FDA-approved indication for Makena® (hydroxyprogesterone caproate injection) and Important Safety Information

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.

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)
Introduction to Makena Auto-Injector

This guide covers some important issues about Makena Auto-Injector insurance coverage and reimbursement, including a coding key to help you and your office with Makena billing procedures. Remember that a patient’s individual insurance benefits will depend on her coverage, and different insurers may have different coverage policies. **Note:** There are formulations of Makena other than Makena Auto-Injector. This guide is specific to Makena Auto-Injector, is provided for informational purposes only, and does not constitute legal advice.

For questions, call Makena Care Connection® at 1-800-847-3418 (fax: 1-800-847-3413), email info@makenacareconnection.com, or you can visit the website at www.makenahcp.com.

**Makena distribution**

As a specialty injectable, Makena can be covered by insurance plans as a pharmacy or medical benefit. Your patient’s insurance plan will determine how Makena is covered.

- To prescribe Makena, submit the Makena Prescription Form to Makena Care Connection via fax at 1-800-847-3413
  - Makena Care Connection investigates the patient’s insurance benefits, and upon approval, sends the Makena prescription to the payer-preferred dispensing pharmacy for processing
  - The pharmacy verifies insurance coverage, collects the patient’s out-of-pocket cost, and ships the product

- Order and stock Makena through one of the specialty distributor partners (ie, buy-and-bill)
  - CuraScript: (877) 599-7748
  - McKesson Plasma and Biologics: (877) 625-2566
  - TheraCom: (888) 214-8313

**Makena dosing and administration**

Makena is a once-weekly injection. Makena is administered by a healthcare provider subcutaneously via an auto-injector once a week (every 7 days). Makena is packaged as a single-use auto-injector (275 mg/1.1 mL).

Makena treatment should be started between 16 weeks, 0 days and 20 weeks, 6 days of gestation and continued until 37 weeks (last injection as late as 36 weeks, 6 days) or delivery, whichever occurs first.
Billing and coding instructions

The following information will be required when completing the CMS 1500 claim form (see sample form on page 6). Please use your clinical judgment to select the appropriate codes where applicable.


Please include the appropriate CPT code for any Makena® (hydroxyprogesterone caproate injection) related service in Box 24D of the CMS 1500 claim form. Submit a charge for the office visit using the injection code OR the appropriate office visit (Evaluation and Management) code (99201–99214), not both.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96372</td>
<td>Therapeutic, prophylactic, or diagnostic injection; subcutaneous or intramuscular</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99201–99205</td>
<td>Office/outpatient visit, new patient; 10 min–60 min</td>
</tr>
<tr>
<td>99211–99214</td>
<td>Office/outpatient visit (by staff), established patient; 5 min–25 min</td>
</tr>
</tbody>
</table>

Note: Duration of appointment will vary depending on the nature of the visit.

Diagnosis Code (ICD-10-CM)

Please include the appropriate ICD-10-CM code to classify the diagnosis in Box 21 of the claim form.

<table>
<thead>
<tr>
<th>ICD-10-CM Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>O09.212</td>
<td>Supervision of pregnancy with history of preterm labor, second trimester</td>
</tr>
<tr>
<td>O09.213</td>
<td>Supervision of pregnancy with history of preterm labor, third trimester</td>
</tr>
<tr>
<td>O09.219</td>
<td>Supervision of pregnancy with history of preterm labor, unspecified trimester</td>
</tr>
</tbody>
</table>

Note: The ICD-10 codes start with an uppercase “O,” which is followed by a zero.

Disclaimer:
This resource and all supporting materials are supplied for information only and are not intended to be a thorough description or analysis of the subject matter herein, nor are they opinions of AMAG Pharmaceuticals. The information and opinions are based on the CPT 2017 and ICD-10-CM 2017 coding manuals and AMA HCPCS 2017. Because payer benefits change regularly, providers are responsible for confirming coverage, coding, and payment with respective payers. Providers are also responsible for ensuring accuracy of service claim forms and supportive documentation sent to payers. AMAG Pharmaceuticals does not make any representation or guarantees concerning the coverage or reimbursement of any service or item.
Important HCPCS billing and coding information

