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Oregon State
UNIVERSITY

Drug Use Research & Management Program

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New Drug Evaluation: 17 alpha-hydroxyprogesterone caproate

Month/Year of Review: May 2013

End date of literature search: January 1, 2013

Generic Name: 17 alpha-hydroxyprogesterone caproate

Brand Name (Manufacturer): Makena® (Baxter Pharmaceutical Solutions LLC)

FDA Approved Indication: Hydroxyprogesterone caproate is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

Research Questions:

- Is 17 alpha-hydroxyprogesterone caproate (17-HP) safe and effective in reducing the risk of recurrent preterm birth?
- Are there efficacy or safety differences in the various formulations of progesterone (e.g. suppositories, intramuscular injection, gel)?
- Are there certain patient subgroups that benefit from the use of 17-HP?

Conclusions:

- Evidence shows that 17-HP is associated with a significant reduction in the rate of recurrent preterm delivery among high risk women, measured by the rate of preterm birth at <37, <35 and <32 weeks. Improvements in these surrogate endpoints did not correlate with an improvement in infant mortality.
- Additional efficacy data is necessary to establish long-term efficacy for clinically meaningful outcomes when using 17-HP for the prevention of preterm birth.
- There is no evidence that shows intramuscular progesterone is safer or more effective than other routes of administration. Limited evidence suggests that vaginal progesterone is more effective than intramuscular progesterone for the prevention of preterm birth and leads to fewer adverse effects. More studies are necessary to determine the optimal route, dose, and duration of progesterone use for preterm birth.
- While the FDA acknowledges that manufactured products provide a greater assurance of safety and effectiveness than compounded products, an FDA-conducted analysis of the compounded product did not identify any major safety problems.

Recommendations:

- Due to limited long term safety and efficacy data, prior authorize 17-HP for appropriate use.
- Limit use of 17-HP in women with a singleton gestation and a prior spontaneous preterm singleton birth between 16 weeks, 0 days and 20 weeks, 6 days of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth. Treatment should be continued through 36 weeks of gestation or delivery, whichever occurs first. 17-HP should not be used in women with multiple gestations.
- Due to insufficient data to support the compounded product and additional inherent compounding risks, prefer the branded product over the compounded product.

Background:

Preterm birth is defined as delivery earlier than 37 weeks of gestation.¹ The risk of infant morbidity and mortality is inversely proportional to gestational age, as the highest risk is for neonates born prior to 34 weeks, and lowest for those born between 39 and 40 weeks.² Infants who are born prematurely 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.³ Approximately 20-30% of preterm deliveries are due to premature rupture of membranes, 20-25% are due to infection and/or inflammation, and 25-30% are spontaneous (unexplained).¹

A history of preterm birth is the most significant risk factor for a subsequent preterm birth. It is estimated that the risk of recurrence in a woman with a history of preterm birth is about 15%, and this increases to 32% in women who have had two prior preterm births.³ Short cervical length (<35mm) has also been associated with a risk of preterm birth. There are a number of other risk factors that have been identified (poor nutrition, low prepregnancy weight, socioeconomic status, poor prenatal care, etc.), but are unreliable in predicting preterm labor with accuracy and precision.¹

Until the approval of 17 α -hydroxyprogesterone caproate (17-HP) in 2011, there was no FDA approved product available to reduce the risk of preterm birth, however, 17-HP has been compounded by pharmacists in the past and widely used for this indication.^{4,5} Related studies have been conducted since 1975, with a number of small clinical trials showing conflicting results. It wasn't until the National Institute of Health conducted a large clinical trial in 2003 that a manufacturer sought FDA approval of a manufactured form of 17-HP. Compounded formulations of 17-HP are known to be much more affordable.⁶ Other formulations of progesterone have also been used to reduce the risk of preterm birth in patients who are at high risk, including intravaginal and oral delivery, but none are approved for this purpose. Clinical head-to-head studies are not available for 17-HP.

