

PRIOR AUTHORIZATION POLICY

- POLICY:** Makena (hydroxyprogesterone caproate) Prior Authorization Policy
- Makena® (hydroxyprogesterone caproate injection [subcutaneous and intramuscular] – AMAG, generics [intramuscular only])

REVIEW DATE: 11/16/2022

OVERVIEW

Makena is an injectable progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.¹ The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no clinical trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena is administered by the intramuscular (IM) route at a dose of 250 mg (1 mL) once weekly or by the subcutaneous route using an auto-injector at a dose of 275 mg (1.1 mL) once weekly; both products require administration by a healthcare professional. Generic Makena, hydroxyprogesterone caproate injection, is available for IM administration only. Makena is administered beginning between 16 weeks, 0 days and 20 weeks, 6 days gestation and continued once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first.

Makena was originally approved in 2011 via an accelerated approval (based on a study funded by the National Institute of Health that was published in 2003 [the Meis trial⁸]).⁹ After examination of the Meis trial, the FDA concluded there was substantial evidence of effectiveness that Makena reduced preterm birth prior to 37 weeks and that this surrogate endpoint was reasonably likely to predict clinical benefit (clinical benefit being a confirmation of reduced fetal or neonatal deaths). As part of the accelerated approval, a confirmatory trial was required to verify Makena's clinical benefit (the Prevent Recurrent Preterm Birth in Singleton Gestations [PROLONG¹⁰] trial). In March 2019 the manufacturer (AMAG) announced that the PROLONG trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the coprimary endpoints (which involved preterm birth prior to 35 weeks and a neonatal morbidity composite index).¹¹ On October 29, 2019, the FDA held an Advisory Committee Meeting to discuss the results of PROLONG. On October 17, 2022 through October 19, 2022, a second hearing, requested by Covis (and granted by the FDA), took place. At this meeting, the Advisory Committee recommended to withdrawal Makena and its generic from the market.¹² Currently, the FDA has not made a final determination regarding removal of Makena from the market.

GUIDELINES

The American College of Obstetricians and Gynecologists (ACOG) continues to recommend progesterone supplementation (either vaginal or IM) for women with a singleton pregnancy and a prior spontaneous preterm birth.² ACOG put out a statement on October 20, 2022,¹³ which notes that it is aware of the recommendation to withdrawal Makena and its generics from the market. ACOG additionally stated that, pending an FDA final determination on the status of Makena, ACOG's current guidance will remain in effect. The Society of Maternal-Fetal Medicine (SMFM) statement on the use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth (2019) states it is reasonable to use 17-alpha hydroxyprogesterone caproate in women with a very-high-risk profile.³ A SMFM statement (2021) notes that 17-alpha hydroxyprogesterone caproate should be considered in women with a singleton

gestation and a history of prior pre-term birth.⁴ For women at risk of recurrent spontaneous preterm birth, the risk-benefit discussion should incorporate a shared decision-making approach.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Makena (hydroxyprogesterone caproate). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of hydroxyprogesterone caproate (Makane, generics) is recommended in those who meet the following criteria:

FDA-Approved Indication

1. Reduce Risk of Preterm Birth. Approve for up to 5 months of therapy (21 injections) in patients who meet the following criteria (A, B, and C):

A) Patient is pregnant with a singleton pregnancy; AND

B) Patient has a history of singleton spontaneous preterm birth prior to 37 weeks gestation; AND

C) Treatment will begin in patients who are at least 16 weeks, 0 days of gestation, according to the prescribing physician or other prescriber.

