POLICY: Makena® (hydroxyprogesterone caproate injection [subcutaneous and intramuscular] – AMAG, Pharmaceuticals, Inc.; generics [intramuscular only])

APPROVAL DATE: 09/04/2019

OVERVIEW

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy that have a history of singleton spontaneous preterm birth (SPTB).[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. Limitations of Use: 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 intramuscular (IM) route at a dose of 250 mg (1 mL) once weekly or by subcutaneously (SC) 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 once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occur first.

Clinical Efficacy

The efficacy and safety of Makena was established in one randomized, double-blind, multicenter, vehicle-controlled, pivotal study in women between the ages of 16 and 43 years.[1] Women were pregnant with a singleton pregnancy with a documented history of singleton SPTB, defined as delivery < 37 weeks gestation following spontaneous preterm labor or premature rupture of membranes (PROM). Major exclusion criteria included a pregnancy with multiple gestations. Patients were randomized between 16 weeks, 0 days gestation and 20 weeks, 6 days gestation. The primary endpoint was the proportion of women in each treatment arm who delivered at < 37 weeks gestation. The study took place in the US and was conducted with an investigational formulation of hydroxyprogesterone caproate identical to Makena.[2] Patients were assigned to treatment with Makena, 250 mg in 1 mL (n = 310), or vehicle (castor oil) [n = 153] in a 2:1 ratio.

There was a statistically significant reduction in the rate of delivery before 37 weeks gestation in patients treated with Makena compared with vehicle. The rates of delivery prior to Week 37 were similar for Black and non-Black women.[2] Among women of similar risk, the number-needed-to-treat (NNT) was 5 to 6 women (95% confidence interval [CI]: 3.6, 11.1) to prevent one preterm delivery prior to 37 weeks gestation. Patients treated with Makena also had statistically significant reductions in the rates of delivery prior to 35 weeks and 32 weeks gestation. A small increase in the rate of miscarriage and stillbirth occurred in the Makena group; however, this difference was not statistically significant compared with the patients treated with vehicle.

The approval of Makena for SC use was based on usability studies and one pharmacokinetic study that confirmed bioequivalence between the IM dosing regimen and the SC dosing regimen.[3]

Dosing Information

Makena is supplied as a 5 mL multi-dose vial and a preservative-free 1 mL single-dose vial, each containing 250 mg/mL of hydroxyprogesterone caproate (17P) (for IM use), and as a 1.1 mL single-patient-use auto-injector containing 275 mg of 17P (for SC use).[1] The intramuscular product is available as a generic in the 1 mL single-dose vials and the 5 mL multi-dose vials.

Guidelines

The Society for Maternal-Fetal Medicine (SMFM) published guidelines (2012, reaffirmed 2014) regarding the use of progesterone in preterm birth prevention.[4] Intramuscular 17 alpha hydroxyprogesterone caproate (17P) is recommended for use in women with singleton pregnancy with prior history of spontaneous preterm birth (approved indication). A SMFM statement (2017) continued to recommend all women with a prior spontaneous preterm birth of a singleton pregnancy be offered 17P therapy in subsequent pregnancy with a singleton gestation.[5] Also included in this statement are discussions about women with a prior SPTB who start 17P and subsequently develop cervical shortening. It is unknown whether there is any benefit to change progestogen to vaginal progesterone (with or without cervical cerclage placement) in this circumstance. Based on data regarding the lack of benefit of vaginal progesterone in women with a history of a prior SPTB, the SMFM recommends the continuation of 17P in women with a history of a prior SPTB throughout pregnancy despite the development of cervical shortening (with or without cervical cerclage placement).[5]

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Makena for IM and SC injection and generics. Approval is recommended for those who meet the Criteria and Dosing for the listed indication. Requests for dosing outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Makena and generics are recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

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 (SPTB) 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 of the pregnancy, a one-month authorization may be granted to patients who have already received 21 injections and are < 37 weeks pregnant.

   Dosing. Approve the following dosing (A or B):
   - **A)** Makena (or generics) given by the intramuscular route: 250 mg once weekly; OR
   - **B)** Makena given by the subcutaneous route: 275 mg once weekly.

NOTE: According to the Makena prescribing information, treatment should begin between 16 weeks, 0 days and 20 weeks, 6 days gestation. Weekly administration of Makena should continue until Week 37 of gestation or delivery, whichever occurs first.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Makena (SC and IM) and generics have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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.[6-7] 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.[8]

3. **Patients Pregnant with Multiple Gestations.** Makena is <u>not</u> indicated in patients pregnant with multiple gestations (e.g., twins, triplets, or other multiples).[1] Hydroxyprogesterone caproate has failed to decrease preterm birth in women pregnant with twins and triplets.[9-11] In a randomized, double-blind, placebo-controlled study in 661 women, delivery or fetal death prior to Week 35 occurred in 41.5% of women pregnant with twins in the hydroxyprogesterone caproate group compared to 37.3% of those pregnant with twins in the placebo group (relative risk [RR]: 1.1; 95% CI: 0.9, 1.5).[9] In a randomized, double-blind, placebo-controlled study in women pregnant with triplets (n = 134), treatment with hydroxyprogesterone caproate did not affect the rate of delivery or fetal loss prior to Week 35 (RR: 1.0; 95% CI: 0.9, 1.1).[10] In another randomized, double-blind, placebo-controlled study, 56 women pregnant with triplets were assigned to treatment with hydroxyprogesterone caproate and 25 were assigned to placebo.[11] There was not a significant difference in delivery prior to Week 28, 32, or 35 in either treatment group; however, significantly more stillbirths/miscarriages occurred in the hydroxyprogesterone group (8%) compared to the placebo group (0%) (P = 0.01). In one randomized, double-blind, controlled trial in unselected women with twin pregnancies, IM 17P (not Makena; another marketed product in Europe) did not reduce preterm birth before 37 weeks of gestation; however, it did reduce neonatal morbidity parameters and also increased birthweight.[12] Other studies in women with multiple gestations (primarily twin gestations) have not shown a prolonged gestation or a reduction in neonatal morbidity with 17P compared to placebo.[13-15]

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 <u>no</u> history of singleton SPTB prior to 37 weeks gestation. IM 17P is recommended for use in singleton pregnancies with prior spontaneous preterm birth (approved indication).[4,5]

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

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HISTORY

Type of Revision	Summary of Changes	Approval Date
Annual revision	--	08/10/2016
Annual revision	No criteria changes	08/16/2017
Selected revision	Added Makena for subcutaneous route; Added Without a History of a Prior Singleton SPTB to the exclusion Pregnant Patient with Short Cervix	03/07/2018
Annual revision	No criteria changes. Generic intramuscular product added.	08/29/2018
Annual revision	No criteria changes. Formatting changes.	09/04/2019