In an effort to improve access to this drug, the FDA issued a statement in March 2011, indicating that the agency does not intend to take enforcement action against pharmacies that compound 17-HP based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards.⁴ The manufacturer of Makena maintained that compounded products are not as safe or as effective as the manufactured product, and the FDA responded by conducting its own analysis. The FDA later announced, "although the analysis of this limited sample...did not identify any major safety problems, approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products." The FDA also said it was applying its "normal enforcement policies" in declining to stop compounding pharmacies from making Makena, and focusing its actions on products that are likely to cause harm.⁷

In April 2013, the Oregon Board of pharmacy discussed the compounding of 17-HP and indicated that because a branded product is commercially available, a pharmacy may not compound 17-HP unless it is compounded pursuant to a prescription for an individual patient and the prescriber has clearly intended for the patient to receive the compounded product. There also must be documentation that the prescriber considered the availability of the manufactured product and that the compounded medication is necessary for the patient.

The American College of Obstetricians and Gynecologists (ACOG) recently published their recommendations for the prediction and prevention of preterm birth. The recommendations state that women with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16-24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth. This is a Level A recommendation, based on good and consistent scientific evidence. ACOG does not specify what type of progesterone formulation is preferred.²

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Clinical Efficacy:

A phase 3 study evaluated the efficacy of 17-HP in reducing preterm delivery in 463 high-risk women. In the double-blind, placebo-controlled, multicenter trial, patients were randomized to receive 17-HP or an inert oil placebo. Women were eligible if they had a history of spontaneous preterm delivery in a previous pregnancy and a current pregnancy between 15 weeks and 20 weeks, 3 days of gestation. Women were enrolled at 16 to 20 weeks of gestation and received weekly injections of 17-HP or placebo until delivery or to 36 weeks of gestation. Analyses were performed on the intent-to-treat principal.⁸

Baseline characteristics between the two groups were similar. Results show that 17-HP significantly reduced the risk of delivery at less than 37 weeks with an incidence of 36.3% in the treatment group versus 54.9% in the placebo group [RR 0.66 (95% CI 0.54-0.811)]. Statistically significant reductions were seen in the 17-HP group for delivery at less than 35 weeks of gestation [20.6% vs. 30.7% for placebo; RR 0.67 (95% CI 0.48-0.93)] and 32 weeks of gestation [11.4% vs. 19.6%; RR 0.58 (95% CI 0.37-0.91)]. Results for fetal death, antepartum or intrapartum were not statistically different [2.0% 17-HP vs. 1.3% placebo; RR 1.50 (95% CI 0.31-7.34)]. There were lower rates of birth weights <2500g, necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen in infants whose mothers were treated with 17-HP.⁸

The study is limited in that over 27% of the study participants came from one center, the University of Alabama, raising concern about whether study results can be extrapolated to larger populations. Additionally, for the endpoints of preterm birth rates at <35 and <32 weeks, the magnitude of statistical significance was lower than expected to support approval of a drug based on these findings.⁵ Due to the modest clinical benefit noted in the trial, the FDA is requiring a second confirmatory trial, with anticipated completion in 2016.⁵

There are a number of studies that evaluate the efficacy and safety of other formulations of progesterone (suppositories, gel) compared to placebo; some that show benefit⁹ and some that do not.¹⁰ There is only one published head-to-head trial that directly compares intramuscular progesterone to a different formulation, specifically, vaginal progesterone gel. In this prospective, randomized, open-label trial, 518 women with a history of preterm birth and a current singleton pregnancy were randomized to 90mg of vaginal progesterone gel daily, or 250mg intramuscular progesterone weekly. The IM progesterone product was Proluton® Depot, manufactured by Bayer Schering Pharma AG, Berlin, Germany.¹¹

In this head-to-head trial, patients receiving vaginal progesterone experienced a significantly lower rate of preterm birth at <34 weeks compared to those treated with intramuscular progesterone [16.6% vs 25.7%, p=0.02; OR 0.58(95%CI 0.37-0.89)]. However, patients were not blinded which increases the risk of bias and the study was conducted at a single center in Saudi Arabia, limiting the generalizability of the results.¹¹

