IF YOU HAD A SINGLETON SPONTANEOUS PRETERM BIRTH (BEFORE 37 WEEKS), YOU ARE AT RISK FOR ANOTHER EARLY DELIVERY

Every week counts when you’re pregnant

Your baby keeps growing and developing every week of pregnancy until your due date.1-3 Together, you and your healthcare provider can take an important step to help give your baby more time to develop.

Ask your healthcare provider about the importance of having a full-term delivery.

Full Prescribing Information attached here.

If missing, please visit http://www.makena.com/pi.

LEARN MORE about a medicine that may help you stay pregnant longer.

Have Questions?  Connect with us.
1-800-847-3418 • 8 AM–8 PM ET
info@makenacareconnection.com
Makena (hydroxyprogesterone caproate injection) is a prescription hormone medicine (progestin) used to lower the risk of preterm birth in women who are pregnant with one baby and who have delivered one baby too early (preterm) in the past. Makena was shown to work based on a lower number of women who delivered babies at less than 37 weeks of pregnancy. There are no studies showing Makena reduces the number of babies who have serious problems shortly after birth or who die. **It is not known whether Makena is safe and effective in women who have other risk factors for preterm birth.**

**What is preterm birth?**

Staying pregnant full term (40 weeks) is one of the best ways to give your baby the time needed to grow and develop.1,3 If you deliver a baby too early—before 37 weeks of pregnancy, or 3 weeks prior to the due date—this is known as **preterm birth.**1,4 Sometimes preterm births are unexpected or unplanned, though an early delivery may be necessary in some medical situations.5

**Preterm birth can happen to any pregnant woman**

In most cases, healthcare providers don’t fully understand what actually causes preterm birth. But women who’ve already delivered a baby too early (before 37 weeks)—regardless of the number of weeks early they’ve delivered—are at a higher risk for having another preterm birth.1,4

Talk with your healthcare provider to make sure you are familiar with the risks associated with preterm birth.

“I was at risk for another preterm birth, I was a nervous wreck because I knew what could happen.”

—Katie, mother of 3
Have you had a preterm birth before?

You’re not alone. If you’ve had a preterm birth before, you may be at risk for another.

In the US, 1 in 10 babies is born prematurely each year. That’s nearly 400,000 babies born too early.

Preterm birth rates are different for different racial and ethnic groups. African Americans have a 13.3% preterm birth rate, Native Americans 10.4%, Hispanics 9.1%, Whites 9.0%, and Asians 8.5%.

Even if you’re healthy and do all the right things during pregnancy, you still could have a premature baby. The good news is there are things you can do to decrease your risk for a preterm delivery, especially if you have already delivered early before.

Could you be at risk for a preterm birth?

Below are risk factors for preterm birth. Please check the ones that apply to you and talk to your healthcare provider if you are pregnant or planning to get pregnant in the future.

The below checklist includes common risk factors for preterm birth. Depending on your risk factor(s), Makena® (hydroxyprogesterone caproate injection) may not be right for you.

While there are many causes for preterm birth, the safety and benefits of Makena have been demonstrated only in women who’ve unexpectedly delivered their baby prior to 37 weeks of pregnancy. It’s not meant for use in women with multiple gestations or other risk factors for preterm birth.

- Prior spontaneous (unexpected) preterm birth before 37 weeks
- Pregnant with twins, triplets, or other multiples
- Problems with the uterus or cervix
- African American heritage
- High blood pressure, stress, diabetes, or being overweight
- Short time between pregnancies (6–18 months)
- Certain infections during pregnancy such as an infection of the uterus, vagina, or urinary tract infection, or sexually transmitted disease
- Smoking, drinking alcohol, or using illegal drugs

If you’ve checked 1 or more of the above, now is the time to talk with your healthcare provider.
Steps you can take to reduce your risk of preterm birth

While there are no guarantees, you can still take steps to help reduce the chances of your baby being born prematurely. It’s important that you speak to your healthcare provider before you get pregnant and during your pregnancy about your risk for preterm birth, especially if you’ve delivered too early (less than 37 weeks) before.

