New Drug Overview
Makena (hydroxyprogesterone caproate)

INTRODUCTION

- Preterm birth is defined as delivery between 20 and 37 weeks of gestation and preterm delivery is the leading cause of perinatal morbidity and mortality. Preterm labor is the most common reason for antenatal hospitalization. The diagnosis is generally based on criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of ≥ 2 cm. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation (*Iams 2014, Fuchs et al 2004, American College of Obstetricians and Gynecologists [ACOG] 2016).*
- In the United States (US), the annual rate of preterm births was estimated at 11.7% in 2011, which was nearly twice the rate in European nations. Preterm birth in the US accounts for 35% of deaths in the first year of life (*Iams 2014).* Premature infants have a higher risk of mortality in their first year of life, and those that survive have a higher risk of hospital readmissions and long-term impairment (*Dodd et al 2013, Manuck et al 2016, Norwitz et al 2017*).
- The strongest risk factor for preterm birth is a prior history of preterm birth. Other major risk factors for spontaneous preterm birth in cases of singleton pregnancies include Black maternal race, previous pregnancy with an adverse outcome, genitourinary infection, smoking, extremes of body weight, and social disadvantage. Maternal depression, pre-pregnancy stress, poor diet, assisted fertility, and periodontal disease are also associated with preterm birth (*Iams 2014, Manuck et al 2016, Norwitz et al 2017*).
- Progesterone is an important natural hormone in the process of labor. Progesterone is naturally produced by the corpus luteum and is critical in early pregnancy and labor begins when the ratio of progesterone activity to estrogen activity is reversed or when progesterone activity is blocked, resulting in cervical ripening and uterine contractility (*Iams 2014, Meis et al 2003, Norwitz et al 2017*).
- Hydroxyprogesterone caproate (or 17-alpha [α]-hydroxyprogesterone caproate, HPC, or 17P) is a natural metabolite of progesterone that was first approved by the Food and Drug Administration (FDA) in 1956 as Delalutin for several indications. Delalutin was withdrawn from the market in 2000 for reasons unrelated to efficacy or safety. After market withdrawal, hydroxyprogesterone caproate was compounded by pharmacies into an injectable formulation. In February 2011, Makena was FDA-approved as an orphan drug under the FDA's accelerated approval process (*Clinical Pharmacology 2017*, *FDA summary review 2011*).
- Progesterone is available in the US in natural and synthetic forms and intramuscular (IM), oral, and vaginal routes of administration. Only hydroxyprogesterone caproate is FDA-approved for the reduction in the risk of preterm birth; however, there is compendia support for the use of progesterone off-label for this indication (*Clinical Pharmacology 2017*). Different routes of administration have different pharmacokinetic and pharmacodynamic effects. Experts concede that more information is needed regarding the appropriate dose, mode of administration, gestation age to initiate therapy, and duration of therapy for treatment (*Caritis et al 2014, Dodd et al 2013, Manuck et al 2016*).
- Medispan class: Progestins; Hydroxyprogesterone

INDICATION

- Hydroxyprogesterone caproate injection is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.
  - Limitation of use: Makena is not intended for use in women with multiple gestations or other risk factors for preterm birth.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The approval of Makena was based primarily on a multicenter (MC), randomized, double-blinded (DB), placebo controlled trial conducted by the National Institute of Child Health and Human Development Maternal-Fetal Medicine