Clinical Safety:

In the phase 3 trial which led to the FDA approval of 17-HP, there was no significant difference in neonatal deaths [2.6% 17-HP vs. 5.9% placebo; RR 0.44 (95% CI 0.17-1.13)], however the study was not powered to assess this endpoint. Overall, 50% of the women in the study experienced at a least one adverse effect with the most common event being injection site reactions. More women in the progesterone group than placebo group had swelling at the injection site (1.2% vs. 7.8%, P=0.007) or a lump at injection site (5.5% vs. 1.3%, P=0.03).⁸

A follow-up study was conducted to evaluate children who were exposed to 17-HP in utero versus placebo.¹² This study evaluated 278 of the 348 (80%) eligible surviving children of the multicenter, placebo controlled study conducted by Meis et al. In this study the guardian was interviewed about the child's general health and children underwent a physical examination and developmental screen using the Ages and Stages Questionnaire. The mean age at follow-up was 48 months. The Ages and Stages Questionnaire showed no differences between the 17-HP and placebo groups (P=0.61). The Preschool Activities Inventory, designed to find gender-specific differences, resulted in a mean score for boys of 67.3 and 66.5 for the placebo and 17-HP groups, respectively (P=0.3). For females the mean scores were 33 and 32 for the 17-HP and placebo groups, respectively (p=0.50). There were no significant differences in the physical characteristics of height, weight, head circumference, or blood pressure. Study participants had growth similar to national averages. Genital abnormalities were found in 2.1% of the study group and 1.2% of the placebo group (P=1.0). Genital abnormalities in the 17-HP group were two males with micropenis, one male with an undescended testicle that had been surgically repaired, and one female with early puberty (3.5 years). In the placebo group one female had pubic hair present. Based on these results, 17-HP appears to be safe for the fetus when administered in the second and third trimesters, however the sample size was smaller than planned there was limited statistical power to detect treatment differences.¹²

In the head-to-head trial comparing vaginal and intramuscular formulations, patients using the intramuscular formulation experienced a higher rate of adverse events than those using the vaginal gel (14.1% vs 7.5%, respectively, P=0.017). The most common adverse events in the intramuscular group were pain and swelling related to the injection site, and headaches. The most common adverse events in the vaginal group were bloating, nausea and vaginal soreness. Infants who had been exposed to intramuscular progesterone in utero also experienced a higher rate of neonatal intensive care unit admissions than those in the vaginal progesterone group (25.7% vs 15.4%, respectively, P=0.006). There were no significant differences in the other safety parameters.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

- 1) Neonatal mortality
- 2) Neonatal morbidity
- 3) Premature birth rate (the rate of preterm birth prior to 37 weeks is a surrogate endpoint that is likely to predict clinical benefit).⁵

Primary Study Endpoint:

- 1) Delivery at less than 37 weeks of gestation.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
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<p>Meis et al.8 RCT, DB, PC, MC</p>	<p>1. 17-HP 250 mg weekly (n= 310) 2. Placebo (Pbo) injection weekly (n=153)</p>	<p>Demographics (17-HP, Pbo):</p> <ul style="list-style-type: none"> • Age: 26.0, 26.5 • Duration of gestation at time of delivery (wk): 30.6, 31.3 • No. of previous preterm deliveries 1.4, 1.6 • Duration of gestation at randomization (wk): 18.4, 18.4 <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • History of spontaneous preterm delivery in previous pregnancy • Current pregnancy between 15 weeks and 20 weeks 3 days of gestation <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Multifetal gestation, known fetal anomaly, progesterone or heparin treatment during the current pregnancy • Current or planned cervical cerclage • Hypertension requiring medication • Seizure disorder • Plan to deliver elsewhere 	<p>Randomized: 17-HP: 310 Pbo: 153</p>	<p><u>Delivery before 37 wk of gestation:</u> 17-HP: 36.3% Pbo: 54.9% P-value: <0.001 RR 0.66, 95% CI (0.54-0.81).</p> <p><u>Delivery before 35 wk of gestation:</u> 17-HP: 20.6% Pbo: 30.7% P-value: 0.02 RR 0.67, 95% CI (0.48-0.93).</p> <p><u>Delivery before 32 wk of gestation:</u> 17-HP: 11.4% Pbo: 19.6% P-value: 0.02 RR 0.58, 95% CI (0.37-0.91).</p> <p><u>Fetal death, antepartum or intrapartum:</u> 17-HP 2.0% Pbo: 1.3% RR 1.50, 95% CI (0.31-7.34).</p> <p><u>Birth weight <2500 g:</u> 17-HP: 27.2% Pbo: 41.1% P-value: 0.003 RR 0.66, 95% CI (0.51-0.87).</p> <p><u>Neonatal Death:</u> 17-HP: 2.6% Pbo: 5.9% RR 0.44, 95% CI (0.17-1.13).</p>	<p>18.6%/5</p> <p>10.1%/10</p> <p>8.2%/12</p> <p>N/A</p> <p>13.9%/7</p> <p>3.3%/30</p>	<p>206 women (50%) had at least one adverse effect.</p> <p>The most common were injection-site reactions (34.2%), swelling (14.1%), itching (11.3%), and bruising (6.7%). More women in the progesterone group than placebo group had swelling at injection site (1.2% vs. 7.8%, p= 0.007) or lump at injection site (5.5% vs. 1.3%, P=0.03).</p>	<p>Quality Rating: Fair</p> <p>Internal Validity: <u>Selection:</u> Adequate randomization assignment (computer generated algorithm); patients were given test injections; groups similar at baseline. <u>Performance:</u> The women, their caregivers, and research personnel were unaware of study-group assignment. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Data on hospital visit for preterm labor were missing for 1 woman in the placebo group; data on tocolytic therapy were missing for 2 women in the placebo group, and data on corticosteroids for fetal lung maturity were missing for 14 women in the progesterone group and 1 women in the placebo group.</p> <p>External Validity: <u>Recruitment:</u> A research nurse approached candidates from the 19 participating centers and explained the study. If candidates met inclusion criteria they were deemed eligible and invited to participate. After trial injections, women who returned one week after were included in the study. <u>Patient Characteristics:</u> Ave age: 26 years; 59% non-Hispanic black women; average body-mass index before pregnancy was 27 (17-HP) and 26 (Pbo); 20% smoked during pregnancy; 6% used alcohol; and 3% reported substance use in each group. <u>Setting:</u> Women returned weekly for injections and received prenatal care at their institutions. Patients came from a single center. <u>Outcomes:</u> After delivery study personnel reviewed all records. Infants were followed until hospital discharge.</p>
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<p>¹¹ Maher et al. R, OL, AC, SS</p>	<p>1. IM progesterone, 250mg once a week</p> <p>2. Progesterone gel, 90mg applied once daily</p>	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • History of at least 1 mid-trimester preterm birth or cerclage suture inserted in a previous pregnancy, but not the current pregnancy between 14 and 18 weeks gestation <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Fetal anomaly or loss • Advanced cervical dilatation • Membranes bulging into the vagina • History of ruptured membranes • Short cervix or significant funneling • Plans to undergo cervical cerclage or who already had cerclage inserted • Major chronic medical disorder • Multiple pregnancy 	<p>Randomized IM: 249 Vaginal: 253</p>	<p><u>Delivery before 34 wk of gestation:</u> IM: 25.7% Vaginal: 16.6% P-value: 0.02 OR 0.58, 95% CI (0.37-0.89).</p>	<p>9.1%/11</p>	<p>Adverse effects: IM: 14.1% Vaginal: 7.5% P-Value: 0.017 OR 2.01, 95% CI (1.12-3.63).</p> <p>The most common adverse effects in the intramuscular group were pain and swelling related to injection site and headache.</p> <p>In the vaginal group the adverse reactions were bloating, nausea and vaginal soreness.</p>	<p>6.6%/15</p>	<p>Quality Rating: Fair</p> <p>Internal Validity: <u>Selection:</u> Adequate randomization using a computer-generated random list; groups were similar at baseline. <u>Performance:</u> This was an unblinded study using two different routes of administration. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> 9 of the original 262 subjects in the vaginal progesterone group were lost to follow-up and 7 of the 256 patients in the intramuscular progesterone were lost to follow-up.</p> <p>External Validity: <u>Recruitment:</u> Study was conducted at a single study center that has 8000-9000 deliveries per year. <u>Patient Characteristics:</u> Average age of women was between 27 and 28 years old. Average body mass index was 25 and the average gestational age at randomization was just over 15 weeks. <u>Setting:</u> Patients assigned to IM progesterone received 2 week supply at each visit, with one of the shots administered at each visit. Drug packaging was used to assess compliance. All patients were instructed to undergo periods of bed rest and were educated about the symptoms of preterm birth. This specific drug formulation is not available in the U.S. <u>Outcomes:</u> Returned for visits every 2 weeks. All data for timing of labor onset, along with maternal and neonatal complications were documented.</p>
<p>RCT: randomized controlled trial, DB: double-blind, PC: placebo controlled; MC: multi-centered, OL: open-label, AC: active-comparator, SC: single-center, RR: relative risk, CI: confidence interval, OR: Odds Ratio</p>								