**Eat right**

Eating healthy during pregnancy provides essential nutrients that you and your baby need. Ask your healthcare provider about which foods are good for you and your baby, and which foods you should avoid. You may also be instructed to take prenatal vitamins. 4

**Maintain a healthy lifestyle**

Be sure to get enough rest and relaxation during your pregnancy, especially if you are feeling stressed. You may also need to make some lifestyle changes, such as avoiding smoking, alcohol, and drugs. Ask your healthcare provider about support programs that can help you quit. 4

**Talk to your healthcare provider**

If you are at risk for having a preterm birth, talk to your doctor about ways to help you stay pregnant until full term. There are potential treatments that may help give your baby the time needed to develop.

“Since my first daughter was born preterm at 35 weeks, we were at greater risk for delivering our next baby early. I wanted to help reduce that risk.”

– Heather, mother of 2
Makena®, (hydroxyprogesterone caproate injection) may help you stay pregnant longer

Makena, pronounced Ma-keen-a, is the first and only FDA-approved hormone medicine (progestin) prescribed to lower the risk of having a preterm baby in women:

• Who are pregnant with one baby, and
• Who’ve unexpectedly delivered one baby too early (before 37 weeks) in the past

Makena is a weekly injection given (every 7 days) by your healthcare provider either at their office or in your home.

You can start Makena between 16 weeks and 20 weeks, 6 days of your pregnancy, depending on your healthcare provider’s direction.

FDA: Food and Drug Administration.

Every additional week makes a difference for your baby

Your baby needs every week of pregnancy to develop, both inside and out. For example, your baby’s brain and lungs are still developing in the last few weeks of pregnancy.

Makena® (hydroxyprogesterone caproate injection) was studied in women who were at risk for having a preterm baby because they had given birth to a preterm baby before.

• In that clinical study, taking Makena significantly lowered the rate of preterm birth compared to moms who did not take Makena.
• It’s not known whether Makena is safe and effective in women who have other risk factors for preterm birth
• Makena is not intended for use to stop active preterm labor

Ask your healthcare provider if FDA-approved Makena is right for you.

“For me, Makena gives that extra protection to reduce the chance of preterm birth.”
– Lyn, mother of 2

Hear moms’ personal stories at Makena.com.

For more information, visit Makena.com.

Please see Important Safety Information on page 23 and accompanying full Prescribing Information for Makena (hydroxyprogesterone caproate injection).
Benefits of using an FDA-approved medicine

Makena® (hydroxyprogesterone caproate injection) is the first and only FDA-approved medicine to reduce the risk of preterm birth in women who are currently pregnant with one baby and who have unexpectedly delivered a baby preterm (before 37 weeks) in the past.8

Makena is made in a facility that follows FDA’s Good Manufacturing Practices (GMPs).9,10 Before it was approved, the FDA thoroughly reviewed the safety, effectiveness, and manufacturing quality. These requirements help ensure the quality of the product, including9-11:

• The right drug
• The right amount of drug
• Free of contamination
• Sterile

The majority of drugs used in the United States are FDA approved and made under GMPs. Occasionally, due to a patient’s unique medical need, a pharmacist may need to compound an alternative formulation. Compounded drugs are not FDA approved and should only be prescribed when a patient has a medical need that can’t be met with the approved drug.12

Using Makena® (hydroxyprogesterone caproate injection)

• Makena is an injection given by a healthcare provider8:
  – In the healthcare provider’s office or
  – At home during a home healthcare visit (if covered by your insurance)

• You will get one injection into your hip (upper outer area of your buttocks) each week (every 7 days) until week 37 or until you deliver your baby—whichever happens first8
  – Injections start between week 16 and week 20, 6 days of your pregnancy, depending on your healthcare provider’s direction8

Home injections by healthcare professionals

We can help coordinate Makena injections through a home healthcare organization. Once approved by insurance, moms prescribed Makena can choose to receive their injections by a healthcare professional in the comfort of their home or another location that’s convenient for them.

Before you receive Makena, tell your healthcare provider if you have an allergy to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in Makena; diabetes or prediabetes, epilepsy, migraine headaches, asthma, heart problems, kidney problems, depression, or high blood pressure.
Is Makena® (hydroxyprogesterone caproate injection) safe?

You and your healthcare provider should consider the benefits and risks of treatment with Makena prior to deciding if Makena is right for you.

