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.**

Please see Important Safety Information on the back and full Prescribing Information for Makena in pocket.
Connecting you, your staff, & your patients to personalized support for Makena® (hydroxyprogesterone caproate injection)

When you choose Makena for your patients, you get more than the medicine. You get one centralized resource that’s designed specifically to assist your patients throughout their Makena experience.

At Makena Care Connection®, we offer personalized support that helps make filling prescriptions easier, addresses your patients’ financial concerns, and encourages adherence to therapy. Your patients won’t just get Makena to help reduce the risk of recurrent preterm birth; they’ll also get support when they need it.

We speak your patients’ language

We’re ready to help your patients with translation services in more than 240 languages. So communicating with moms on Makena isn’t a barrier.

Connecting your patients to support

Together we can work toward one goal—helping your patients achieve a full-term pregnancy. Our dedicated staff at Makena Care Connection is ready to provide an extra layer of personalized support.

Have Questions? Connect with us.
1-800-847-3418 • M–F 8am–8pm ET • info@makenacareconnection.com

“We’ve been able to connect moms to the Makena Care Connection® for education, financial assistance, and adherence support. They’ve made the process easy and allowed me to focus on taking care of my patients.”

—Deborah Carpenter, WHNP-BC*

*Deborah Carpenter is a consultant for AMAG Pharmaceuticals Inc.
Working together to help ensure moms get off to a good start with Makena® (hydroxyprogesterone caproate injection) as prescribed

Goal of 24 HOURS

**Prescription form tips:**
- Include a copy of both sides of the patient insurance card(s) when you submit the prescription form
- If patient does not have insurance, check “uninsured”
- Encourage patient to sign the HIPAA waiver*

**Financial assistance tips:**
- If a patient is concerned about her out-of-pocket cost for Makena, she should call Makena Care Connection at 1-800-847-3418 to see if she is eligible for financial assistance

---

*By signing the HIPAA waiver, the patient allows the Makena Care Connection to communicate with the HCP, insurer, and pharmacy on her behalf. If the patient does not sign the HIPAA waiver, the Makena Care Connection will not have the ability to check the patient’s status with the pharmacy.

---

**Medicine delivery tips:**
- If the prescription is submitted before 13 weeks gestation, it may be held and processed once the patient reaches 13 weeks gestation†
- Patient needs to respond to the pharmacy’s phone call in order to ship medicine

---

† Some insurance companies will not approve Makena until a patient reaches 13 weeks gestation. In those cases, Makena Care Connection holds the prescription until the patient reaches 13 weeks, at which point they will triage the prescription to the payer-preferred pharmacy.

Please see Important Safety Information on the back and full Prescribing Information for Makena in pocket.
Personalized support that helps Makena® (hydroxyprogesterone caproate injection) moms access therapy and encourages adherence

Financial Assistance
We believe patients should be able to focus more on their pregnancy than the cost of their medication. To support that, AMAG Pharmaceuticals is committed to ensuring affordable access to Makena. We proactively screen and offer eligible patients financial assistance with no income caps.

<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.

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. Benefits may include:
- Supporting adherence with weekly injections
- Addressing logistical barriers for patients
- Simplifying scheduling challenges for your office

Education and Adherence
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 women to make Makena part of their pregnancy and take an active role in their health.
- Injection reminders that support weekly treatment
- Educational materials to address topics during pregnancy
- Encouragement so patients can take an active role in their health

Please see Important Safety Information on the back and full Prescribing Information for Makena in pocket.
Connecting you, your staff, & your patients to personalized support for Makena® (hydroxyprogesterone caproate injection)

When you choose Makena for your patients, you get more than the medicine. You get one centralized resource that’s designed specifically to assist your patients throughout their Makena experience.

At Makena Care Connection®, we offer personalized support that helps make filling prescriptions easier, addresses your patients’ financial concerns, and encourages adherence to therapy. Your patients won’t just get Makena to help reduce the risk of recurrent preterm birth; they’ll also get support when they need it.

Connecting your patients to support
Together we can work toward one goal—helping your patients achieve a full-term pregnancy. Our dedicated staff at Makena Care Connection is ready to provide an extra layer of personalized support.

We speak your patients’ language
We’re ready to help your patients with translation services in more than 240 languages. So communicating with moms on Makena isn’t a barrier.

