

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

HELP GIVE YOUR BABY MORE TIME TO DEVELOP



Actor Portrayal

Giving moms an extra layer of personalized support through Makena Care Connection[®]

Makena[®]
hydroxyprogesterone
caproate injection



Makena® (hydroxyprogesterone caproate injection) helps give baby more time to develop¹

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. 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.**

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

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What is preterm birth?

The goal of a healthy pregnancy is to deliver full term (39 to 40 weeks) to give your baby the time needed to grow and develop. For example, your baby's brain and lungs are still developing during the last weeks of pregnancy.^{2,3}

Preterm birth is when a baby arrives too early; that's before 37 weeks of pregnancy, or 3 weeks prior to the baby's due date.⁴ Preterm birth can be unexpected or unplanned. Sometimes, a baby needs to be delivered earlier than normal in certain medical situations.⁵

Preterm birth can happen to any pregnant woman.

In many cases, healthcare providers don't fully understand what actually causes preterm birth. **But moms who have delivered a baby too early (before 37 weeks) in the past—regardless of the number of weeks early they've delivered—are at a higher risk for having another preterm birth.**⁶

Every week counts—every additional week makes a difference for your baby. Talk with your healthcare provider about the risks for preterm birth and what you can do to reduce your risk

Have you delivered preterm before?

In the United States, approximately 1 in 10 babies is born prematurely each year.² That's nearly 400,000 babies born too early.⁷

Preterm birth rates vary for different racial and ethnic groups. African Americans have a 13.4% preterm birth rate, Native Americans 10.8%, Hispanics 9.2%, Caucasians 8.9%, and Asians 8.6%.⁸

Even if you're healthy and do all the right things during pregnancy, such as maintaining a healthy lifestyle and eating a well-balanced diet, you still could have a premature baby. The good news is there are things you can do to decrease your risk for preterm delivery, especially if you have unexpectedly delivered a baby before 37 weeks of pregnancy in the past.



“My doctor told me that having a previous preterm birth increased my risk of having another preterm baby. My husband and I were very surprised to hear that I was at risk again.”

– Lyn, mom of a 36-week preemie

For more Makena mom stories, [visit makena.com](https://www.makena.com)

What are the potential risk factors for preterm birth?

The below checklist includes common risk factors for preterm birth.⁶ Depending on your risk factor(s), Makena® (hydroxyprogesterone caproate injection) may or 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. **Makena is 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, being overweight or underweight
- 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

You're not alone. If one or more of the above applies to you, **see page 17** of this brochure and talk with your healthcare provider about the risks associated with preterm birth.

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

What is Makena?

Makena helps get you closer to term.

Makena, pronounced mah-KEE-na, is a hormone medicine (progestin) prescribed to lower the risk of having another 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.



“My doctor and I discussed the option of taking Makena to reduce my risk of another preterm birth. This gave me peace of mind knowing I was doing everything I could to help give my baby time to develop.”

– Sarah, mom of a 34-week preemie

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hydroxyprogesterone
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About Makena® (hydroxyprogesterone caproate injection) Auto-Injector

Makena is an injection given by a healthcare provider:

- In the healthcare provider's office or
- At home during a home healthcare visit (if covered by your insurance)

Get to know the auto-injector:

- Designed so you never see the needle
- Given in the back of the upper arm (triceps area) under the surface of the skin with a short, thin needle
- Full dose delivered in ~15 seconds
- No need for private exam room or for you to disrobe



Not actual size

“My doctor told me about Makena Auto-Injector and was able to show me what to expect with a demonstration device. With the needle being not visible, I felt more comfortable with the thought of receiving a weekly injection for up to 21 weeks throughout my pregnancy.”

– Danielle, mom of a 30-week preemie

Makena therapy schedule

Makena therapy starts between week 16 and week 20, 6 days of your pregnancy, depending on your healthcare provider's direction. You will receive 1 injection each week (every 7 days) until week 37 (your last injection could be as late as 36 weeks, 6 days) or until you deliver your baby, whichever happens first.



Your Makena Weekly Injection Tracker

To help make Makena part of your routine, **please see page 18** for an injection tracker.

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.

When you choose Makena Auto-Injector, you have the opportunity to receive personalized support throughout your pregnancy from Makena Care Connection®

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

Is Makena® (hydroxyprogesterone caproate injection) safe?

You and your healthcare provider should consider the benefits and risks of therapy 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

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

What are the possible side effects?