Makena should not be used if you:

- Have now or have had a history of blood clots or other blood clotting problems
- Have now or have had a history of breast cancer or other hormone-sensitive cancers
- Have unusual vaginal bleeding not related to your current pregnancy
- Have yellowing of your skin due to liver problems during your pregnancy
- Have liver problems, including liver tumors
- Have uncontrolled high blood pressure

Before you receive Makena, tell your healthcare provider if you:

- Have an allergy to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in Makena
- Have diabetes or prediabetes
- Have epilepsy
- Have migraine headaches
- Have asthma
- Have heart problems
- Have kidney problems
- Have depression
- Have high blood pressure

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

What are the possible side effects?

FOR MOMS: Makena® (hydroxyprogesterone caproate injection) may cause serious side effects including:

- Blood clots—Symptoms of a blood clot may include leg swelling, redness in your leg, a spot on your leg that is warm to touch, or leg pain that worsens when you bend your foot
- Allergic reactions—Symptoms of an allergic reaction may include hives, itching, or swelling of the face
- Depression
- Yellowing of your skin and the whites of your eyes

The most common adverse reactions observed with Makena were injection site reactions (pain, swelling, itching, bruising, or a hard bump), hives, itching, nausea, and diarrhea. In a clinical study, certain complications or events associated with pregnancy occurred more often in women who received Makena. These included miscarriage (pregnancy loss before 20 weeks of pregnancy), stillbirth (fetal death occurring during or after the 20th week of pregnancy), hospital admission for preterm labor, preeclampsia (high blood pressure and too much protein in your urine), gestational hypertension (high blood pressure caused by pregnancy), gestational diabetes, and oligohydramnios (low amniotic fluid levels).

FOR BABIES: In a follow-up study, children between the ages of 2–5 years old were evaluated for development in various physical, mental, and social measures. The results were similar to children born to non–Makena-treated moms.
Giving you an extra layer of support with Makena Care Connection®

When you start Makena® (hydroxyprogesterone caproate injection), you get more than the medicine. You get personalized resources that are specifically designed to help you throughout your experience with Makena. Think of us as an extra layer of support.

Prescription Support

Helps you get your prescription approved in a timely manner

You’re unique and so are your insurance benefits. Because getting your medicine in a timely manner is important, we’re here to lend a hand. We have a dedicated team who understands the coverage policies for Makena. Our experts can handle the details between your healthcare professional, insurance company, and pharmacy so you receive your Makena when you need it.

“‘It was helpful to lean on Makena Care Connection to help facilitate getting my medication. It was one less thing for me to worry about.’”

– Amber, mother of 2

Financial Assistance

Helps ensure affordable access to Makena

We believe that you should be able to focus on your pregnancy more than the cost of your medication. To support that, AMAG Pharmaceuticals is committed to making sure that moms like you have affordable access to Makena. We offer eligible patients’ financial assistance.

<table>
<thead>
<tr>
<th>Commercially insured moms whose health plan covers Makena</th>
<th>Helps lower out-of-pocket costs associated with copays, coinsurance, and deductibles.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uninsured and commercially underinsured moms</td>
<td>A free course of therapy.*</td>
</tr>
</tbody>
</table>

*Each patient’s eligibility is evaluated on an individual basis. To be eligible, patients must meet the FDA-approved indication (pregnant with a single baby with a history of singleton spontaneous preterm birth <37 weeks). In compliance with federal regulations, patients insured by a government-funded program (e.g., Medicaid, TRICARE, etc.) are not eligible. There are no upper-level income caps.

“I was so happy that I was approved for financial assistance. I feel very thankful that my family and I had this opportunity with the Makena Care Connection.”

– Nalleli, mother of 3

Hear moms’ personal stories at Makena.com.

Please see Important Safety Information on page 23 and accompanying full Prescribing Information for Makena (hydroxyprogesterone caproate injection).
Education & Adherence
Support that helps keep you on track with weekly injections

We understand that moms receiving Makena injections may need some encouragement and support to stick to their weekly injection schedule, and we want to help. This free service offers educational and adherence support to encourage you to make Makena part of your pregnancy and take an active role in your health.

A level of personalized support you can expect:

• Injection reminders that support weekly treatment
• Educational materials to address topics during pregnancy
• Encouragement so you can take an active role in your health

Have Questions? Connect with us.
1-800-847-3418 • 8 AM–8 PM ET
info@makenacareconnection.com

“Knowing she was just a phone call away gave me peace of mind. I appreciated feeling like I had someone supporting me every step of the way.”
– Shanise, Makena mom

Home Injections by Healthcare Professionals
Provides injection administration in the comfort of your home

We can help coordinate Makena injections through a home healthcare organization. Once you’re approved by insurance, you can choose to receive your injections by a healthcare professional in the comfort of your home or another location that’s convenient for you.