Unit (NICHD-MFMU). The study was published, but not designed or intended for marketing approval (*FDA summary review 2011*).
  - In one cohort (N = 463), hydroxyprogesterone caproate was evaluated at 16 to 20 weeks of gestation in very high-risk women with a documented history of singleton spontaneous preterm delivery. Results demonstrated a significantly reduced risk of delivery at < 37 weeks of gestation for hydroxyprogesterone caproate vs placebo (36.3 vs 54.9%, respectively; relative risk [RR], 0.66; 95% confidence interval [CI], 0.54 to 0.81), at < 35 weeks (20.6 vs 30.7%, respectively; RR, 0.67; 95% CI, 0.48 to 0.93), and at < 32 weeks (11.4 vs 19.6%, respectively; RR, 0.58; 95% CI, 0.37 to 0.91). There was no significant difference in neonatal deaths (2.6 vs. 5.9%, respectively; RR, 0.44; 95% CI, 0.17 to 1.13); however, the study was not powered to assess this endpoint. Infants of women treated with hydroxyprogesterone had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage (any Grade), and need for supplemental oxygen (*Meis et al 2003*, *FDA summary review 2011*).
- In a study in a home nursing program setting (N = 5493), compounded 17-*α*-hydroxyprogesterone was safe and effective, with preterm birth rates similar to those reported in the NICHD-MFMU study. No pregnancy outcome differences were noted based on the gestational age at which 17-*α*-hydroxyprogesterone caproate was initiated, either overall or within the Black and non-Black race groups. Miscarriage, stillbirth, or neonatal death was reported in 0.8% of cases, and there was no difference in these outcomes based on the gestational age at which 17-*α*-hydroxyprogesterone caproate was initiated. In an analysis performed based on race, there was a significant decrease in delivery at 35 weeks to 36 weeks in Black women vs non-Black women, (17.3 vs 21.7%, respectively) and a significant increase in delivery < 35 weeks (19.2 vs 12%, respectively). (*FDA summary review 2011, Meis et al 2003, Sibai et al 2012).*
- One meta-analysis (MA) reviewed 39 randomized trials of progesterone (IM, oral, or vaginal formulations) administration for the prevention of preterm birth in women at increased risk. A total of 11 trials (N = 1899) included women with a history of spontaneous preterm birth, and results demonstrated progesterone supplementation lowered the risks of preterm birth (including birth < 34 to 37 weeks, use of assisted ventilation, necrotizing enterocolitis, and neonatal intensive care unit admission), in addition to neonatal morbidities compared to placebo. Differences in the risks of intraventricular hemorrhage, neonatal sepsis, and retinopathy of prematurity did not differ significantly from placebo (*Dodd et al 2013*).
- Additional studies have supported the use of hydroxyprogesterone caproate for spontaneous preterm birth, although the results the optimal time to administer is highly debated. One study examined the administration of hydroxyprogesterone caproate 250 mg IM weekly starting between weeks 16 and 20 and continuing through week 36 in high-risk women, and demonstrated a decreased incidence of recurrent preterm birth (*Meis et al 2004*). Another study replicated the findings using vaginal progesterone suppositories (100 mg) (*da Fonseca et al 2003).* However, progesterone supplementation in women whose previous preterm birth occurred beyond 34 weeks produced similar rates of preterm delivery compared with placebo based on a secondary analysis of *Meis et al 2003* (*Spong et al 2005*).
- Compared to placebo, prophylactic IM weekly injections of hydroxyprogesterone caproate did not prolong pregnancy until a favorable gestation age or fetal lung maturity (3 vs 8%) or improve perinatal outcomes when given to mothers with singleton pregnancies, gestational age 23 to 30 weeks, with spontaneous preterm rupture of membranes. The randomized study (N = 152) was terminated early. There were no significant between-group differences observed in the days from randomization to delivery, gestational age at delivery, or any neonatal outcome (eg, neonatal death, respiratory distress syndrome, stage 2 or 3 necrotizing enterocolitis). A numerical increase in cesarean deliveries with hydroxyprogesterone caproate was observed (60 vs 44%); however, this was not statistically significant (*Combs et al 2015*).
- Very few studies have been conducted head-to-head comparing IM formulations to other formulations of progesterone therapy. The following summarizes current outcomes:
  - One prospective, randomized, open-label (OL) trial compared progesterone IM 250 mg once weekly (manufactured as Proluton Depot, manufactured by Bayer Schering Pharma AG, Germany; not available in the US) to vaginal progesterone 90 mg once daily gel in 518 women with a history of preterm birth and a current singleton pregnancy. Patients receiving vaginal progesterone experienced a significantly lower rate of preterm birth at < 34 weeks vs those treated with progesterone IM (16.6 vs 25.7%; odds ratio [OR], 0.58; 95% CI, 0.37 to 0.89; p = 0.02) (*Maher et al 2013*).
  - Another prospective RCT compared hydroxyprogesterone caproate IM 250 mg once weekly to vaginal progesterone suppositories 400 mg daily as prevention of preterm birth in 304 women with a sonographically short cervix. The women were between 16 and 24 gestational weeks with a cervical length of < 25 mm. The rates of preterm birth were