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS¹³

Parameter	Result
Peak serum levels	3-7 days
Protein Binding	Extensively binds to plasma proteins including albumin and corticosteroid binding globulins
Excretion	50% recovered in feces, and 30.5% recovered in the urine
Half-Life	7.8 (+/-3.0) days
Metabolism	Phase I and II reactions in hepatocytes

DOSE & AVAILABILITY¹³

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
250 mg/ 1mL	Intramuscularly (IM)	Once weekly until week 37 of gestation or delivery, whichever occurs first	250 mg	Not studied	Not studied	Not indicated for use in children	Not intended for use in postmenopausal women	Treatment should begin between 16 weeks, 0 days and 20 weeks, 6 days of gestation.

DRUG SAFETY¹³

Serious (REMS, Black Box Warnings, Contraindications):

Contraindicated in women with a current or history of thrombosis or thromboembolic disorders; hepatic impairment, hepatic tumors or cholestatic jaundice of pregnancy; carcinoma of the breast (known or suspected) or other hormone sensitive cancers; undiagnosed vaginal bleeding unrelated to pregnancy; uncontrolled hypertension; current or history of thrombosis or thromboembolic disorders.

Warnings and Precautions:

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Discontinue if arterial thrombosis, DVT, or thromboembolic events occur. May have adverse effects on glucose tolerance. Use in caution in women with diabetes, depression, or diseases exacerbated by fluid retention.

Not for use in women with multiple gestations or other risk factors for preterm birth.

Appendix 2: Suggested PA Criteria

17 alfa-hydroxyprogesterone caproate (Makena®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which hydroxyprogesterone caproate injection has been shown to be effective and safe.

Length of Authorization: Up to 20 weeks

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the client between 16 weeks and 0 days and 36 weeks 6 days gestation with a singleton pregnancy?	Yes: Go to #3.	No: Pass to RPH; Deny (medical appropriateness)
3. Has the patient had a prior history of preterm delivery before 37 weeks gestation (spontaneous preterm singleton birth)?	Yes: Go to #4.	No: Pass to RPH; Deny (medical appropriateness)
4. Is treatment being initiated at 16 weeks, 0 days and to 20 weeks, 6 days of gestation?	Yes: Approve through week 37 of gestation or delivery, whichever occurs first (no more than 20 doses).	No: Pass to RPH; Deny (medical appropriateness)