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Makena®: A Drug for Reducing the Risk of Preterm Labor

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Makena®: A Drug for Reducing the Risk of Preterm Labor

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-13-177-H01-P

Objectives

After completion of this program, the reader should be able to:

1. Recognize for which patients Makena® is indicated.
2. List risk factors for preterm labor and potential consequences for premature infants.
3. State the side effects associated with Makena®.
4. Explain the potential role of the pharmacist in dispensing Makena®.

Abstract

Makena®, hydroxyprogesterone caproate, is an intramuscular injection that is U.S. Food and Drug Administration (FDA) approved to reduce the risk of preterm delivery before 37 weeks of pregnancy in pregnant women with a history of spontaneous preterm birth, who are not currently carrying multiple children. One in nine babies born in the United States each year is born prematurely, or before 37 weeks gestation, and mothers who have previously delivered a premature baby are 2.5 times more likely to deliver another baby prematurely. Makena® is administered by a health care professional as a single intramuscular injection to the hip and has a strict window for safe administration. Hydroxyprogesterone caproate has been available as a compounded product for years since the removal of Delalutin® from the market in 2000. The price of Makena® has been a controversial subject since its introduction into the market due to the increase in cost as compared to the compounded injections that have been available in the past.

Introduction

A synthetic progestin, 17-alpha-hydroxyprogesterone caproate, (17-OHPC, Makena®) is an intramuscular injection that was approved by the FDA on Feb. 4, 2011, to reduce the risk of preterm delivery before 37 weeks of pregnancy in pregnant women with a history of at least one spontaneous preterm birth, who are not currently carrying multiple children.[1] Makena® was accepted under accelerated approval regulations that allow drugs to be approved based on a surrogate endpoint. For Makena®, this endpoint was the reduction of risk of delivery before 37 weeks of pregnancy. The approval committee determined that the reduced risk of delivery before 37 weeks gestation observed with Makena® treatment was reasonably likely to predict a clinical benefit to mothers at risk for preterm delivery.[1]

Preterm Labor

One in nine babies born in the United States each year is born prematurely, or before 37 weeks gestation.[2] Mothers who have previously delivered a premature baby are 2.5 times more likely to deliver another baby prematurely, compared to mothers who have delivered full term.[3] Prevalence of premature births is greater in women who are African American, less than 17 years old but older than 35 years old, and those women with low income.[2]

There are many risk factors for preterm labor, ranging from the physical anatomy of the uterus and cervix to certain lifestyle factors and disease states.[2] Women who have previously had a preterm labor, women who are pregnant within six months of a previous pregnancy, women who are pregnant with more than one baby, women who underwent *in vitro* fertilization, and women who have certain uterus and/or cervical abnormalities are all at an increased risk of preterm labor. Lifestyle factors such as smoking, alcohol and drug use, standing for long periods of time, long working hours, and exposure to chemicals and pollutants can increase the risk of premature delivery. Additionally, stress, injuries/accidents, violence/abuse and lack of social support can lead to a greater risk. Certain disease states can also put a woman at higher risk for preterm labor including diabetes, high blood pressure or preeclampsia, obesity or underweight and infections (sexually transmitted infections, urinary infections, vaginal infections, placental infections). Birth defects present in the unborn baby can also put the mother at increased risk for premature delivery.

Premature infants may experience several complications involving multiple organs and organ systems.[4] Occurrence of complications often depends on how early the infant is born. The respiratory system matures by week 36, but this can often vary depending on the infant's individual development. Infants born before 36 weeks gestation are at an increased risk of having immature lungs, which can lead to a variety of consequences. One potential risk is the development of respiratory distress syndrome (RDS), where the infant's immature lungs do not produce enough surfactant, which normally prevents the lungs from collapsing. Transient tachypnea can also occur, causing the infant to have shallow and rapid breathing. In addition to tachypnea, infants may also experience apnea, or the absence of breathing, and bradycardia, or a slowed heart rate. Infection and pneumonia are also a risk due to a reduced ability to fight infections as well as possible immature lungs.

