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NEWS

Preterm births: US panel recommends withdrawal of prevention drug in controversial vote

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The BMJ

An independent advisory panel to the US Food and Drug Administration has recommended that approval should be removed for Makena (hydroxyprogesterone caproate), a drug used in the US to prevent preterm birth, because of a lack of evidence that it works.

In a meeting on 29 October the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee voted by nine to seven to withdraw approval for the drug. But the American College of Obstetricians and Gynecologists has warned that removing the drug from the market could be a mistake, and its manufacturer has claimed that five of the six obstetricians on the committee voted to keep Makena on the market.

The FDA is not bound by the committee's decision and will conduct its own review of the committee's feedback before making a final decision. However, the agency typically follows advisory panel recommendations.

In the UK, this treatment is not recommended by the National Institute for Health and Care Excellence and does not form part of routine care.

Similar outcomes

The review was undertaken in response to a trial published last month in the *American Journal of Perinatology*.[1] The paper—funded by the manufacturer AMAG Pharmaceuticals to show the drug's effectiveness—compared 1130 women who received Makena with 578 women who received a placebo. It reported no significant differences in the frequency of preterm birth at less than 35 weeks or in the frequency of fetal or early infant death. It also reported similar maternal outcomes between groups.

These findings seemed to go against the previous trial conducted by AMAG and published in 2003 by the *New England Journal of Medicine*.[2] That trial included just over 450 women and reported that Makena "significantly reduced" the risk of delivery at less than 37 weeks' gestation (incidence 36.3% in the progesterone group *v* 54.9% in the placebo group; relative risk 0.66 (95% confidence interval 0.54 to 0.81)), delivery at less than 35 weeks' gestation (incidence 20.6% *v* 30.7%; relative risk 0.67 (0.48 to 0.93)), and delivery at less than 32 weeks' gestation (11.4% *v* 19.6%; relative risk 0.58 (0.37 to 0.91)).

The advisory committee was asked to consider the findings from the two trials and to decide whether there was "substantial evidence of effectiveness of Makena in reducing the risk of recurrent preterm birth": 13 committee members said no, and three said yes.

They were then asked to decide whether the FDA should pursue withdrawal of approval for Makena, leave the drug on the market and require a new confirmatory trial, or leave it on the market without requiring a new confirmatory trial.

The committee voted for withdrawal with nine of the 16 votes; however, the seven others voted to leave Makena on the market and require a new trial.

Difficult comparison

This split decision has caused controversy. AMAG released a statement saying that it "agrees with several committee members who voiced concern that withdrawal of Makena would leave providers with no safe treatment options for pregnant women."[3]

Christopher Zahn, vice president for practice for the American College of Obstetricians and Gynecologists, said that the more recent study, which showed poor results, included a far higher percentage of women at low risk of preterm delivery, making a direct comparison with the first study difficult.

Zahn told National Public Radio[4] that the conflicting findings highlighted the need for further confirmatory research, but he added that, because Makena was the only medicine currently available to prevent preterm birth, removing it would remove all options for women and could lead to an increase in premature births.

However, others such as Public Citizen, a non-profit consumer advocacy group, have been campaigning for the FDA to ban Makena.[5] Meena Aladdin, health researcher at Public Citizen's Health Research Group, testified in front of the committee.

She said, "Maintaining approval of Makena in the absence of any clinical benefits being demonstrated by [the two trials] would make a mockery of the more than 50 year FDA legal standard requiring substantial evidence of a drug's effectiveness.

"Therefore, Public Citizen strongly urges the committee to recommend that the FDA withdraw approval of Makena from the market, as it fails to provide any clinical benefit."

1 Blackwell S, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial. Oct 2019. https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0039-3400227.pdf.

2 Meis PJ, Klebanoff M, Thom E, etal. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm

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3 AMAG Pharmaceuticals. AMAG reports on FDA advisory committee meeting for Makena (hydroxyprogesterone caproate injection). Oct 2019. https://www.amagpharma.com/news/amag-reports-on-fda-advisory-committee-meeting-for-makena-hydroxyprogesterone-caproate-injection/.

4 Neighmond P. Controversy kicks up over a drug meant to prevent premature birth. *NPR* 2019 Nov. https://www.npr.org/sections/health-shots/2019/11/04/776172053/controversy-kicks-up-over-a-drug-meant-to-prevent-preterm-birth.

5 Aladdin M. Food and Drug Administration Bone, Reproductive and Urologic Drug Advisory Committee regarding Makena: a lack of substantial evidence of effectiveness testimony of Meena M Aladdin, PhD, health researcher, Public Citizen's Health Research Group. Public Citizen. 2019. https://www.citizen.org/wp-content/uploads/2494a.pdf.

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