Have Questions?
Connect with us.
1-800-847-3418  •  M - F 8 am–8 pm ET  •  info@makenacareconnection.com

Important Safety Information for Makena® (hydroxyprogesterone caproate injection)

- Do not use Makena in women with any of the following conditions:
  - Current or history of thrombosis or thromboembolic disorders
  - Known or suspected breast cancer, other hormone-sensitive cancer or history of these conditions
  - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
  - Cholestatic jaundice of pregnancy
  - Liver tumors, benign or malignant, or active liver disease
  - Uncontrolled hypertension
- Makena should be discontinued if thrombosis or thromboembolism occurs
- Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil
- Women receiving Makena should be monitored if they:
  - Are prediabetic or diabetic
  - Have conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction
  - Have a history of clinical depression; Makena should be discontinued if depression recurs
  - Develop jaundice; consider whether benefit of use warrants continuation
  - Develop hypertension
- Certain pregnancy-related fetal and maternal complications or events were numerically increased in Makena-treated subjects as compared to placebo subjects, including miscarriage (2.4% vs. 0%) and stillbirth (2% vs. 1.3%), admission for preterm labor (16% vs. 13.8%), preeclampsia or gestational hypertension (8.8% vs. 4.6%), gestational diabetes (5.6% vs. 4.6%), and oligohydramnios (3.6% vs. 1.3%)
- 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 ≥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%)
- 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)

Please see full Prescribing Information for Makena in pocket.
When you start Makena® (hydroxyprogesterone caproate injection), you get more than the medicine. You’ll get personalized resources that are specifically designed to help you throughout your experience with Makena. Think of us as an extra layer of support.

**Rx Support** 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 that you receive your Makena when you need it.

**Financial Assistance** 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. We offer eligible patients financial assistance, which helps to lower out-of-pocket costs.*

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**Education and Adherence** 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.

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

Ready to Refill? About 1 week before you are scheduled to refill your Makena prescription, your pharmacy will call you to confirm shipment and arrange payment. Your Makena prescription cannot ship until you speak with the pharmacy to arrange payment and delivery. Your pharmacy’s number may show up as an “unknown number,” or an 800 number on caller ID. So if you do not receive this call, please call Makena Care Connection at 1-800-847-3418, and we’ll help.

Please see Important Safety Information on the back and ensure you receive the full Prescribing Information for Makena from your healthcare provider, or visit www.makena.com/pi.
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.

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.

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.
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 ---

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

--- INDICATIONS AND USAGE ---

MAKENA is a progesterin 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)

--- WARNINGS AND PRECAUTIONS ---

- 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)

- 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 pre eclampsia, 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 ≥ 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.

--- PATIENT COUNSELING INFORMATION ---

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.

--- FULL PRESCRIBING INFORMATION: CONTENTS* ---

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2 DOSAGE AND ADMINISTRATION
2.1 Dosing
2.2 Preparation and Administration
2.3 Instructions for Use (MAKENA Auto-injector)
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Thromboembolic Disorders
5.2 Allergic Reactions
5.3 Decrease in Glucose Tolerance
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12 CLINICAL PHARMACOLOGY
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13 NONCLINICAL TOXICOLOGY
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* Sections or subsections omitted from the full prescribing information are not listed

--- DOUBLE SPACING ON PAGE ---

--- FULL PRESCRIBING INFORMATION ---

1 INDICATIONS AND USAGE

MAKENA is a progesterin 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 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 (every 7 days) in the upper outer quadrant of the gluteus maximus by a healthcare provider (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)

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use. 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 for intramuscular use only. These vials are 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:
  1. Clean the vial top with an alcohol wipe before use.
  2. Draw up 1 mL of drug into a 3 mL syringe with an 18 gauge needle.
  3. Change the needle to a 21 gauge 1½ inch needle.
  4. 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.
  5. Applying pressure to the injection site may minimize bruising and swelling.
  6. 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.
The most common adverse reaction with intramuscular injection 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 and 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=340</th>
<th>Control N=133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>61.4%</td>
<td>46.3%</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>12.7%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>12.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Erythema</td>
<td>9.7%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Injection site puritus</td>
<td>3.9%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>4.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2.3%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolism in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects who received intramuscular injection. In the second study, injection site pain occurred in 20/39 (51%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

8.6 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. OVERDOSAGE

Table 4  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=340</th>
<th>Control N=133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction to progestin</td>
<td>3.7%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Hydroxyprogesterone caproate</td>
<td>3.3%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

Common Adverse Reactions

The most common adverse reaction with intramuscular injection 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 and at a higher rate in the Makena group than in the control group.