Hear moms’ personal stories at Makena.com.

Please see Important Safety Information on page 23 and accompanying full Prescribing Information for Makena (hydroxyprogesterone caproate injection).
Frequently asked questions

Q: My first baby was born preterm but has developed normally. Am I a candidate for Makena® (hydroxyprogesterone caproate injection)?
A: Even if your baby developed normally, you are still at risk for another preterm birth because delivering preterm is a significant risk factor for another preterm birth.¹⁴

Q: My first baby was born preterm but was not admitted to the NICU. Am I at risk for another preterm birth?
A: Delivering preterm is a significant risk factor for another preterm birth.¹⁴ Therefore, even if your baby did not require admittance to the NICU (neonatal intensive care unit), you are still at risk for another preterm birth.

Q: What is the active ingredient in Makena?
A: Makena, or hydroxyprogesterone caproate injection, is a prescription hormone medicine (progestin) used in women who are pregnant and who have unexpectedly delivered a baby too early (preterm) in the past.⁸

Q: I am afraid of needles, and Makena is a shot. Is it worth it for me to take Makena?
A: Talk to your healthcare provider about the benefits and risks of Makena. Receiving shots of Makena helps reduce your risk of another preterm birth. The site of the shot is your backside, so you will not have to watch as you are given the injection.⁸

Q: Will my health insurance cover Makena® (hydroxyprogesterone caproate injection)?
A: Makena Care Connection® will work with you, your healthcare provider, and your insurance company to understand your insurance coverage for Makena.

Q: Am I eligible for financial assistance?
A: We believe that you should be able to focus on your pregnancy more than the cost of your medication. To support that, AMAG Pharmaceuticals is committed to making sure that moms like you have affordable access to Makena. We offer eligible patients* financial assistance, which helps lower out-of-pocket costs.

*Each patient’s eligibility is evaluated on an individual basis. To be eligible, patients must meet the FDA-approved indication (pregnant with a single baby with a history of singleton spontaneous preterm birth <37 weeks).¹⁴ In compliance with federal regulations, patients insured by a government-funded program (e.g., Medicaid, TRICARE, etc.) are not eligible. There are no upper-level income caps.

Makena (hydroxyprogesterone caproate injection) is a prescription hormone medicine (progestin) used to lower the risk of preterm birth in women who are pregnant with one baby and who have delivered one baby too early (preterm) in the past. Makena was shown to work based on a lower number of women who delivered babies at less than 37 weeks of pregnancy. There are no studies showing Makena reduces the number of babies who have serious problems shortly after birth or who die. It is not known whether Makena is safe and effective in women who have other risk factors for preterm birth.
Healthcare provider discussion guide

Here are some questions to help you start a conversation about your prior preterm birth experience and how Makena® (hydroxyprogesterone caproate injection) may be able to help you.

Bring these questions when you see your healthcare provider.

QUESTIONS

I delivered a baby unexpectedly before 37 weeks. Could this happen again?

How can I reduce my risk and have a better chance for a full-term pregnancy?

How early could I go into labor?

What are some of the risk factors for preterm birth?

What are the signs and symptoms of preterm labor?

How does Makena work?

Is Makena safe for me and my baby?

Is Makena right for me?

While there are many causes for preterm birth, the safety and benefits of Makena have been demonstrated only in women who’ve unexpectedly delivered their baby prior to 37 weeks of pregnancy. It’s not meant for use in women with multiple gestations or other risk factors for preterm birth.

If you think you are at risk for another preterm birth due to a history of preterm birth, ask if FDA-approved Makena may be right for you.

Makena® (hydroxyprogesterone caproate injection) is a prescription hormone medicine (progestin) used to lower the risk of preterm birth in women who are pregnant with one baby and who have delivered one baby too early (preterm) in the past. Makena was shown to work based on a lower number of women who delivered babies at less than 37 weeks of pregnancy. There are no studies showing Makena reduces the number of babies who have serious problems shortly after birth or who die. It is not known whether Makena is safe and effective in women who have other risk factors for preterm birth.

Please see Important Safety Information on page 23 and accompanying full Prescribing Information for Makena (hydroxyprogesterone caproate injection).
FDA-approved indication for Makena® (hydroxyprogesterone caproate injection)

Makena (hydroxyprogesterone caproate injection) 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. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation 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.