For moms: 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, 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 side effects of Makena included 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 and 5 years old were evaluated for development in various physical, mental, and social measures. The results were comparable to children born to non-Makena-treated moms.⁹

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Personalized support with Makena Care Connection®

When you start Makena® (hydroxyprogesterone caproate injection) Auto-Injector, 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, mom of a 36-week preemie

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.



Makena
Care Connection®



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 Makena-eligible moms have affordable access to Makena Auto-Injector. We offer eligible patients financial assistance.

Commercially insured moms whose health plan covers Makena Auto-Injector*

Most pay no more than

\$35

per injection

- Helps lower out-of-pocket costs associated with copays, coinsurance, and deductibles
- Based on a sliding scale from \$0-\$35/injection
- Maximum AMAG contribution of \$5,000

Uninsured & commercially underinsured moms†

- A full course of therapy at no cost

Each patient's eligibility is evaluated on an individual basis. To be eligible, patients must meet the FDA-approved indication for Makena. In compliance with federal regulations, patients insured by a government-funded program (Medicaid, TRICARE, etc) are not eligible. These programs and any assistance provided may be discontinued or modified at any time based on eligibility, state and local laws, and program availability.

*Financial assistance applies to the patient's copay, coinsurance and deductibles for patients receiving Makena Auto-Injector. AMAG Pharmaceuticals will help lower the out-of-pocket cost each month, providing up to \$5,000 in financial assistance, or until therapy is completed, whichever comes first. The cost per injection is based on the household income with no upper-level income caps. Enrollment into the program cannot be retroactive.

†Restrictions apply. Patient must be at or below 500% federal poverty level based on residency to participate in patient assistance program.

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Education & Adherence

Support that helps keep you on track with weekly injections

We understand that moms receiving Makena® (hydroxyprogesterone caproate injection) 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.

Select personalized support services to best fit your needs:

- Calls on a weekly, bi-weekly, or monthly basis to support weekly therapy
- Injection reminders via text message
- Educational materials to address topics during pregnancy
- Encouragement so you can take an active role in your health



“Knowing my Care Manager 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, mom of a 22-week preemie



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 so you can receive your injections by a healthcare professional in the comfort of your home or another location that is convenient for you, if covered by your insurance.

Have Questions? Connect with us.

info@makenacareconnection.com
1-800-847-3418 (M–F, 8AM–8PM ET)

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

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Is Makena® (hydroxyprogesterone caproate injection) right for you?

In a clinical study, taking Makena significantly lowered the rate of preterm birth compared to moms who did not take Makena.¹

If you answer “yes” to all of the questions below, talk with your healthcare provider to see if Makena is right for you to reduce your risk of another preterm birth.

- Have you unexpectedly delivered a baby preterm (less than 37 weeks gestation, or more than 3 weeks too early) before?
- Was your preterm birth due to preterm labor or your water breaking?
- Are you currently pregnant with one baby?

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.

Makena is 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 spontaneous preterm birth, ask if Makena may be right for you

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

Questions to ask your healthcare provider

Here are some questions to help you start a conversation about your prior preterm birth experience and how Makena may be able to help reduce your risk of another preterm birth.

Ask your healthcare provider these questions to see if Makena is right for you:

- I delivered a baby unexpectedly before 37 weeks. Could this happen again?
- What are some of the risk factors for preterm birth?
- 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 the signs and symptoms of preterm labor?
- Is Makena right for me?

References: 1. Makena® (hydroxyprogesterone caproate injection) prescribing information, AMAG Pharmaceuticals, 2018. 2. March of Dimes. Long-term health effects of premature birth. <https://www.marchofdimes.org/complications/long-term-health-effects-of-premature-birth.aspx>. October 2013. Accessed January 22, 2019. 3. American College of Obstetricians and Gynecologists. Committee opinion no. 579: definition of term pregnancy. *Obstet Gynecol.* 2013;122:1139-1140. 4. American College of Obstetricians and Gynecologists. Preterm (premature) labor and birth. <https://www.acog.org/-/media/For-Patients/faq087.pdf>. November 2016. Accessed January 22, 2019. 5. March of Dimes. Why at least 39 weeks is best for your baby. <https://www.marchofdimes.org/pregnancy/why-at-least-39-weeks-is-best-for-your-baby.aspx>. October 2018. Accessed January 22, 2019. 6. March of Dimes. Preterm labor and preterm birth. <https://www.marchofdimes.org/pregnancy/preterm-labor-and-premature-birth.aspx>. October 2014. Accessed January 22, 2019. 7. March of Dimes. Fighting premature birth: the prematurity campaign. <https://www.marchofdimes.org/research/prematurity-research.aspx>. Accessed January 22, 2019. 8. March of Dimes. 2018 premature birth report card – United States. <https://www.marchofdimes.org/materials/PrematureBirthReportCard-United%20States-2018.pdf>. November 2018. Accessed January 22, 2019. 9. Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 α -hydroxyprogesterone caproate compared with placebo. *Obstet Gynecol.* 2007;110(4):865-872.