not statistically significantly different between groups (10.4% in the progesterone suppository group vs 14% in the hydroxyprogesterone caproate IM group; p = 0.416) (*Pirjani et al 2017*).
  - *Eliminian et al* compared hydroxyprogesterone caproate IM 250 mg once weekly to vaginal progesterone suppositories 100 mg daily in 145 women with singleton pregnancies ranging from 16 to 20 weeks of gestation and a history of spontaneous preterm birth. Results demonstrated similar efficacy in reducing the rate of recurrent preterm birth between agents (37.9% in the progesterone suppository group vs 43.9% in the hydroxyprogesterone caproate IM group; p = 0.50) (*Eliminian et al 2016*).
- One MA of 3 RCTs comprising 680 women assessed the benefit of vaginal progesterone to hydroxyprogesterone caproate IM for the prevention of recurrent spontaneous preterm birth in singleton gestations. Studies included vaginal progesterone in doses ranging from 90 mg to 200 mg daily vs hydroxyprogesterone caproate IM 250 mg once weekly. In women with a previous spontaneous preterm birth, vaginal progesterone demonstrated lower rates of spontaneous preterm birth < 34 weeks vs hydroxyprogesterone caproate IM (17.5 vs 25.0%; RR, 0.71; 95% CI, 0.53 to 0.95). Additionally, lower rates of adverse events were reported in the vaginal progesterone group vs hydroxyprogesterone caproate IM (7.1 vs 13.2%; RR, 0.53; 95% CI, 0.31 to 0.91). Although daily vaginal progesterone starting at 16 weeks of gestation appeared to be better than hydroxyprogesterone caproate IM, conclusions were based mainly on low quality evidence. More large comparative trials are needed to validate superiority of one formulation over the other for all pregnancies at high risk for preterm birth (*Saccone et al 2017*).
- Progesterone may not be effective in unselected multiple gestations, which may in part be due to the lack of influence progesterone changes impart on multiple gestations compared to singleton (*Norwitz et al 2017*). In a 2017 MA of unselected twin gestations, neither IM nor vaginal progesterone improved preterm or neonatal outcomes. Other publications have supported that hydroxyprogesterone caproate IM may not have benefit in women with twin pregnancies and a short cervix or in asymptomatic women with triplet pregnancies, and some publications concluded that IM formulations may increase adverse perinatal outcomes in twin pregnancies (*Combs et al 2016, Dodd et al 2017, Schuit et al 2015, Senat et al 2013*).
  - Two trials in which women with singleton gestations and a short cervical length were randomly assigned to weekly hydroxyprogesterone caproate IM 250 mg or 500 mg vs placebo through 36 weeks reported that treatment with hydroxyprogesterone caproate did not reduce the risk of preterm birth in women with a short cervix and other risk factors for preterm delivery, such as previous preterm birth, cervical surgery, uterine anomalies, or prenatal diethylstilbestrol (DES) exposure. The frequency of preterm birth at < 37 weeks did not differ from placebo (25.1 vs 24.2%; RR, 1.03; 95% CI, 0.79 to 1.35) (*Grobman et al 2012*). In *Winer et al 2015*, after enrolling 105 patients an interim analysis demonstrated a lack of efficacy for hydroxyprogesterone caproate IM in prolonging pregnancy. There may have been methodological issues that influenced outcomes. Both trials were stopped before completion because of lack of efficacy at the scheduled interim analysis. Also *Grobman et al 2012* was limited to nulliparous women with a short cervix while *Winer et al 2015* included women with both a short cervix and risk factors for preterm birth (*Grobman et al 2012, Winer et al 2015*).

CLINICAL GUIDELINES

- **Note**: Makena (hydroxyprogesterone caproate) was FDA-approved in February 2011. Prior to the approval, compounding pharmacies were supplying hydroxyprogesterone caproate for this use. The FDA has recommended that when an FDA-approved drug is commercially available, the commercially available product be used instead of a compounded form. However, the FDA is not aware of any scientifically reliable evidence demonstrating that compounding 17P without a preservative or in an oil base different than the one used in Makena produces a significant difference for an identifiable group of patients (aside from the rare patient who is known to be allergic to either the preservative or the oil base). Trials have evaluated compounded drug use. Although compounded hydroxyprogesterone caproate preparations may be tailored to an individual patient's particular medical needs, practitioners should be aware of regulation and quality concerns related to this practice. (*FDA 2012*).

