Healthcare provider discussion guide

Below are some of the most common risk factors for preterm birth:

- Prior spontaneous (unexpected) preterm delivery 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

Depending on your risk factors, Makena may or may not be appropriate for you.

When talking with your healthcare provider about your pregnancy and concerns about another preterm birth, being prepared may make the conversation easier. The following are some questions you can discuss with your healthcare provider.

- I delivered a baby unexpectedly before 37 weeks. Could this happen again?
- How can I reduce my risk and have a better chance for a full-term pregnancy?
- How early could I go into labor?
- What are some of the risk factors for preterm birth?
- What are the signs and symptoms of preterm labor?
- How does Makena® (hydroxyprogesterone caproate injection) work?
- Is Makena safe for me and my baby?
- Is Makena right for me?

**Indication**

Makena is a prescription hormone medicine (progestin) used to lower the risk of preterm birth in women who are pregnant with one baby and who have delivered one baby too early (preterm) in the past. Another study of Makena is going on to see whether Makena improves the number of babies who have serious problems shortly after birth or who die. It is not known whether Makena is safe and effective in women who have other risk factors for preterm birth.

**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. 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 may report an adverse event related to AMAG Pharmaceuticals’ products by calling 1-877-411-2510 or emailing amag@druginfo.com. If you prefer, you may contact the U.S Food and Drug Administration (FDA) directly at fda.gov/medwatch or call 1-800-FDA-1088.

Please see accompanying full Prescribing Information for Makena.

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

Full Prescribing Information: Contents*

1 mL single-dose vial for intramuscular use contains 250 mg of hydroxyprogesterone caproate (250 mg/mL) (3)

Dosage and Administration, Preparation & Administration

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)

Full Prescribing Information: Contents*

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 (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)

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 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)

3 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)

4 Contraindications

Liver tumors, benign or malignant, or active liver disease (4)

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)

5 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)

6 Adverse Reactions

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 Drug Interactions

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12 Clinical Pharmacology

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14.2 Infant Follow-Up Safety Study

16 How Supplied/Storage and Handling

17 Patient Counseling Information

* Sections or subsections omitted from the full prescribing information are not listed

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)

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:

1. Clean the vial top with an alcohol swab 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 1 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.
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5. Applying pressure to the injection site may minimize bruising and swelling.

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.

8.4 Pediatric Use

8.6 Hepatic Impairment

11 Description

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12.3 Pharmacokinetics

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

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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.

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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 1 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.

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.
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 uterine and injection site pain/swelling (1% each).

Pulmonary embolus 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 subcutaneously to 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 who used an intramuscular injection. In the second study, injection site pain occurred in 2/25 (8%) of subjects who used the subcutaneous auto-injector vs. 5/81 (6%) of subjects receiving intramuscular injection.

6.2 Postmarketing Experience

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

Because progestational drugs may cause uterine bleeding, advise women taking Makena to use a form of contraception including barrier methods, if possible, to prevent conception.

Body as a whole: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth), fatigue, fever, hot flashes/flashes

Disorder of skin: Urticaria

Disorder of the nervous system: Dizziness

Pregnancy, puerperium and perinatal conditions: Cervical incompetence, premature rupture of membranes

Respiratory system and breast disorders: Cervical dilation, shortened cervix

Risk factors for increased risk of adverse reactions have been identified as follows:

6.3 Drug Interactions

In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal inhibition of CYP2C8, CYP2C9, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. In vitro data indicated that therapeutic concentration of hydroxyprogesterone caproate was not likely to inhibit the activity of CYP2C8, CYP2C9, CYP3A4, CYP2D6, CYP2E1, and CYP3A4.

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. Fetal, 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)) did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are not sufficient 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 of 20 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

Studies in animals 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 not 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 progesterone-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 dosing experience were limited to the same in women aged 16 years and above as for users 18 years and older (See Clinical Studies (14.1)).

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 overdose, 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 20α-hydroxy-4-ene-3,20-dione, 17(1-oxohexyl) oxy. It has an empirical formula of C27H40O4 and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C. The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17α-(1-oxohexyl) oxy. It has an empirical formula of C27H40O4 and a molecular weight of 428.60. Hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C. The structural formula is:

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.

Other than delivery admission.