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Weekly therapy tracker

Make Makena® (hydroxyprogesterone caproate injection) a part of your weekly routine! Use this calendar as a resource to track your injections.

My Makena injection is every _____

SECOND TRIMESTER			
Week 16	Week 17	Week 18	Week 19
Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____
Week 20	Week 21	Week 22	Week 23
Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____
Week 24	Week 25	Week 26	Week 27
Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____

THIRD TRIMESTER			
Week 28	Week 29	Week 30	Week 31
Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____
Week 32	Week 33	Week 34	Week 35
Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____	Ⓛ Ⓜ ____ / ____
Week 36	<p>Weeks 37-38: This is early term, and baby is still growing³</p> <p>Weeks 39-40: This is full term—the goal of a healthy pregnancy³</p>		
Ⓛ Ⓜ ____ / ____			

Please note that your results and duration of therapy may vary.

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

Tips & best practices

To make the most of Makena therapy through Makena Care Connection, follow the tips and best practices below:

- To access the free personalized support from Makena Care Connection, complete the authorization as part of the prescription process
- Provide your mobile phone number if you would like to sign up for reminders via text message
- Confirm with your pharmacy that Makena Auto-Injector is being shipped

When in doubt, contact your Care Manager:

Name: _____

Extension: _____

What to expect when receiving therapy

- You'll hear an audible 'click' - this is what activates the device
- While it's a short, thin needle, it's still an injection. Some patients may experience a mild to moderate short-term burning sensation

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

Every week counts when you're pregnant

Your baby keeps growing and developing every week of pregnancy until your due date.^{2,4}

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.

Have Questions? Connect with us.

1-800-847-3418 (M–F, 8AM–8PM ET)

Full Prescribing Information
attached here.

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

Please see **Important Safety Information** on pages 9, 10, and 11 and attached **full Prescribing Information**.

Marketed by AMAG Pharmaceuticals, Inc. Waltham, MA 02451

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAKENA safely and effectively. See full prescribing information for MAKENA.

MAKENA® (hydroxyprogesterone caproate injection) for intramuscular or subcutaneous use.

Initial U.S. Approval: 1956

RECENT MAJOR CHANGES

Dosage and Administration, Dosing (2.1) 02/2018
Dosage and Administration, Preparation & Administration (2.2) 02/2018

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 (1). The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation (14). There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

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

DOSAGE AND ADMINISTRATION

- Makena auto-injector: Administer subcutaneously using Makena auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Makena (single- and multi-dose vials): Administer intramuscularly at a dose of 250 mg (1 mL) once weekly in the upper outer quadrant of the gluteus maximus (2.1)
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation (2.1)
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first (2.1)

DOSAGE FORMS AND STRENGTHS

- 1.1 mL single-use auto-injector for subcutaneous use contains 275 mg of hydroxyprogesterone caproate (250 mg/mL) (3)
- 1 mL single-dose vial for intramuscular use contains 250 mg of hydroxyprogesterone caproate. (3)
- 5 mL multi-dose vial for intramuscular use contains 1250 mg of hydroxyprogesterone caproate (250 mg/mL). (3)

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)

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)

ADVERSE REACTIONS

- In a study where the Makena intramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in $\geq 2\%$ of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena auto-injector use (and higher than with Makena intramuscular injection) was injection site pain (10% in one study and 34% in another). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AMAG Pharmaceuticals at 1-877-411-2510 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 02/2018

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FULL PRESCRIBING INFORMATION

1 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. 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.**

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

- Makena auto-injector: Administer **subcutaneously** using auto-injector at a dose of 275 mg (1.1 mL) once weekly (every 7 days) in the back of either upper arm by a healthcare provider
- Makena (single- and multi-dose vials): Administer **intramuscularly** at a dose of 250 mg (1 mL) once weekly (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider
- 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

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Makena is a clear, yellow solution. The solution must be clear at the time of use; replace vial if visible particles or crystals are present.