Note: In cases where there was an inaccuracy in dating the pregnancy, a one-month authorization may be granted to patients who have already received 21 injections and are < 37 weeks pregnant.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Makena (hydroxyprogesterone caproate (Makena, generics) is not recommended in the following situations:

1. History of a Threatened Preterm Birth. Makena is not indicated in pregnant women who experienced a past threatened preterm birth but delivered a full-term infant after 36 completed weeks of gestation.¹

2. Infertility. Some studies have evaluated hydroxyprogesterone caproate as the progesterone used in *in vitro* fertilization.^{5,6} However, progesterone in oil or vaginally administered progesterone are mentioned for use during the luteal phase and in early pregnancy in the treatment of infertility by an educational bulletin by the Practice Committee of the American Society of Reproductive Medicine.⁷

3. Patients Pregnant with Multiple Gestations. Makena is not indicated in patients pregnant with multiple gestations (e.g., twins, triplets, or other multiples).¹

4. Pregnant Patient with Short Cervix Without a History of a Prior Singleton Spontaneous Preterm Birth. Makena is not indicated for use in pregnant women with short cervix and no of singleton spontaneous pre-term birth prior to 37 weeks gestation.¹

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Makena® for intramuscular or subcutaneous use [prescribing information]. Waltham, MA: AMAG Pharmaceuticals; February 2018.
2. Prediction and Prevention of Spontaneous Preterm Birth. American College of Obstetricians and Gynecologists Practice Bulletin. Number 234. August 2021. Available at: <https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2021/08/prediction-and-prevention-of-spontaneous-preterm-birth>. Accessed on November 22, 2021.
3. The Society for Maternal-Fetal Medicine (SMFM): Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. SMFM Statement 2019. Available at: <https://www.smfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth>. Accessed on October 22, 2021.
4. SMFM Statement: Response to EPPPIC and considerations of the use of progestogens for the prevention of preterm birth. SMFM Statement 2021. Available at: <https://www.smfm.org/publications/383-smfm-statement-response-to-epppic-and-considerations-of-the-use-of-progestogens-for-the-prevention-of-preterm-birth>. Accessed on October 22, 2021.
5. Rjosk HK, Abendstein BJ, Kreuzer E, Schwärzler P. Preliminary experience with steroidal ovarian suppression for prevention of severe ovarian hyperstimulation syndrome in IVF patients. *Hum Fertil (Camb)*. 2001;4(4):246-248.
6. Costabile L, Gerli S, Manna C, et al. A prospective randomized study comparing intramuscular progesterone and 17alpha-hydroxyprogesterone caproate in patients undergoing *in vitro* fertilization-embryo transfer cycles. *Fertil Steril*. 2001;76(2):394-396.
7. Fritz M, Adamson GD, Barnhart K, et al. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. *Fertil Steril*. 2008;89(4):789-792.
8. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm birth delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med*. 2003;348(24):2379-85.
9. US FDA Makena (hydroxyprogesterone caproate injection) Information. August 29, 2022. Available at: [Makena \(hydroxyprogesterone caproate injection\) Information | FDA](#). Accessed on November 7, 2022.
10. Blackwell SC, Gyamfi-Bannerman C, Biggio Jr. JR, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG Study): A multicenter, international, randomized double-blind trial. *Am J Perinatol*. 2020;37(2):127-136.
11. AMAG Pharmaceuticals announces topline results from the PROLONG trial evaluating Makena (hydroxyprogesterone caproate injection) [press release]. Waltham, MA: AMAG Pharmaceuticals; March 8, 2019. Available at: [AMAG PHARMACEUTICALS ANNOUNCES TOPLINE RESULTS FROM THE PROLONG TRIAL EVALUATING MAKENA® \(hydroxyprogesterone caproate injection\) – AMAG Pharmaceuticals](#). Accessed on November 7, 2022.
12. Endpoints news. Zachary Brennan. October 19, 2022. Available at: <https://endpts.com/breaking-adcomm-again-votes-against-keeping-covis-pre-term-birth-drug-on-the-market/>. Accessed on November 7, 2022.
13. ACOG statement on FDA Committee recommendation to withdraw 17p Hydroxyprogesterone caproate. October 22, 2022. Available at: [ACOG Statement on FDA Committee Recommendation to Withdraw 17p Hydroxyprogesterone Caproate | ACOG](#). Accessed on November 5, 2022.