Other consequences of prematurity include jaundice, or yellowing of the skin due to the buildup of bilirubin in the blood, and anemia due to abnormally low levels of red blood cells.[4] Due to their small size and low body fat, premature infants may also be unable to maintain their own body temperature. The heart can be affected by a condition known as patent ductus arteriosus (PDA) in which a specialized blood vessel in the fetal heart, the ductus arteriosus, does not close. Patent ductus arteriosus can lead to respiratory problems and may ultimately cause heart failure if left untreated. The infant's gastrointestinal system is also at risk for complications. Infants born early may not have a fully developed gastrointestinal tract, which can lead to the inability of the infant to absorb nutrients properly and effectively. Parts of the gastrointestinal tract may also receive inadequate blood flow, which can lead to bowel wall infection and cause a serious and potentially life threatening condition known as necrotizing enterocolitis. If born before 34 weeks of gestation, the newborn may experience additional complications such as intraventricular hemorrhage (IVH) and retinopathy of prematurity (ROP). Intraventricular hemorrhage is a condition that leads to bleeding in the brain due to immature blood vessels that are unable to handle the strain of labor and birth, which can lead to mental retardation, learning disabilities and cerebral palsy. Retinopathy of prematurity can potentially cause blindness in the newborn.[2,4]

Management of Preterm Labor

Women experiencing premature labor are often put on bed rest to decrease physical activity and are advised to increase fluid intake. Doctors may also tell women to refrain from the use of tampons and douches and to avoid having sex. If the cervix starts to open too early, a procedure known as a cerclage is performed. During a cerclage, a stitch is put in the cervix and left in place until the mother is 37 weeks pregnant.[2]

Pharmacologic treatment of preterm labor often involves the use of progesterone and tocolytics.[5] Tocolytics include drugs such as magnesium sulfate, indomethacin, nifedipine and terbutaline, and may also be used to slow contractions during preterm labor. Health care providers may give tocolytics after 17 to 20 weeks gestation and prior to 34 weeks gestation. The specific medication used as well as duration of therapy depend on time in pregnancy, the status of the fetus and the overall risk of actual preterm labor. Tocolytics can delay labor for approximately 48 hours, but for some women labor may be delayed several days.

Progesterone is used, either as a vaginal gel or as an injection, to relax the uterus and prevent contractions.[6] Progesterone injections may be used weekly starting at 16 weeks, while the gel can be started around 20 weeks and is applied daily. The gel or injection may be used until 37 weeks gestation. To qualify for the use of the injections, a woman must be pregnant with only one baby or have previously experienced preterm labor with a single baby.

Makena®

Makena® is a synthetic progestin that has effects similar to progesterone. Progesterone is needed for implantation of a fertilized egg into the uterus and is also responsible for maintaining pregnancy. The mechanism in which progesterone accomplishes this is unknown, but is hypothesized to help relax the muscles of the uterus and reduce the rate of cervical shortening.[7,8] The synthetic progestin appears to have differing effects on the muscles of the uterus and has either produced no change or increase in uterine contraction.[9] A review by O'Brien[9] analyzed several studies primarily to determine the safety of progesterone and 17-OHPC. The author makes a distinction that natural progesterone is handled differently in the body from the synthetic and, therefore, may have different safety profiles. The author also reviews differences in the efficacy and safety when comparing women with singleton pregnancies to those with multiple pregnancies. The studies have shown that in patients with multiple fetuses, 17-OHPC can reverse the intended agonism on the progesterone receptor and create an antagonistic effect. Progesterone receptor antagonism is based on the patient's genotype and the number of fetuses per pregnancy. It may also lead to a miscarriage or impaired fetal growth in some populations. Studies have shown that the progesterone receptor gene is located on chromosome 11q. Polymorphisms in this gene may result in adverse events in pregnancy such as preterm labor. Manuck et al.[10] examined the progesterone receptor polymorphisms in women with previous spontaneous preterm births and the clinical response to 17-OHPC. This was an exploratory study conducted as a secondary review of patients from a previous study [11] so the results must be considered with caution. The authors noted several polymorphisms associated with a greater risk of spontaneous preterm births, as well as differences in response to 17-OHPC depending on genotype.[10] Therefore, based on the patient's progesterone receptor, treatment with 17-OHPC may trigger preterm labor; however, at this time genetic testing is not required or suggested prior to starting Makena® therapy.

The approval of Makena® did not mark the first instance of FDA approval of hydroxyprogesterone caproate. In 1956, Delalutin® was approved by the FDA for indications that included the threat of miscarriage.[1,12] This was prior to the FDA Drug Amendment Act of 1962 which required that efficacy be shown in a controlled clinical trial for market approval. In 2000, the FDA removed Delalutin® from the market at the request of the manufacturer (who was no longer producing the drug); this withdrawal was unrelated to safety.[1,12] A compounded form of injectable hydroxyprogesterone caproate has been used off-label for many years. The approval of Makena® was made on a single controlled clinical trial with the expectation that the manufacturer would provide additional data. The study conducted was a multicenter, randomized, double-blind clinical trial that enrolled 463 women who were pregnant with a single fetus and had a history of preterm birth. In the placebo control group of the study, 55 percent of patients delivered before week 37 as compared to 37 percent delivered before week 37 in the group treated with 17-OHPC.[1,11] There was also a significant decrease in preterm deliveries at weeks 35 and 32 as compared to the placebo group, although this was not as strong statistically. The authors calculated the number-needed-to-