Specific instructions for administration by dosage form:

Makena single-dose or multi-dose vials (intramuscular use only)

Makena single-dose or multi-dose vials are only for intramuscular injection with a syringe into the upper outer quadrant of the gluteus maximus, rotating the injection site to the alternate side from the previous week, using the following preparation and administration procedure:

- Clean the vial top with an alcohol swab before use.
- Draw up 1 mL of drug into a 3 mL syringe with an 18 gauge needle.
- Change the needle to a 21 gauge 1½ inch needle.
- After preparing the skin, inject in the upper outer quadrant of the gluteus maximus. The solution is viscous and oily. Slow injection (over one minute or longer) is recommended.
- Applying pressure to the injection site may minimize bruising and swelling.
- If the 5 mL multi-dose vial is used, discard any unused product 5 weeks after first use.

Makena auto-injector (subcutaneous use only)

Makena auto-injector is a single-use, pre-filled, disposable device containing a 27 gauge, 0.5 inch needle that delivers one dose subcutaneously in the back of the upper arm.

Because Makena auto-injector is preservative-free, once the cap is removed the device should be used immediately or discarded.

Rotate the injection site to the alternate arm from the previous week. Do not use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard. Avoid areas with scars, tattoos, or stretch marks.

The solution is viscous and oily. The auto-injector takes approximately 15 seconds to deliver the dose; when the viewing window is fully blocked (completely orange), the full dose has been administered.

The "Instructions for Use" contains detailed steps for administering the subcutaneous injection using the auto-injector [see *Dosage and Administration* (2.3)]. Read the "Instructions for Use" carefully before administering Makena auto-injector.

2.3 Instructions for Use (Makena Auto-injector)

Instructions for Use: Read this carefully before each use.

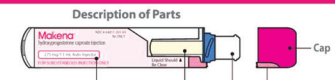
FOR SUBCUTANEOUS USE ONLY

Makena®

hydroxyprogesterone caproate injection
275 mg/1.1 mL (250 mg/mL) Auto-injector

Single Use.
Administer one injection weekly.

Administration by Healthcare Professionals only.



Preparation

If you need help or instructions, call:
1-877-411-2510

- Carefully read all steps before beginning injection.
- Injection process must be completed without interruption.

Supplies You Will Need

- 1 Makena Auto-injector
- 1 alcohol swab
- 1 cotton ball or gauze

Storage Conditions

- DO NOT refrigerate or freeze.
- Protect from light.
- Store at 20° - 25°C (68° - 77°F).
- Keep away from children.

1 Inspect Makena Auto-injector

- Inspect the Makena Auto-injector for any visible damage. **DO NOT** use if it appears damaged or broken, or if cap is missing or not secure.
- Check the expiration date. **DO NOT** use if expired.
- Inspect the medication liquid through the Viewing Window; it should be clear to light yellow and free of particles. (See Figure 1). **DO NOT** use if the liquid is cloudy or if particles are present. You may notice an air bubble; this is normal.

Figure 1:



2 Select & Prepare Subcutaneous Injection Site

- Only use the back of either upper arm for injection site.
- Rotate the injection site to the alternate arm from the previous week. (See Figure 2).
- Wash your hands with soap and water. Wipe the injection site with an alcohol swab.
- Allow the site to dry on its own. **DO NOT** fan or blow on the injection site. **DO NOT** touch the site again before injecting.
- DO NOT** use in areas where the skin is tender, bruised, red, scaly, raised, thick, or hard. Avoid areas with scars, tattoos, or stretch marks.

Figure 2:



INJECT SUBCUTANEOUSLY IN THE BACK OF EITHER UPPER ARM

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks 0 days and 20 weeks 6 days. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

Table 4 Summary of Mean (Standard Deviation) Pharmacokinetic Parameters for Hydroxyprogesterone Caproate

Group (N)	C _{max} (ng/mL)	T _{max} (days) ^a	AUC ₍₀₋₇₎ (ng·hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0-7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9-1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0-3.0)	1268.0 (511.6)

Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16-20 (Group 1), (2) after a dose between Weeks 24-28 (Group 2), or (3) after a dose between Weeks 32-36 (Group 3)

^a Reported as median (range)

^b t = 7 days

For all three groups, peak concentration (C_{max}) and area under the curve (AUC_(0-7 days)) of the mono-hydroxylated metabolites were approximately 3-8-fold lower than the respective parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived due to the absence of reference standards for these multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study who reached full-term in their pregnancies, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when Makena was administered subcutaneously with the auto-injector (1.1 mL) in the back of the upper arm and when Makena was dosed intramuscularly (1 mL) in the upper outer quadrant of the gluteus maximus.