Makena® (hydroxyprogesterone caproate injection) has a unique J code J1726 as of January 1, 2018. The code should be used in column 24D of the CMS 1500 claim form.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Code</th>
<th>Description</th>
<th>Unit of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>J code</td>
<td>J1726</td>
<td>Makena® (hydroxyprogesterone caproate injection)</td>
<td>10 mg=1 billable unit</td>
</tr>
</tbody>
</table>

• Enter the number of billable units in Box 24G

Important information about reimbursement

When calculating reimbursement, it is important to record the appropriate billable unit. The reimbursement per billable unit may vary based on your contracted payer rate; check with the payer to ensure that your claim is recorded correctly. Below is an example of how to calculate reimbursement using the Makena Auto-Injector:

There are 275 mg in one weekly dose (1.1 mL) of Makena therapy, administered subcutaneously via auto-injector.\(^5\)

• J1726
  - 1 billable unit=10 mg
  - 1 Makena injection=27.5 billable units (275 mg/10 mg)
  - Calculation: 27.5 billable units x (reimbursement rate per billable unit)

Please confirm with the payer if partial billable units is acceptable or if rounding up of billable units is required.

Completing the CMS 1500 claim form

A National Drug Code (NDC) and quantity should be used when billing Makena. Use one of the following codes in Box 19 of the CMS 1500 claim form.

<table>
<thead>
<tr>
<th>NDC</th>
<th>Product</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subcutaneous auto-injector</strong>&lt;br&gt;64011-301-03 OR 64011-0301-03</td>
<td>Makena® (hydroxyprogesterone caproate injection) Auto-Injector</td>
<td>275 mg/1.1 mL</td>
</tr>
</tbody>
</table>

Payer requirements regarding 10-digit and 11-digit NDC may vary.
Completing the CMS 1500 claim form

Please see the following “Physician or supplier information” section of a sample CMS 1500 claim form for Makena® (hydroxyprogesterone caproate injection), completed using Makena Auto-Injector as an example.

Box 19: Local use information

Always enter the drug name, strength, dosage, and NDC (64011-301-03 OR 64011-0301-03). It is recommended that a copy of the published pricing source (e.g., Red Book price page) for Makena be attached when a claim form is submitted.

Box 21: Diagnosis or nature of illness or injury

Document appropriate ICD-10-CM diagnosis codes corresponding to patient’s diagnosis:
Line 1—primary diagnosis code.
Please see page 4 for a code description.

Box 24D: Procedure code

Document product administration with appropriate CPT and modifier codes. For example: 96372; therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular and/or the office visit code based on the third-party payer’s reimbursement policy, plus a modifier code such as 644.2. Please see page 4 for a list of potential codes.

Box 24G: Service units

Report unit of service.
J1726: 10 mg=1 billable unit.
Some payers may require the use of J3490. Please check with payer.
Enter the additional information in Box 24, including (in order): date and place of service, charges, and qualifier.

Disclaimer: The sample CMS 1500 claim form above only includes the coding information outlined on prior page and should be used for information purposes only.
Frequently asked questions

The following are answers to some of the most frequently asked questions regarding insurance coverage.

Q. How can Makena Auto-Injector insurance coverage be determined for a specific patient?

A. To determine if the health insurance plan provides coverage and payment for Makena, fax a completed Makena Prescription Form to 1-800-847-3413 or call Makena Care Connection® at 1-800-847-3418 to initiate the process. If the patient’s insurance plan requires you to order Makena and submit a claim for each dose, contact the insurance plan directly to confirm the reimbursement rate for each injection.

Q. Which billing code should be used to submit to the insurance company?

A. Makena has a unique J code (J1726) which should be used in column 24D of the CMS 1500 claim form. Some payers may require use of J3490. Please check with payer before submitting claims for reimbursement.

Many payers/insurers will reimburse a healthcare provider for the appropriate office visit CPT code or the injection code. Therefore, the submitted charge for the office visit should include the appropriate office visit CPT code that corresponds to the level of service provided or for the injection using CPT code 96372—therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular.

Please verify the individual patient’s benefits and confirm the reimbursement rate prior to submitting claims for therapy. Additionally, the reimbursement per billable unit may vary based on payer rates and/or the structure of the reimbursement policy.

