

FDA Approves Drug for Recurrent Preterm Birth

Progesterone injection 17P 'will be widely available,' nearly 5 years after an FDA panel's recommendation.

BY JENNIE SMITH

The Food and Drug Administration has approved 17-alpha-hydroxyprogesterone caproate, a progesterone injection also known as 17P, for the prevention of recurrent preterm birth in women with singleton pregnancies.

The FDA said in a press statement that it had approved 17P (Makena) under the

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agency's accelerated approval regulations that allow drugs to be approved based on a surrogate end point benefit that is "reasonably likely to predict a clinical benefit."

Hydroxyprogesterone caproate was initially approved in 1956 for the treatment and prevention of recurrent miscarriage, among other indications, but was withdrawn in 2000 because of manufacturing problems. Hospital pharmacies continued to mix the compound, and it remained available in many settings.

The March of Dimes said in a statement that it welcomed 17P's approval. "Prior to today's approval of Makena, health care providers ordered prescriptions of 17P from compounding pharmacies; however, many eligible patients faced logistical and financial barriers to access. FDA approval means the drug now will be widely available."

It also should raise patient confidence. "Patients are much more accepting and comfortable when you can tell them it's FDA approved," Dr. Laura E. Riley, medical director of labor and delivery at Massachusetts General Hospital in Boston, said in an interview.

The drug was first marketed in the 1950s as Delalutin. It was resubmitted to the FDA in 2006 as Gestiva by a California firm, and will now be marketed by its current manufacturer, the Massachusetts-based Hologic, as Makena.

The approval comes nearly 5 years after an FDA advisory panel voted in 17P's favor, based on results from a publicly funded, randomized, double-blind, placebo-controlled trial of 463 women with at least one preterm delivery (N. Engl. J. Med. 2003;348:2379-85).

That trial showed that women receiving weekly injections of 250 mg of 17P, starting at 20 weeks and continuing to 36 weeks or delivery, saw a 24% reduced risk of delivery before 37 weeks,

compared with the control group.

The study also showed reductions in the rates of preterm delivery before 35 weeks and before 32 weeks in the treatment arm.

After the FDA panel's vote in August 2006, the agency demanded further safety studies, including now-completed studies of children born to women taking 17P, from the medicine's then-devel-

oper, which later sold its rights to 17P. In 2010 the drug's current developer, Hologic, resubmitted its filing for 17P.

The FDA said that the drug's approval comes with the manufacturer's responsibility to complete ongoing confirmatory studies, including a new infant follow-up study, expected to end in 2018 and to include between 580 and 750 infants. ■

Availability a 'Great Advancement'

VIEW ON THE NEWS

Dr. Sarah J. Kilpatrick called the FDA approval of 17-alpha-hydroxyprogesterone caproate a "great advancement." Before the approval, special pharmacies had to compound the drug, also known as 17P. She said that she's "very confident" with the amount of long-term data about progesterone, which is a normal hormone that the body produces during pregnancy.

"It was not as accessible as presumably it will be now," Dr. Kilpatrick said in an interview.

In addition to wider availability, another advantage is greater accuracy in dosage, because with compounding pharmacies there was always the potential for error, she said.

Before the drug's approval, insurance did not cover the cost in some states, according to Dr. Kil-

patrick. "Hopefully, with an FDA approval, that will not be a problem now." Even so, she added that the cost of 20 weeks of progesterone injections is still less than the cost of a preterm baby in the hospital.

There may be a possible downside to the drug's approval. "If it's easier to obtain, it could be used for the wrong people," she said. Progesterone should only be used to prevent preterm delivery – not treat it – and only for women who have had prior preterm deliveries.

DR. KILPATRICK is the chair of the department of obstetrics and gynecology at Cedars-Sinai Medical Center in Los Angeles. She is also a past president of the Society for Maternal-Fetal Medicine. Dr. Kilpatrick reported having no relevant financial disclosures.