Distribution: Hydroxyprogesterone caproate binds extensively to plasma proteins including albumin and corticosteroid binding globulins.

Metabolism: In vitro studies have shown that hydroxyprogesterone caproate can be metabolized by human hepatocytes, both by phase I and phase II reactions. Hydroxyprogesterone caproate undergoes extensive reduction, hydroxylation and conjugation. The conjugated metabolites include sulfated, glucuronidated and acetylated products. In vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the caproate group is retained during metabolism of hydroxyprogesterone caproate.

Excretion: Both conjugated metabolites and free steroids are excreted in the urine and feces, with the conjugated metabolites being prominent. Following intramuscular administration to pregnant women at 10-12 weeks gestation, approximately 50% of a dose was recovered in the feces and approximately 30% recovered in the urine.

Drug Interactions

Cytochrome P450 (CYP) enzymes: An *in vitro* inhibition study using human liver microsomes and CYP isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another *in vitro* study using human hepatocytes under conditions where the prototypical inducers or inhibitors caused the anticipated increases or decreases in CYP enzyme activities, hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the findings indicate that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations.

In vitro data indicate that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

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. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F₀) dams, their developing offspring (F₁), or the latter offspring's ability to produce a viable, normal second (F₂) 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 at less than 37 weeks of gestation 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 had 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 cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 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 37 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.9 kg/m².

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 5.

Table 5 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

Delivery Outcome	Makena ¹ (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval ²
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

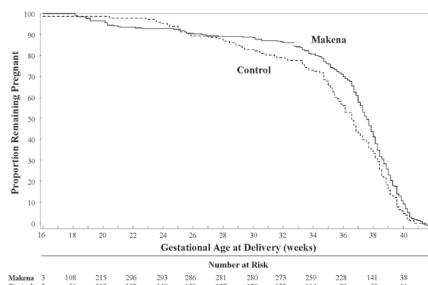
¹ Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18¹, 22¹, 34¹ and 36¹ weeks).

² 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 difference at < 35 and < 32 weeks were close to zero. Inclusion of zero in a confidence interval would indicate the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the number 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.

Figure 1 Proportion of Women Remaining Pregnant as a Function of Gestational Age



The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 6. Due to the higher rate of miscarriages and stillbirths in the Makena arm, there was no overall survival difference demonstrated in this clinical trial.

Table 6 Fetal Losses and Neonatal Deaths

Complication	Makena N=306 ^A n (%) ^B	Control N=153 n (%) ^B
Miscarriages <20 weeks gestation ^C	5 (2.4)	0
Stillbirth	6 (2.0)	2 (1.3)
Antepartum stillbirth	5 (1.6)	1 (0.6)
Intrapartum stillbirth	1 (0.3)	1 (0.6)
Neonatal deaths	8 (2.6)	9 (5.9)
Total Deaths	19 (6.2)	11 (7.2)

^A Four of the 310 Makena-treated subjects were lost to follow-up and stillbirth or neonatal status could not be determined

^B Percentages are based on the number of enrolled subjects and not adjusted for time on drug

^C Percentage adjusted for the number of at risk subjects (n=209 for Makena, n=107 for control) enrolled at <20 weeks gestation.

A composite neonatal morbidity/mortality index evaluated adverse outcomes in live births. It was based on the number of neonates who died or experienced respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis. Although the proportion of neonates who experienced 1 or more events was numerically lower in the Makena arm (11.9% vs. 17.2%), the number of adverse outcomes was limited and the difference between arms was not statistically significant.

14.2 Infant Follow-Up Safety Study

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated women and 84 children of control subjects. The primary endpoint was the score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

16 HOW SUPPLIED/STORAGE AND HANDLING

Makena auto-injector (for subcutaneous injection)

Makena auto-injector (NDC 64011-301-03) is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a pre-filled syringe. Each 1.1 mL auto-injector 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 1.1 mL single-patient-use auto-injector of Makena containing 275 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Caution: Protect auto-injector from light. Store auto-injector in its box.