treat (NNT) to prevent one preterm delivery before 37 weeks in patients with similar risk to those in this study was between five and six (95 percent confidence interval, 3.6 to 11.1).[11] In order to prevent one preterm delivery before 32 weeks, the NNT was calculated to be 12 (95 percent confidence interval, 6.3 to 74.6). Given that the greatest risk to the neonate is when delivery is prior to 32 weeks, the use of 37 weeks as the surrogate endpoint may not be as telling.[12] The authors did review outcomes in the infants and found in patients who received 17-OHPC versus placebo a significant decrease: in infants weighing less than 2500 gm at birth; in rates of necrotizing enterocolitis; in IVH of any grade; and need for supplemental oxygen.[11] There was a decrease (nonsignificant) in: infants weighing less than 1500 gm at birth; neonatal death; transient tachypnea; respiratory distress syndrome; bronchopulmonary dysplasia; ventilator support; patent ductus arteriosus; and retinopathy. Of concern was a nonsignificant increase in fetal death in the 17-OHPC treated group. Further trials are needed to evaluate this and more long term effects on the children born to mothers treated with 17-OHPC.

Makena® is administered by a health care professional as a single intramuscular injection to the hip.[3] Women may receive 250 mg of Makena® via intramuscular injection once weekly starting between 16 weeks and zero days, and 20 weeks and six days of gestation. The weekly doses of Makena® continue until week 37 of gestation or delivery of the baby.

The most common side effects of Makena® are pain, pruritis, and/or swelling at the injection site, as well as some gastrointestinal upset such as nausea and diarrhea.[13] Some women may experience urticaria, or hives, in the area of injection. A more serious side effect that is often a risk when taking hormone replacement therapy is a thromboembolic disorder. This can become a life threatening event and the patient should receive medical attention if a thromboembolic disorder develops.[4] Women should not use Makena® if they have a history of thromboembolic events, have hormone sensitive cancer, unusual vaginal bleeding, active liver disease or uncontrolled hypertension.[13] Makena® is not shown at this time to have negative impacts on the infants later in life. Further safety studies are continuing to detect these potential outcomes. Hydroxyprogesterone caproate is a CYP3A substrate and a strong CYP2A6 inhibitor. Drug interactions can be expected with other drugs that affect these enzyme systems.[14]

Controversy has surrounded this drug and its manufacturer, KV Pharmaceuticals, since its approval. The compounded form of hydroxyprogesterone caproate was available for around $15 per injection. When Makena® came on the market, the cost was $1,500 per injection.[15] When the FDA made its original approval as an orphan drug, KV Pharmaceuticals was allowed exclusive rights to the product for seven years. The FDA, however, decided not to enforce the exclusivity of KV pharmaceuticals and allowed pharmacists to continue to compound hydroxyprogesterone caproate at a lower price. This led to a large drop in stock of Makena® and eventually KV pharmaceuticals decreased the cost of the drug to $690 per injection.[16] Even with this reduction in price, the cost of use of Makena® may still exceed the savings in overall health care costs due to less preterm births. Based on a conservative NNT of 14, 139,000 at-risk women would need to be treated to prevent 10,000 premature births.[17] The total direct and indirect medical costs for 10,000 premature births is estimated at $519 million. Even at the new, reduced price of $690 per injection of Makena®, the cost of treatment of 139,000 women with Makena® for 20 weeks would exceed $1.9 billion. In comparison, the cost of the compounded form of 17-OHPC to treat 139,000 women would be approximately $41,700,000—considerably less than the medical costs associated with 10,000 premature births.

To help assist patients with the costs of Makena®, KV pharmaceuticals developed a patient assistance program. The financial aid is based on the patient's insurance status, as well as their household income. This financial assistance may make Makena® an option for those who need it but cannot afford it.[18] Table 1 displays the financial assistance available based on a family's income and insurance for Makena®.

Conclusion

Makena®, though not the first drug of its kind, has been FDA approved for the treatment of preterm labor in patients at risk. This medication has gained recent media attention due to the FDA decision to not enforce the exclusivity of KV Pharmaceutical to market the drug, which has significantly increased patient awareness of this drug and its benefits in preventing preterm delivery. As pharmacists, it is important to understand how Makena® works and which patients qualify for administration in order to refer patients to their gynecologist for further treatment. Though this product is very expensive, pharmacists are available to give information about the compounded hydroxyprogesterone caproate injection that may be available in their area, as well as information on financial assistance for Makena®. The accessibility of pharmacists within the community allows for an increased availability to patients and physicians with questions about preterm labor and the benefits that treatment options, such as Makena®, may provide.