AMG 479 Fails to Stem Resistance to Endocrine Therapy

BY KERRI WACHTER

FROM THE SAN ANTONIO BREAST CANCER SYMPOSIUM

SAN ANTONIO – The investigational agent AMG 479 failed to alter resistance to hormonal therapy in patients with endocrine therapy-resistant, hormone receptor-positive metastatic breast cancer in the adjuvant setting. Indeed, the drug showed a trend toward worse progres-

AMG 479 with fulvestrant or exemestane does not appear to delay or reverse resistance to hormonal therapy in hormone receptor-positive metastatic breast cancer patients.

sion-free survival and objective response in a phase II trial.

When AMG 479 was paired with exemestane or fulvestrant, patients in the experimental arm had a median progression-free survival of 3.9 months, compared with 5.7 months for patients on exemestane or ful-

vestrant alone, a nonsignificant difference.

"AMG 479 in combination with either fulvestrant or exemestane does not appear to delay or reverse resistance to hormonal therapy in this population of patients with prior endocrine therapy-resistant hormone receptor-positive metastatic breast cancer," Dr. Peter A. Kaufman said at the symposium.

AMG 479 is an investigational fully human monoclonal antibody antagonist of the type I insulin-like growth factor (IGF-I) receptor, blocking the binding of both IGF-I and IGF-II to the receptor.

Resistance to hormonal therapy is thought to possibly occur through increased IGF-I receptor (IGF-IR) signaling, and the researchers hypothesized that inhibition of the IGF-IR signaling pathway may enhance the activity of a second line of hormonal therapy in breast cancer

VITALS

Major Finding: When paired with exemestane or fulvestrant, AMG 479 produced a median progression-free survival of 3.9 months, compared with 5.7 months for patients on exemestane or fulvestrant alone (HR, 1.17; $P = .435$).

Data Source: A phase II study in 156 women with hormone receptor-positive metastatic or locally advanced breast cancer.

Disclosures: Dr. Kaufman received grant support from trial sponsor Amgen Inc. He has also disclosed that he is a shareholder of Amgen. Three of the study authors are employees of Amgen.

patients, according to Dr. Kaufman of Dartmouth-Hitchcock Medical Center in Lebanon, N.H.

In this study, patients were randomized to receive either treatment with AMG 479 along with exemestane or fulvestrant, or placebo plus exemestane or fulvestrant. (The choice was left to the investigator.) Stratification factors included which hormonal therapy the patient received, as well as the extent of disease.

AMG 479 (12 mg/kg) and placebo were given intravenously every 2 weeks. Exemestane (25 mg) was given orally every day; oral fulvestrant

was given in a dose of 500 mg on day 1 and then at a dose of 250 mg on days 15 and 29 and every 4 weeks thereafter.

The primary end point was progression-free survival, as measured by modified RECIST (Response Evaluation Criteria in Solid Tumors) v1.0.

In all, 106 women were included in the AMG 479 group and 50 in the placebo group. In the treatment group, 98% of women were estrogen receptor positive, 70% were progesterone receptor positive, and 7% were HER2 positive.

In the placebo group, 94% of women were ER positive, 70% were PR positive, and 2% were

HER2 positive.

Median progression-free survival among women who received exemestane was 4.8 months with AMG 479 and 7.3 months with placebo (HR, 1.31). Among women who received fulvestrant, it was 3.7 months and 5.4, respectively (HR, 1.11).

"There really is no difference in the overall response rate," said Dr. Kaufman. The objective response rate for patients in the AMG 479 group was 8% vs. 13% for those in the control group.

The overall clinical benefit rate was 35% for women on AMG 479 and 31% of women on placebo, which was not significant.

Serious adverse events occurred in 25% of patients who were given AMG 479 and 18% of the placebo group. "We saw no meaningful difference in any of those symptoms," said Dr. Kaufman. He did note elevated but nonsignificant rates of hyperglycemia, neutropenia, and thrombocytopenia for those on AMG, however. ■