Makena single- and multi-dose vials (for intramuscular injection)

Makena (NDC 64011-247-02) is supplied as 1 mL of a sterile preservative-free clear yellow 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 clear yellow solution in a multi-dose 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 multi-dose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F). Do not refrigerate or freeze.

Use multi-dose vials within 5 weeks after first use.

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the 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)].

Distributed by: AMAG Pharmaceuticals, Inc. Waltham, MA 02451

02/2018

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PATIENT INFORMATION

MAKENA (mah-KEE-na)

(hydroxyprogesterone caproate injection)

auto-injector for subcutaneous use

MAKENA (mah-KEE-na)

(hydroxyprogesterone caproate injection)

vial for intramuscular use

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. It is not known if MAKENA reduces the number of babies who are born with serious medical conditions or die shortly after birth. MAKENA is for women who:

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

MAKENA is not intended for use to stop active preterm labor.

It is not known if MAKENA is safe and effective in women who have other risk factors for preterm birth.

MAKENA is not for use in women under 16 years of age.

Who should not receive MAKENA?

MAKENA should not be used if you have:

- blood clots or other blood clotting problems now **or** in the past
- breast cancer or other hormone-sensitive cancers now **or** in the past
- unusual vaginal bleeding not related to your current pregnancy
- yellowing of your skin due to liver problems during your pregnancy
- liver problems, including liver tumors
- high blood pressure that is not controlled

What should I tell my healthcare provider before receiving MAKENA?

Before you receive MAKENA, tell your healthcare provider about all of your medical conditions, including if you have:

- a history of allergic reaction to hydroxyprogesterone caproate, castor oil, or any of the other ingredients in MAKENA. See the end of this Patient Information leaflet for a complete list of ingredients in MAKENA.
- diabetes or pre-diabetes.
- epilepsy (seizures).
- migraine headaches.
- asthma.
- heart problems.
- kidney problems.
- depression.
- high blood pressure.

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

MAKENA may affect the way other medicines work, and other medicines may affect how MAKENA works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive MAKENA?

- **Do not** give yourself MAKENA injections. A healthcare provider will give you the MAKENA injection 1 time each week (every 7 days) either:
 - in the back of your upper arm as an injection under the skin (subcutaneous), **or**
 - in the upper outer area of the buttocks as an injection into the muscle (intramuscular).
- You will start receiving MAKENA injections anytime from 16 weeks and 0 days of your pregnancy, up to 20 weeks and 6 days of your pregnancy.
- You will continue to receive MAKENA injections 1 time each week until week 37 (through 36 weeks and 6 days) of your pregnancy or when your baby is delivered, whichever comes first.

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 the touch
 - leg pain that gets worse when you bend your foot

Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.

- **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 during treatment with MAKENA.

- **Decrease in glucose (blood sugar) tolerance.** Your healthcare provider will need to monitor your blood sugar while taking MAKENA if you have diabetes or pre-diabetes.
- **Your body may hold too much fluid (fluid retention).**
- **Depression.**
- **Yellowing of your skin and the whites of your eyes (jaundice).**
- **High blood pressure.**

The most common side effects of MAKENA include:

- pain, swelling, itching 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

Other side effects that may happen more often in women who receive MAKENA include:

- 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)

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.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAKENA?

• **MAKENA auto-injector for subcutaneous use:**

- Store the auto-injector at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not refrigerate or freeze.
- Protect the auto-injector from light.
- Store the auto-injector in its box.

• **MAKENA vial for intramuscular use:**

- Store the vial at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not refrigerate or freeze.
- Protect the vial from light.
- Store the vial in its box in an upright position.

Keep MAKENA and all medicines 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 listed in a Patient Information leaflet. Do not use MAKENA for a condition for which it was not prescribed. Do not give MAKENA to other people, even if they have the same symptoms 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 your healthcare provider or pharmacist for information about MAKENA that is written for health professionals.

What are the ingredients in MAKENA?

Active ingredient: hydroxyprogesterone caproate

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

Distributed by: AMAG Pharmaceuticals, Inc.
Makena is a registered trademark of AMAG Pharmaceuticals, Inc.
For more information, go to www.MAKENA.com or call AMAG Pharmaceuticals Customer Service at the toll-free number 1-877-411-2510.

This Patient Information has been approved by the U.S. Food and Drug Administration
Revised: 02/2018