Table 2  Selected Fetal Complications

<table>
<thead>
<tr>
<th>Pregnancy Complication</th>
<th>Makena N=330</th>
<th>Control N=133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>34 (2.5%)</td>
<td>35 (2.9%)</td>
</tr>
<tr>
<td>Admission due to labor</td>
<td>7/30</td>
<td>8/29</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>2.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Table 1  Selected Fetal Complications

<table>
<thead>
<tr>
<th>Pregnancy Complication</th>
<th>Makena N=340</th>
<th>Control N=133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>33.4 (1.8)</td>
<td>33.2 (1.7)</td>
</tr>
<tr>
<td>Admission due to labor</td>
<td>8/30</td>
<td>8/29</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
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<td>2.6</td>
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Table 2  Selected Fetal Complications

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>33.7 (1.8)</td>
<td>33.5 (1.7)</td>
</tr>
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</tr>
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<td>Hospital stay (days)</td>
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</table>

Other than delivery admission.

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

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Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects who received intramuscular injection. In the second study, injection site pain occurred in 20/39 (51%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Makena. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Body as a whole: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth), fatigue, fever, hot flashes/fleas
- Digestive disorders: Vomiting
- Infections: Urinary tract infection
- Nervous system disorders: Headache, dizziness
- Pregnancy, puerperium and perinatal conditions: Cervical incompetence, premature rupture of membranes
- Reproductive system and breast disorders: Cervical dilation, shortened cervix
- Respiratory disorders: Dyspnea, chest discomfort

Skin: Rash

7  DRUG INTERACTIONS

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP2C19, CYP2D6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is unlikely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5. [See Clinical Pharmacology (12.3)]. No in vivo drug-drug interaction studies were conducted with Makena.
Female patients with a singleton pregnancy received intramuscular doses of 250 mg hydroxyprogesterone caproate for the reduction of preterm birth starting between 16 weeks and 32 weeks of gestation. All patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Hydroxyprogesterone Caproate</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLIVEC</td>
<td>Active metabolites</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>0.005</td>
</tr>
<tr>
<td>17-OH-progesterone</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dihydroxyprogesterone</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**12.3 Pharmacokinetics**

No specific pharmacodynamic studies were conducted with Makena. Hydroxyprogesterone caproate is a synthetic progestin. The mechanism by which hydroxyprogesterone caproate reduces the risk of recurrent preterm birth is not known.

**12.1 Mechanism of Action**

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena was evaluated in a population of women who were at risk for a recurrent preterm delivery. The study was conducted in 24 centers in the United States and enrolled 463 pregnant women. The study population included women with a prior history of preterm birth and a singleton pregnancy at 16 to 32 weeks of gestation. The primary endpoint was the rate of preterm birth at <37 weeks of gestation. The secondary endpoints included the rates of preterm birth at <35 and <32 weeks of gestation, as well as the rates of fetal losses and neonatal deaths in each treatment arm.

**12.2 Pharmacodynamics**

Hydroxyprogesterone caproate does not appear to interfere with the synthesis of other hormones in the body, and it is not known whether hydroxyprogesterone caproate affects the metabolism of other drugs.

**12.3 Pharmacokinetics**

Hydroxyprogesterone caproate is metabolized by human hepatic cytochrome P450 (CYP) enzymes. The main metabolic pathways for hydroxyprogesterone caproate include hydroxylation at the 17α-position, 17β-position, and 11β-position. The relative activity and significance of these metabolites are not known.

**12.3.1 Mechanism of Action**

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy postmenopausal women, the oral bioavailability of hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. However, a significant interaction was observed between hydroxyprogesterone caproate and CYP2A6 related drug-drug interactions at the clinically relevant concentrations. 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.

**16.1.4 Infant Follow-Up Safety Study**

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were randomized to receive either Makena or control treatment (n=209 for Makena, n=107 for control) enrolled at <20 weeks gestation. 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. The structural formula is:

\[
\begin{align*}
\text{CH}_3 & \quad \text{O} \\
& \quad \text{C} \\
& \quad \text{H}_2 \text{C} \\
& \quad \text{H} \\
& \quad \text{H}
\end{align*}
\]

**17.1.3 Patient Counseling Information**

There were no significant differences in the occurrence of adverse events between the Makena and control groups. The most common adverse events reported in the Makena group were injection site reactions (30.6%) and injection site pain (28.6%). The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 6. The number of preterm births at <32 weeks was limited.

**17.1.4 Patient Counseling Information**

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).

**17.1.5 Patient Counseling Information**

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. 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.
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

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