Q. How do I bill using the Makena J code?

A. The unique Makena J code—J1726—should be used in column 24D of the CMS 1500 claim form. The billable units for the Makena J code are in mg, which can be used in column 24G.

When calculating reimbursement, it is important to record the appropriate billable unit in Box 24G of the CMS 1500 claim form. Using Makena Auto-Injector as an example, there are 275 mg in one weekly dose (1.1 mL) of therapy.

- J code calculation: 27.5 billable units x (reimbursement rate per billable unit)
- Cost per billable unit will vary based on contracted payer rate

Please confirm with the payer if partial billable units is acceptable or if rounding up of billable units is required. Some payers may require use of J3490. Please check with payer.

Please see Important Safety Information on page 2 and attached full Prescribing Information for Makena.
Q. Will the insurance company require a prior authorization for Makena® (hydroxyprogesterone caproate injection)?
A. As with other injectable drugs, some insurance companies will require a prior authorization for Makena. The prior authorization is often in place to ensure the patient meets the eligibility criteria for therapy based on the FDA-approved indication. Clinical eligibility includes women who:
• Are pregnant with a single baby, and
• Have a history of singleton spontaneous preterm birth (<37 weeks)
You may be contacted by Makena Care Connection®, the assigned pharmacy, and/or the insurance plans with questions regarding prior authorization for Makena.

Q. How does my patient get connected to financial assistance in a buy-and-bill scenario?
A. If your patient feels as though her out-of-pocket expense is too high for Makena Auto-Injector, please have her call Makena Care Connection to see if she is eligible for financial assistance. Please ensure the patient informs Makena Care Connection that she is receiving injections of Makena in your office that you purchased directly from a specialty distributor.
Eligibility criteria include:
• Patient meets the FDA-approved indication (pregnant with a singleton with a history of singleton spontaneous preterm birth <37 weeks of gestation)

In compliance with federal regulations, patients insured by a government-funded program (eg, Medicaid, TRICARE, etc.) are not eligible.

Q. What can I do for my patients who do not have insurance?
A. Make sure to check “Patient does not have insurance and should be evaluated for patient assistance program” in Step 1 of the Makena Prescription Form in order for your patient to be screened for eligibility for the Makena Patient Assistance Program.
Eligibility criteria include:
• Patient meets the FDA-approved indication (pregnant with a singleton with a history of singleton spontaneous preterm birth <37 weeks of gestation)
Restrictions apply. Patient must be ≤ 500% federal poverty level based on residency to participate in patient assistance program.

Q. Where can I access the CMS 1500 form?
Q. What is the return policy?
A. Under certain circumstances, Makena can be returned for credit. Please see our returns policy at www.makenahcp.com to see if your order qualifies.

Q. Is 340B/PHS pricing available?
A. 340B-eligible hospitals and other eligible facilities can obtain Makena through CuraScript, Inc., McKesson Plasma and Biologics, or TheraCom.

Q. Will I pay the list price or is the price higher due to distributor markups?
A. You will purchase Makena at the product acquisition price (ie, list price/WAC, or 340B pricing for eligible hospitals). There are no distributor markups when Makena is purchased through CuraScript, Inc., McKesson Plasma and Biologics, or TheraCom.