Important Safety Information for Makena® (hydroxyprogesterone caproate injection)

Makena should not be used in women with any of the following conditions: blood clots or other blood clotting problems, breast cancer or other hormone-sensitive cancers, or history of these conditions; unusual vaginal bleeding not related to your current pregnancy, yellowing of the skin due to liver problems during pregnancy, liver problems, including liver tumors, or uncontrolled high blood pressure.

In a clinical study, certain complications or events associated with pregnancy occurred more often in women who received Makena. These included miscarriage (pregnancy loss before 20 weeks of pregnancy), stillbirth (fetal death occurring during or after the 20th week of pregnancy), hospital admission for preterm labor, preeclampsia (high blood pressure and too much protein in your urine), gestational hypertension (high blood pressure caused by pregnancy), gestational diabetes, and oligohydramnios (low amniotic fluid levels).

Makena may cause serious side effects including blood clots, allergic reactions, depression, and yellowing of your skin and the whites of your eyes. Call your healthcare provider right away if you think you have symptoms of a blood clot (leg swelling, redness in your leg, a spot on your leg that is warm to touch, or leg pain that worsens when you bend your foot) or symptoms of an allergic reaction (hives, itching, or swelling of the face). The most common side effects of Makena include injection site reactions (pain, swelling, itching, bruising, or a hard bump), hives, itching, nausea, and diarrhea.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
IF YOU HAD A SINGLETON SPONTANEOUS PRETERM BIRTH (BEFORE 37 WEEKS), YOU ARE AT RISK FOR ANOTHER EARLY DELIVERY

Every week counts when you’re pregnant

Your baby keeps growing and developing every week of pregnancy until your due date.1-3 Together, you and your healthcare provider can take an important step to help give your baby more time to develop.

Ask your healthcare provider about the importance of having a full-term delivery.

LEARN MORE about a medicine that may help you stay pregnant longer.

Have Questions? Connect with us.
1-800-847-3418 • 8 AM–8 PM ET
info@makenacareconnection.com
Administer intramuscularly at a dose of 250 mg (1 mL) once weekly.

Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation.

This highlights do not include all the information needed to use MAKENA safely and effectively.

**MAKENA® (hydroxyprogesterone caproate injection) for intramuscular use.**

Initial U.S. Approval: 1956

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**INDICATIONS AND USAGE**

Makena 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.

Limitation of use: Makena is not indicated for women with multiple gestations or other risk factors for preterm birth. (1)

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**DOSE AND ADMINISTRATION**

- Administer intramuscularly at a dose of 250 mg (1 mL) once weekly.
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation.
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first. (2.1)

**DOSE FORMS AND STRENGTHS**

1 mL single dose vial contains 250 mg of hydroxyprogesterone caproate. 5 mL multidose vial (250 mg/mL) contains 1250 mg hydroxyprogesterone caproate. (3)

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**CONTRAINDICATIONS**

- Current or history of thrombosis or thromboembolic disorders (4)
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions (4)
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy (4)
- Cholestatic jaundice of pregnancy (4)
- Liver tumors, benign or malignant, or active liver disease (4)
- Uncontrolled hypertension (4)

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**ADVERSE REACTIONS**

- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

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**WARNINGS AND PRECAUTIONS**

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

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**ADVERSE REACTIONS**

Most common adverse reactions reported in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group were injection site reactions (pain [35%], swelling [17%], pruritus [9%], nodule [5%]).

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**REFERENCES**

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 04/2016
Table 2 Selected Maternal Complications

<table>
<thead>
<tr>
<th>Pregnancy Complication</th>
<th>Makena N=310</th>
<th>Control N=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission for preterm labor</td>
<td>16.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Preeclampsia or gestational hypertension</td>
<td>8.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>3.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Other than delivery admission</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Common Adverse Reactions:

The most common adverse reaction was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥2% of subjects at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Makena N=310</th>
<th>Control N=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>34.8</td>
<td>32.7</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>17.1</td>
<td>7.8</td>
</tr>
<tr>
<td>Urticaria</td>
<td>12.7</td>
<td>11.3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>5.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Tachyphylaxis</td>
<td>5.8</td>
<td>4.6</td>
</tr>
<tr>
<td>Injection site induration</td>
<td>4.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

D. Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of Makena. Because these reactions are reported voluntarily from a population that is not necessarily representative of the population as a whole, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most common adverse reactions that led to discontinuation in both groups were uticaria and injection site pain/swelling (1% each).