- **American College of Obstetricians and Gynecologists** (*ACOG 2012*, *ACOG 2016*)
  - Women with a prior spontaneous preterm birth should be evaluated by obtaining a detailed medical history, reviewing comprehensively aspects of all previous pregnancies, reviewing risk factors, and determining their candidacy for prophylactic interventions, such as progesterone supplementation, cervical cerclage, or both.

- ACOG recommends that progesterone supplementation be limited to women with a singleton pregnancy and a previous history of spontaneous preterm birth, starting at 16 to 24 weeks of gestation, to reduce the risk of recurrent spontaneous preterm birth (Level A).
- Progesterone treatment does not reduce the incidence of preterm birth in women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations (Level A).
- Insufficient evidence exists to assess if progesterone and cerclage together have an additive effect in reducing the risk of preterm birth in women at high risk for preterm birth (Level B).
- ACOG does not specify what type of progesterone formulation is preferred.
- The 2012 Practice Bulletin was reaffirmed in 2016.
- See Appendix for definitions of the levels of evidence.

- **Society for Maternal-Fetal Medicine** (*SMFM 2017*)
  - In women with a singleton gestation and a history of prior spontaneous preterm birth between 20 and 36 6/7 weeks of gestation, hydroxyprogesterone caproate is recommended at 250 mg IM weekly, starting at 16 to 20 weeks of gestation until 36 weeks of gestation or delivery.
  - Few studies directly compare hydroxyprogesterone caproate and vaginal progesterone in women with a history of a prior spontaneous preterm birth.
  - Vaginal progesterone has not been adequately proven to decrease recurrent preterm birth in women with a history of a prior spontaneous preterm birth. SMFM stipulates that vaginal progesterone should not be considered a substitute for hydroxyprogesterone caproate in these patients.
  - However, SMFM recommends the use of vaginal progesterone to prevent preterm birth in women with a sonographically short cervix of ≤ 20 mm without a history of a prior spontaneous preterm birth.
  - In women with a prior spontaneous preterm birth who start hydroxyprogesterone caproate therapy and then develop cervical shortening, it is not clear if there is any benefit to changing the progestogen choice to vaginal progesterone (with or without cervical cerclage placement).

SAFETY SUMMARY

- **Contraindications**
  - Makena should not be used in women with current or history of thrombosis or thromboembolic disorders; known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions; undiagnosed abnormal vaginal bleeding unrelated to pregnancy; cholestatic jaundice of pregnancy; liver tumors, benign or malignant, or active liver disease; or uncontrolled hypertension.
- **Key Warnings/Precautions**
  - Thromboembolic disorders: Should an arterial or deep vein thrombosis or thromboembolic event occur, therapy should be discontinued.
  - Allergic reactions: As with other products that contain castor oil, reactions including urticaria, pruritus, and angioedema have been reported. Therapy should be discontinued should such reactions occur.
  - Decreased glucose tolerance: A lowering of glucose tolerance has been observed. Prediabetic and diabetic women should be monitored closely.
  - Fluid retention: May occur with progestational drugs; therefore, conditions affected by this should be monitored (eg, preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).
  - Depression: Women who have a history of clinical depression should be monitored and treatment discontinued if clinical depression recurs.
  - Jaundice: Women who develop jaundice should be monitored and benefits/risks of continued therapy considered.
  - Hypertension: Women who develop hypertension should be monitored and benefits/risks of continued therapy considered.
- **Adverse effects**
  - Common adverse events (incidence ≥ 2% and at a higher rate compared to the control group) with hydroxyprogesterone caproate IM were injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%).

