risk of a preterm birth who had previously delivered a baby before 37 weeks' gestation. Congress authorised the FDA to make such preliminary decisions to speed up access to drugs for serious or life-threatening diseases that have few or no treatment alternatives. Approval is typically based on a clinical trial documenting the drug's beneficial impact on a biomarker or other surrogate related to the disease. Manufacturers must provide post-market clinical studies to determine whether the drug is beneficial.

The 3-year initial clinical trial of hydroxyprogesterone caproate, completed in 2002, included 468 women in the USA. It showed that women who took the drug had a lower rate of preterm births than those who took a placebo. A second study of 1708 women, mostly outside the USA, was completed in 2018, more than 5 years late. It failed to demonstrate that hydroxyprogesterone caproate reduces the risk of preterm births.

Allowing Makena to remain on the market would "up-end the intention behind the accelerated approval pathway, one that pairs earlier access for promising treatments with withdrawal if the drug does not pan out", Peter Stein, Director of the Office of New Drugs at FDA's Center for Drug Evaluation and Research, told the committee.

Covis Pharma, which makes Makena, said that the second study could not confirm the earlier findings because it was poorly designed and based on a population that was substantially different from the subjects in the first trial.

Nevertheless, Raghav Chari, the company's Chief Innovation Officer, told the committee that a potential beneficial effect was observed in some higher risk subgroups. He urged the committee to keep the drug on the market while a third study attempted to confirm "the higher risk population where Makena is most likely to be effective".

Looking for beneficial effects in subgroups in the second study is "a fishing expedition", said Susan Ellenberg, another committee member and Professor Emerita of Biostatistics, Medical Ethics, and Health Policy at the University of Pennsylvania's Perelman School of Medicine. "When you do these subgroup analyses, the chance of a false positive is very high." She said a third study would be needed to confirm any potential benefits in these subgroups.

The accelerated approval programme has received increasing critcism ever since the FDA used it in 2021 to approve aducanumab (Aduhelm), a treatment for Alzheimer's disease. The agency acted despite the objections of an advisory committee, which found that there was insufficient evidence that the drug would slow disease progression. The FDA gave the manufacturer 9 years to complete a post-approval confirmatory trial.

Makena is another example of how "sometimes the promise of accelerated approval doesn't work out", said Aaron Kesselheim, Professor of Medicine at Brigham and Women's Hospital and Harvard Medical School. He was one of three members of the aducanumab advisory committee who resigned in protest after the approval. "This shows why accelerated approval drugs need to have rigorous studies done in a timely fashion after approval", he said. "The FDA needs more authority and encouragement to act quickly on accelerated approval drugs when they don't live up to their promise."

FDA Commissioner Robert Califf and Chief Scientist Namandjé Bumpus are expected to issue a final decision on Makena early in 2023.

Susan Jaffe

For the **Health and Human Services Inspector General's investigation of the FDA accelerated approval process** see https://oig.hhs.gov/oei/reports/OEI-01-21-00401.pdf

For more on the **FDA approval of aducanumab** see **World Report** *Lancet* 2021; **398:** 12