If purchasing auto-injector (1.1 mL) you may be eligible to receive a 15% volume discount. Please contact CuraScript (877-599-7748) or TheraCom (888-214-8313) for more information.
<table>
<thead>
<tr>
<th>State</th>
<th>Phone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabama</td>
<td>(800) 362-1504</td>
</tr>
<tr>
<td>Alaska</td>
<td>(907) 465-3030</td>
</tr>
<tr>
<td>Arizona</td>
<td>(602) 417-4000</td>
</tr>
<tr>
<td>Arkansas</td>
<td>(800) 457-4454</td>
</tr>
<tr>
<td>California</td>
<td>(800) 541-5555</td>
</tr>
<tr>
<td>Colorado</td>
<td>(800) 221-3943</td>
</tr>
<tr>
<td>Connecticut</td>
<td>(800) 842-8440</td>
</tr>
<tr>
<td>Delaware</td>
<td>(800) 372-2022</td>
</tr>
<tr>
<td>District of Columbia</td>
<td>(202) 442-5988</td>
</tr>
<tr>
<td>Florida</td>
<td>(888) 419-3456</td>
</tr>
<tr>
<td>Georgia</td>
<td>(800) 766-4456</td>
</tr>
<tr>
<td>Hawaii</td>
<td>(800) 316-8005</td>
</tr>
<tr>
<td>Idaho</td>
<td>(208) 334-5747</td>
</tr>
<tr>
<td>Illinois</td>
<td>(800) 843-6154</td>
</tr>
<tr>
<td>Indiana</td>
<td>(800) 577-1278</td>
</tr>
<tr>
<td>Iowa</td>
<td>(800) 338-8366</td>
</tr>
<tr>
<td>Kansas</td>
<td>(800) 766-9012</td>
</tr>
<tr>
<td>Kentucky</td>
<td>(800) 635-2570</td>
</tr>
<tr>
<td>Louisiana</td>
<td>(888) 342-6207</td>
</tr>
<tr>
<td>Maine</td>
<td>(877) 353-3771</td>
</tr>
<tr>
<td>Maryland</td>
<td>(800) 977-7388</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>(800) 841-2900</td>
</tr>
<tr>
<td>Michigan</td>
<td>(517) 373-3740</td>
</tr>
<tr>
<td>Minnesota</td>
<td>(800) 657-3739</td>
</tr>
<tr>
<td>Mississippi</td>
<td>(800) 421-2408</td>
</tr>
<tr>
<td>Missouri</td>
<td>(800) 392-2161</td>
</tr>
<tr>
<td>Montana</td>
<td>(800) 362-8312</td>
</tr>
<tr>
<td>Nebraska</td>
<td>(402) 471-3121</td>
</tr>
<tr>
<td>Nevada</td>
<td>(775) 684-3600</td>
</tr>
<tr>
<td>New Hampshire</td>
<td>(603) 271-2261</td>
</tr>
<tr>
<td>New Jersey</td>
<td>(800) 356-1561</td>
</tr>
<tr>
<td>New Mexico</td>
<td>(505) 827-3103</td>
</tr>
<tr>
<td>New York</td>
<td>(800) 541-2831</td>
</tr>
<tr>
<td>North Carolina</td>
<td>(800) 662-7030</td>
</tr>
<tr>
<td>North Dakota</td>
<td>(701) 328-2321</td>
</tr>
<tr>
<td>Ohio</td>
<td>(800) 324-8680</td>
</tr>
<tr>
<td>Oklahoma</td>
<td>(405) 522-7300</td>
</tr>
<tr>
<td>Oregon</td>
<td>(800) 359-9517</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>(800) 440-3989</td>
</tr>
<tr>
<td>Rhode Island</td>
<td>(401) 462-5300</td>
</tr>
<tr>
<td>South Carolina</td>
<td>(803) 898-2500</td>
</tr>
<tr>
<td>South Dakota</td>
<td>(605) 773-4678</td>
</tr>
<tr>
<td>Tennessee</td>
<td>(800) 342-3145</td>
</tr>
<tr>
<td>Texas</td>
<td>(800) 925-9126</td>
</tr>
<tr>
<td>Utah</td>
<td>(801) 538-6155</td>
</tr>
<tr>
<td>Vermont</td>
<td>(800) 250-8427</td>
</tr>
<tr>
<td>Virginia</td>
<td>(804) 786-6145</td>
</tr>
<tr>
<td>Washington</td>
<td>(800) 562-3022</td>
</tr>
<tr>
<td>West Virginia</td>
<td>(888) 483-0797</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>(800) 362-3002</td>
</tr>
<tr>
<td>Wyoming</td>
<td>(307) 777-7531</td>
</tr>
</tbody>
</table>

More than Makena® (hydroxyprogesterone caproate injection) with personalized patient support

To help support benefits investigations and prior authorizations for your patients, contact Makena Care Connection®.

Rx Support
Each woman is unique and so are her insurance benefits. Because timely access is so important to your practice, we’ll aid in verifying insurance coverage and obtaining prior authorizations (when applicable) to help your patients get their Makena prescription on time.