- Certain pregnancy-related fetal and maternal complications or events were numerically increased in hydroxyprogesterone caproate-treated patients as compared to control patients, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios.
  - Miscarriage (< 20 weeks) occurred in 5 out of 209 hydroxyprogesterone caproate-treated patients compared to 0 out of 107 control patients measured.
  - Stillbirth (≥ 20 weeks) occurred in 6 out of 305 hydroxyprogesterone caproate-treated patients compared to 2 out of 153 control patients measured.
  - Pregnancy complications include preeclampsia or gestational hypertension (4.2% more with hydroxyprogesterone caproate), oligohydramnios or a deficiency of amniotic fluid (2.3% more with hydroxyprogesterone caproate), admission for preterm labor (2.2% more with hydroxyprogesterone caproate), and gestational diabetes (1.0% more with hydroxyprogesterone caproate).

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulation	Usual Recommended Frequency	Comments
Makena (hydroxyprogesterone caproate)	Injection for IM use	Once weekly	• Begin treatment between 16 weeks and 20 weeks + 6 days of gestation. • Continue until week 37 of gestation or delivery, whichever occurs first.

See the current prescribing information for full details

CONCLUSION

- Makena (hydroxyprogesterone caproate) was FDA-approved in February 2011. Prior to the approval, compounding pharmacies were supplying hydroxyprogesterone caproate for use. The FDA does recommend commercially-available manufacturer products above compounded products due to the standardization and oversight associated with good manufacturing practices (*FDA 2012*).
- Hydroxyprogesterone caproate is administered via IM injection and is indicated to reduce the risk of preterm birth in women with a singleton pregnancy and a history of singleton spontaneous preterm birth. Risks are reduced in approximately one-third of women. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Improvement in neonatal mortality and morbidity have not been demonstrated in clinical studies.
  - Based on clinical studies, hydroxyprogesterone caproate has demonstrated an ability to prolong pregnancy, and in high risk women, hydroxyprogesterone caproate demonstrated a reduced rate of recurrent preterm delivery at less than 32, 35, and 37 weeks. Other studies have demonstrated that if preterm birth does occur, babies who survive have fewer complications if their mothers received hydroxyprogesterone caproate before the birth. Observed benefits of hydroxyprogesterone caproate have not been strongly correlated to improvements in infant mortality. Additionally, it is not clear how hydroxyprogesterone caproate compares to other routes of administration or to other formulations, such as vaginal progesterone (*Combs et al 2015, Dodd et al 2013*, *FDA summary review 2011, Meis et al 2003*, *Meis et al 2004*, *Norwitz et al 2017, Sibai et al 2012*).
  - Evidence suggests there could be differences in the pharmacologic action of progesterone formulations. Comparative effectiveness data have methodological limitations and evidence are often of lower quality. Vaginal progesterone may be associated with similar or reduced rates of recurrent spontaneous preterm birth vs hydroxyprogesterone caproate; however, more robust studies are required to validate conclusions (*Eliminian et al 2016, Maher et al 2013, Pirjani et al 2017, Saccone et al 2017*).
- The ACOG recommends progesterone supplementation in women with a singleton gestation and a prior spontaneous preterm singleton birth starting at 16 to 24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth. ACOG does not specify what type of progesterone formulation is preferred. The SMFM takes a stronger stance, rejecting certain evidence, recommending the use of hydroxyprogesterone caproate IM, and concluding that vaginal progesterone has not been adequately proven to decrease recurrent preterm birth in women with a history of a prior spontaneous preterm birth (*ACOG 2012, ACOG 2016, SMFM 2017*).

- Hydroxyprogesterone caproate is contraindicated in patients with current or prior thromboembolic disease, known or suspected breast or hormone-mediated cancer, undiagnosed abnormal vaginal bleeding unrelated to pregnancy, cholestatic jaundice of pregnancy, hepatic tumors, liver disease, or uncontrolled hypertension. Patients with a history of or at risk for depression, fluid retention, or diabetes should be monitored. Allergic reactions have been reported with hydroxyprogesterone caproate and other products containing castor oil.
- Hydroxyprogesterone caproate is correlated with numerically increased fetal and maternal complications or events compared to placebo. Events include miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios. Common adverse events are mostly related to injection-site reactions; however, others include urticaria, pruritus, nausea, and diarrhea.

APPENDIX

ACOG Levels of Evidence

- Level A: Based on good and consistent scientific evidence
- Level B: Based on limited or inconsistent scientific evidence
- Level C: Based primarily on consensus and expert opinion

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