Table 1. Assistance Provided by the Patient Assistance Program for Makena®.[18]

Coverage	Income Level	Copay/Financial Assistance*
Uninsured	Up to $60,000	Receive Makena® at no cost
Uninsured	Above $60,000	Receive Makena® at cost equivalent to what insured patients pay out-of-pocket under the Makena® copay assistance program
Insured	Up to $120,000 *(represents 85 percent of household incomes based on 2009 census data)*	Copay of $0-$20 per injection for Makena®
Insured	Above $120,000 *(represents 15 percent of household incomes based on 2009 census data)*	Copay of $40-$80 per injection for Makena®

** This encompasses 85% of U.S. household incomes. Source: 2009 U.S. Census Data.*
**Gross annual household income and insurance coverage are factors that determine the level of copay or financial assistance for which a patient is eligible. There are additional eligibility requirements (i.e. have a Makena® prescription, etc.) and these can be discussed on patient-by-patient basis with a representative from the Makena® Care Connection, a program designed to help ensure access to Makena®. http://www.kvph.com/Makena/cost-of-bringing-makena-to-market.aspx; reprinted with permission: Medical Information, Ther Rx, division of KV Pharmaceuticals. Accessed May 23, 2013.*

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Assessment Questions

1. Makena® is indicated for:
   A. Women with no prior history of preterm birth
   B. Women carrying multiple children
   C. Women with a singleton pregnancy
   D. Women that are greater than 37 weeks gestation

2. Makena® is a(n):
   A. Self-administered intramuscular injection
   B. Tablet
   C. Intravenous drip
   D. Intramuscular injection administered by a health care professional

3. Hydroxyprogesterone caproate was previously FDA approved under the name:
   A. Delalutin®
   B. Endometrin®
   C. Mirena®
   D. Prometrium®

4. Women who have previously delivered a premature baby are how many more times likely to deliver prematurely again?
   A. 5
   B. 3.5
   C. 2.5
   D. 3

5. Other treatment options for premature labor include:
   A. Tocolytics
   B. Progesterone
   C. Cerclage
   D. A and B
   E. All of the above

6. All of the following increase incidence of premature birth EXCEPT:
   A. Asian descent
   B. Age <17 and >35
   C. Low income
   D. In vitro fertilization

7. Potential risks for the premature baby include:
   A. Respiratory distress syndrome
   B. Jaundice
   C. Intraventricular hemorrhage
   D. All of the above are potential risks of premature delivery

8. Some common side effects a patient receiving Makena® may experience include all of the following EXCEPT:
   A. Pain and swelling at the injection site
   B. Hives in the area of the injection
   C. Headache
   D. Nausea and vomiting

9. Which serious side effect is life-threatening in which the patient should seek medical attention immediately?
   A. Respiratory distress syndrome
   B. Seizures
   C. Depression
   D. Thromboembolic disorder

10. What is/are the best way(s) a pharmacists can assist a patient that may be a candidate for Makena®:
    A. Explaining the benefits Makena® can have on a preterm pregnancy
    B. Provide information about financial assistance to help pay for Makena®
    C. Understand which patients qualify for Makena® and refer the patient to her gynecologist
    D. All of the above are ways a pharmacists can assist a patient

To receive continuing education credit for this program, you must answer the above questions and fill out the evaluation form. Please visit www.onu.edu/pharmacy to enter the required information. Please allow two to three weeks for electronic distribution of your continuing education certificate, which will be sent to your valid email address in PDF format.

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 05/16/16.

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Office of Continuing Education at the Raabe College of Pharmacy
Ohio Northern University
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Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **Makena®: A Drug for Reducing the Risk of Preterm Labor**
UAN: 0048-0000-13-177-H01-P CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

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City:	**State:**	**Zip:**		
Phone:	**Email:**			
Pharmacy License #:	**State:**	**ONU Alumni?**	**Y**	**N**

Program Content:	Strongly Disagree				Strongly Agree
The program objectives were clear.	1	2	3	4	5
The program met the stated goals and objectives:					
Recognize for which patients Makena® is indicated.	1	2	3	4	5
List risk factors for preterm labor and potential consequences for premature infants.	1	2	3	4	5
State the side effects associated with Makena®.	1	2	3	4	5
Explain the potential role of the pharmacist in dispensing Makena®.	1	2	3	4	5
The program met your educational needs.	1	2	3	4	5
Content of the program was interesting.	1	2	3	4	5
Material presented was relevant to my practice.	1	2	3	4	5

Comments/Suggestions for future programs:

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D E
6. A B C D
7. A B C D
8. A B C D
9. A B C D
10. A B C D

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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