Financial Assistance
AMAG Pharmaceuticals is committed to ensuring affordable access to Makena.

Copay Assistance*: Commercially insured patients whose health plan covers Makena Auto-Injector

Most pay no more than $35 per injection

- Based on a sliding scale from $0-$35/injection
- Maximum company benefit of $5,000

Patient Assistance Program*: Uninsured and commercially underinsured patients
- Eligible moms may receive a full course of therapy at no cost

Education & 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.

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 deductible 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.

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

Please see Important Safety Information on page 2 and attached full Prescribing Information for Makena.
Full Prescribing Information attached here.
If missing, please visit http://www.makena.com/pi
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-use 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

- 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 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 [6%]).
  - 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.

---

**Full Prescribing Information: Contents**

1. INDICATIONS AND USAGE
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
   5.4 Fluid Retention
   5.5 Depression
   5.6 Jaundice
   5.7 Hypertension
6. ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Postmarketing Experience
7. DRUG INTERACTIONS
8. USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation
   8.4 Pediatric Use
9. CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
10. OVERDOSAGE
11. DESCRIPTION
12. NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13. CLINICAL STUDIES
   14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth
   14.2 Infant Follow-Up Safety Study
14. HOW SUPPLIED/STORAGE AND HANDLING
15. PATIENT COUNSELING 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 Makena auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm.

**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.

**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 use and 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 swab before use.
2. Draw up 1 mL of drug into a 3 mL syringe with a 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. Change the needle to a 21 gauge 1½ inch needle that delivers one dose subcutaneously in the back of the upper arm.

**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. See full prescribing information for MAKENA. (3)

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. (3)

See full prescribing information for MAKENA. (3)
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. 2/20 (10%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/34 (59%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injections.

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. The most frequently reported adverse reactions are:

- Body as a whole: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warm/hot, fatigue, fever, hot flashes/flickers
- Digestive disorders: Vomiting
- Gastrointestinal disorders: Headache, dizziness
- Gynecological disorders: Menorrhagia
- Hypersensitivity reactions: Urticaria, rash, irritation, hypersensitivity, warmth
- Local injection site reactions: Injection site pain/swelling
- Miscellaneous: Cervical dilatation, 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 interaction with CYP1A2, CYP2D6, CYP2E1, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. In vivo data indicated that therapeutic concentration of hydroxyprogesterone caproate was not likely to inhibit the activity of CYP2C8, CYP2C9, CYP3A4, CYP2D6, CYP2E1, and CYP3A4 [See Clinical Pharmacology (12.3)]. No in vivo drug-drug interaction studies were conducted with Makena.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fatal, neonatal, and maternal risks are discussed throughout the labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study [See Clinical Studies (14.1, 14.2)] did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are limited and further studies to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent. But in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.

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 hydroxyprogesterone caproate.

8.2 Lactation

Risk Summary

Low levels of progesterone are present in human milk with the use of progesterin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progesterone on the breastfed child or on milk production.

8.4 Pediatric Use

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

8.5 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

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

11 DESCRIPTION

The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate, a progestin. The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17-[[(1-oxohexyl)oxy]. It has an empirical formula of C_{27}H_{44}O_{5} and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to off-white crystals or powder with a melting point of 120°-124°C.

The structure is:

-CH\(_2\)\_4-\(\text{O}\)\_2

Makena is a clear, yellow, sterile, non-erogenic solution for intramuscular (vials) or subcutaneous (auto-injector) injection. Each 1 mL Makena auto-injector for subcutaneous use and each 1 mL single-dose vial for intramuscular use contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v) in a preservative-free solution of castor oil USP (50.6% w/v) and benzoic benzoate USP (46% w/v). Each 5 mL, multi-dose vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v) in castor oil USP (28.6%) and benzoic benzoate USP (46% w/v) with the preservative benzyl alcohol NF (2% v/v).