7 Drug Interactions

In vitro drug-drug interaction studies were conducted with Makena. (See Clinical Pharmacology (12.3).) No in vivo drug-drug interaction studies were conducted with Makena.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of Makena use in women in the first trimester of pregnancy. Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received Makena at weekly doses of 250 mg by intramuscular injection in their second and third trimesters, as well as long-term (2-5 years) follow-up safety data on 194 of their infants, did not demonstrate any teratogenic risks to infants from uterine exposure to Makena. Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Makena.

Makena administration produced embryolethality in thrusus monkeys but not in cynomolgus monkeys exposed to 1 and 10 times the human dose equivalent every 7 days between days 20 and 164 of gestation. There were no teratogenic effects in either species.

8.2 Labor and Delivery

Makena is not intended for use to stop active preterm labor. The effect of Makena in active labor is unknown.

8.3 Nursing Mothers

Discontinue Makena at 37 weeks of gestation or upon delivery. Detectable amounts of progesterone have been identified in the milk of mothers carrying pregnant infants. Many studies have found no adverse effects of progesterone on breastfeeding performance, or on the health, growth, or development of infant.

8.4 Pediatric Use

Makena is not indicated for use in children. Safety and effectiveness in pediatric patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 and above for as users 18 years and older. (See Clinical Studies (14).)

8.5 Geriatric Use

Makena is not intended for use in postmenopausal women. Safety and effectiveness in postmenopausal women have not been established.

8.6 Renal Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with renal impairment.

8.7 Hepatic Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

10 OVERDOSE

There have been no reports of adverse events associated with overdose of Makena in clinical trials. In the case of overdose, the patient should be treated symptomatically.

11 DESCRIPTION

The active moiety of the medicinal ingredient in Makena is hydroxyprogesterone caproate. The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, (10β-oxohexyl). It has an empirical formula of C_{27}H_{39}O_2 and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C. The structural formula is:

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of preterm birth is not known.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Peak serum levels of hydroxyprogesterone caproate appeared after 3-7 days in non-pregnant subjects following a single intramuscular injection of 1000 mg hydroxyprogesterone caproate. Based on pharmacokinetic analysis of five non-pregnant female subjects who received a single intramuscular administration of 1000 mg hydroxyprogesterone caproate, the mean (± SD) C_{max} was estimated to be 27.8 (± 5.3) ng/mL, and the T_{1/2} estimated to be 4.8 (± 3) days.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity. No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Makena administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no evidence of development offsprings (F_1) or, the latter offspring’s ability to produce a viable, normal second (F_2) generation.

14 CLINICAL STUDIES

14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in women with a singleton pregnancy (age 16 to 43 years) who had a documented history of singleton spontaneous preterm birth (defined as delivery of less than 37 weeks) following spontaneous preterm labor or premature rupture of membranes. At the time of randomization (between 16 weeks, 0 days and 20 weeks, 6 days of gestation), an ultrasound examination confirmed gestational age and no known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy. A history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cesarean, hypertension requiring medication, or a seizure disorder).

A total of 453 pregnant women were randomized to receive either Makena (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation, and continuing until 27 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 58.5% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 28.4 kg/m^2.

The proportions of women in each treatment arm who delivered at <37 (the primary study endpoint), <35, and <32 weeks of gestation are displayed in Table 4.

Table 4 Proportion of Subjects Delivering at <37, <35 and <32 Gestational Weeks (ITT Population)

<table>
<thead>
<tr>
<th>Delivery Outcome</th>
<th>Makena (N=310)</th>
<th>Control (N=153)</th>
<th>Treatment difference and 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37 weeks</td>
<td>37.1</td>
<td>54.9</td>
<td>-17.8 (-28.0%, -7.4%)</td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>31.3</td>
<td>30.7</td>
<td>-0.6 (-9.0%, 7.8%)</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>19.6</td>
<td>19.0</td>
<td>-0.6 (-6.1%, 4.9%)</td>
</tr>
</tbody>
</table>

Four Makena-treated subjects were lost to follow-up at their gestational ages at time of last contact (18;22; 34; and 36 weeks).

* Adjusted for interim analysis.

Compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at <37 weeks. The proportions of women delivering at <35 and <32 weeks also were lower among women treated with Makena. The upper bounds of the confidence intervals for the treatment differences were 35 and 32 weeks were close to zero, indicating that the confidence interval for the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the proportion of preterm births at <32 weeks was limited.

After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7% of control subjects; see Figure 1.
Patients Information

Makena (mah-KEE-na) (hydroxyprogesterone caproate injection) 250 mg/mL

Read this Patient Information Leaflet before you receive Makena. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is Makena?

Makena is a prescription hormone medicine (progestin) used in women who are pregnant and who have delivered a baby too early (preterm) in the past. Makena is used in these women to help lower the risk of having a preterm baby again.

Makena is for women who:

• Are pregnant with one baby
• Have had a preterm delivery of one baby in the past

How well does Makena work?

Makena was studied in women who were at risk for having a preterm baby because they had previously given birth to a preterm baby. In the main study, about 37 of 100 women who received Makena gave birth preterm (before 37 weeks of pregnancy), compared to about 55 of 100 women who did not receive Makena. Another study of Makena is going on to see whether Makena reduces the number of babies who have serious problems (before 37 weeks of pregnancy), compared to about 55 of 100 women who did not receive Makena. Another study of Makena is going on to see whether Makena reduces the number of babies who have serious problems like bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or genetic abnormalities. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

15 RECOMMENDATIONS


16 HOW SUPPLIED/STORAGE AND HANDLING

Makena (NDC 64011-247-02) is supplied as 1 mL of a sterile solution in a single dose glass vial. Each 1 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (30.6% v/v) and benzyl benzoate USP (46% v/v).

Single unit carton: Contains one 1 mL single dose vial of Makena containing 250 mg of hydroxyprogesterone caproate.

Makena (NDC 64011-243-01) is supplied as 5 mL of a sterile solution in a multidose glass vial. Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Single unit carton: Contains one 5 mL multidose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at controlled room temperature [15°-30° C (59°-86° F)]. Use multidose vials within 5 weeks after first use.

Caution: Protect vial from light. Store vials in its box. Store upright.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site [see Adverse Reactions (6.1)].

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What are the possible side effects of Makena?
Makena may cause serious side effects, including:

- **Blood clots.** Symptoms of a blood clot may include:
  - Leg swelling
  - Redness in your leg
  - A spot on your leg that is warm to touch
  - Leg pain that worsens when you bend your foot
- **Allergic reactions.** Symptoms of an allergic reaction may include:
  - Hives
  - Itching
  - Swelling of the face

Call your healthcare provider right away if you get any of the symptoms above.

- **Depression**
- **Yellowing of your skin and the whites of your eyes**

The most common side effects of Makena include:

- Pain, swelling, itching, bruising or a hard bump at the injection site
- Hives
- Itching
- Nausea
- Diarrhea

Call your healthcare provider if you have the following at your injection site:

- Increased pain over time
- Oozing of blood or fluid
- Swelling

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Makena. For more information, ask your healthcare provider or pharmacist.

In a clinical study, certain complications or events associated with pregnancy occurred more often in women who received Makena compared to women who did not receive Makena, including:

- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

Call your healthcare provider for medical advice about side effects or pregnancy complications. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Makena?

- Store Makena at room temperature (59°F to 86°F or 15°C to 30°C)
- Store Makena in the original box to protect it from light
- Store the Makena box upright
- Makena 5 mL multidose vials should be used within 5 weeks after the first use
- Keep Makena out of the reach of children

General information about the safe and effective use of Makena
Medicines are sometimes prescribed for purposes other than those mentioned in the Patient Information Leaflets. Do not take Makena for conditions for which it was not prescribed. Do not give Makena to other people, even if they have the same condition you have. It may harm them.

This leaflet summarizes the most important information about Makena. If you would like more information, talk with your healthcare provider. You can ask for information about Makena that is written for healthcare professionals.

For more information, go to www.makena.com or call AMAG Pharmaceuticals Customer Service at the toll free number 1-877-411-2510.

To refill a prescription or to check on prescription status, call the Makena Care Connection at the toll free number 1-800-847-3418.

What are the ingredients in Makena?

Active ingredient: hydroxyprogesterone caproate

Inactive ingredients: castor oil and benzyl benzoate. 5 mL multidose vials also contain benzyl alcohol (a preservative)