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 the adverse reactions that occurred in ≥2% of subjects and at a higher rate in the Makena group than the control group.
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: 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 36 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

<table>
<thead>
<tr>
<th>Group (N)</th>
<th>Cmax (μg/mL)</th>
<th>Tmax (h)</th>
<th>AUC0-t (μg·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=11)</td>
<td>12.3 (4.9)</td>
<td>1.0 (0.9-3.0)</td>
<td>1269.6 (285.0)</td>
</tr>
<tr>
<td>Group 2 (N=8)</td>
<td>12.5 (3.9)</td>
<td>1.0 (0.9-1.9)</td>
<td>1269.0 (253.0)</td>
</tr>
</tbody>
</table>

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

For all three groups, peak concentration (Cmax) and area under the curve (AUC0-t) were approximately 3-fold lower than the respective parameters for the control group. While de-acetylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results were derived due to the absence of reference standards for these 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 using linear regression analysis, was 19.7 (9.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy postmenopausal 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 globulin.

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 CYP2A6. The in vivo data indicate that the conjugate group is retained during metabolism of hydroxyprogesterone caproate.

Extensive conjugated metabolites and free sterols 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 substrates incubated using Makena showed that hydroxyprogesterone caproate had approximately 80%, 150%, and 80%, respectively, of the inhibitory activity of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another in vitro inhibition study using human liver microsomes and CYP substrates incubated using Makena, hydroxyprogesterone caproate did not inhibit or induce CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the in vitro in vitro inhibition study using human liver microsomes and CYP substrates incubated using Makena indicated that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6-mediated drug-drug interactions at the clinically relevant concentrations.

In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C9, CYP2C19, CYP2D6, CYP3A1, and CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Hydroxyprogesterone caproate has not been adequately studied 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 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 at risk for preterm birth (N=366) who had a documented history of at least one preterm 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 and 20 weeks 6 days), all patients had blood drawn daily for 7 days to evaluate pharmacokinetics.

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

<table>
<thead>
<tr>
<th>Delivery Outcome</th>
<th>Makena (N=113)</th>
<th>Control (N=153)</th>
<th>Treatment difference %</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37 weeks</td>
<td>37.1 (9.8)</td>
<td>54.9 (10.5)</td>
<td>-17.8% (-28.9%, -6.7%)</td>
<td></td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>31.9 (9.7)</td>
<td>50.7 (12.1)</td>
<td>-18.8% (-30.9%, -6.7%)</td>
<td></td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>11.9 (9.8)</td>
<td>19.6 (17.5)</td>
<td>-7.5% (-16.1%, -0.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Four Makena-treated subjects were lost to follow-up. They were counted as censored 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 at <37 weeks by 17.8% (95% CI: -28.9%, -6.7%), at <35 weeks by 18.8% (95% CI: -30.9%, -6.7%), and at <32 weeks by 7.5% (95% CI: -16.1%, -0.3%). Compared with 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 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: Proportions 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

<table>
<thead>
<tr>
<th>Complication</th>
<th>Makena (N=130)</th>
<th>Control (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriages &lt;20 weeks gestation</td>
<td>5 (2.4)</td>
<td>9 (6.2)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>6 (2.0)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Antepartum stillbirth</td>
<td>5 (1.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Intrapartum stillbirth</td>
<td>1 (0.3)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Neonatal death</td>
<td>8 (2.6)</td>
<td>9 (5.9)</td>
</tr>
</tbody>
</table>

Fetal Deaths 19 (6.2) 11 (7.2)

Four of the 310 Makena-treated subjects were lost to follow-up and stillbirth or neonatal status could not be determined. *13% are based on the number of enrolled subjects and not adjusted for time on drug.

Table 7 Percentages of Women Remaining Pregnant as a Function of gestational age

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Makena (N=113)</th>
<th>Control (N=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37 weeks</td>
<td>37.1 (9.8)</td>
<td>54.9 (10.5)</td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>31.9 (9.7)</td>
<td>50.7 (12.1)</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>11.9 (9.8)</td>
<td>19.6 (17.5)</td>
</tr>
</tbody>
</table>

Complication

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

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

Makena auto-injector (NDA 64011-301-03) is supplied as 1.1 mL of a clear yellow sterile preservative-free solution in an auto-injector containing a prefilled 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 benzene USP (46% v/v).

Single unit: Contains one 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Consult 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 (geastritis, see Adverse Reactions (6.1)).

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

02/2018
ver 1.2
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).
- migraines.
- 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