Table 2  Selected Maternal Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Makena</th>
<th>Control</th>
<th>Change (Makena-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage (&lt; 20 weeks)</td>
<td>5/209</td>
<td>0/107</td>
<td>5/142</td>
</tr>
<tr>
<td>Miscarriage ≥ 20 weeks</td>
<td>0/209</td>
<td>0/107</td>
<td>0/142</td>
</tr>
<tr>
<td>Preeclampsia or gestational hypertension</td>
<td>8.8</td>
<td>4.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>5.6</td>
<td>4.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Cervical incompetence</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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=153</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain</td>
<td>32</td>
<td>32</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>5</td>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>Urticaria</td>
<td>12.3</td>
<td>11.1</td>
<td>1.2%</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3.6</td>
<td>3.6</td>
<td>0%</td>
</tr>
<tr>
<td>Injection site puritus</td>
<td>9.8</td>
<td>3.3</td>
<td>6.5%</td>
</tr>
<tr>
<td>Injection site nodule</td>
<td>4.5</td>
<td>2.0</td>
<td>2.5%</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2.3</td>
<td>0.7</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

For each of the adverse reactions listed in this section, the frequency of adverse reactions was determined using the following scale:

* = in 1 to 10% of subjects
• = in 0.1 to 1% of subjects
0 = in less than 0.1% of subjects

Table 1  Selected Fetal Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Makena</th>
<th>Control</th>
<th>Change (Makena-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage (&lt; 20 weeks)</td>
<td>5/300</td>
<td>0/300</td>
<td>5/300</td>
</tr>
<tr>
<td>Miscarriage ≥ 20 weeks</td>
<td>0/300</td>
<td>0/300</td>
<td>0/300</td>
</tr>
</tbody>
</table>

Table 2  Maternal Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Makena</th>
<th>Control</th>
<th>Change (Makena-Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions for labor</td>
<td>5</td>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>Preecampsia or gestational hypertension</td>
<td>8</td>
<td>16</td>
<td>8%</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>3.6</td>
<td>3.6</td>
<td>0%</td>
</tr>
<tr>
<td>Cervical incompetence</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>
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 and 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</th>
<th>C_{max} (ng/mL)</th>
<th>T_{max} (hr)</th>
<th>AUC_{0-7} (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=25)</td>
<td>7.0 (2.5)</td>
<td>1.5 (0.5)</td>
<td>714.6 (51.1)</td>
</tr>
<tr>
<td>Group 2 (N=8)</td>
<td>7.5 (3.0)</td>
<td>1.0 (0.1)</td>
<td>729.0 (253.0)</td>
</tr>
</tbody>
</table>

Drug elimination was assessed by monitoring 24-hour urines after the first dose. Group 1 (five) after a dose between Week 12-16 (Group 1), Group 2 (one) after a dose between Week 16-19 (Group 2), and one patient after a dose between Week 12-15 (Group 1).

For the three groups, peak concentration (C_{max}) and area under the curve (AUC_{0-7}) of the mono-hydroxylated metabolites were approximately 3-fold lower than the respective parameters for the unconjugated drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful contribution was observed 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 (13.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (8.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy postmenopausal women, intramuscular doses of 250 mg hydroxyprogesterone caproate were given at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days. A total of 463 pregnant women were randomized to receive either Makena and 250 mg/mL (25% w/v) in a preservative-free solution containing castor oil USP (30.6% w/v) or the same solution without castor oil USP, used to prepare the auto-injector.

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Clinical Trials

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 exposure up to 5 times the recommended human dose, had no adverse effects on the parent (F₁) dams, their developing offspring (F₂), 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 Racially, Randomized, Double-Blind, Placebo-Controlled Clinical Trial, the Safety and Effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in 2001 in a multinational, double-blind, placebo-controlled trial involving 15,967 women, who had documented a history of 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, 0 weeks, 6 days and 32 weeks, 6 days), an ultrasound examination had confirmed gestational age and no known fetal anomaly. Women were excluded for prior pregestational treatment or heparin therapy during the current pregnancy; a history of thromboembolic disease, or malformations or congenital anomalies (such as cleft or planned cleft, hypothalamic hypothyroidism, or a seizure disorder).

A total of 463 women were randomized to receive either Makena (N=130), or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 32 weeks, 6 days, 0 days, 6 days, and continuing until 37 weeks of gestation or delivery. Demographics and the Makena treatment groups were similar to those in the control group, and included 59.0% Black, 25.2% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.8 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)

<table>
<thead>
<tr>
<th>Delivery Outcome</th>
<th>Makena (N=153) (%)</th>
<th>Control (N=153) (%)</th>
<th>Treatment difference (%), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37 weeks</td>
<td>37.4</td>
<td>51.4</td>
<td>-13.8 (-18.7%, -8.9%)</td>
</tr>
<tr>
<td>&lt;35 weeks</td>
<td>23.1</td>
<td>37.4</td>
<td>-14.3 (-19.1%, -9.5%)</td>
</tr>
<tr>
<td>&lt;32 weeks</td>
<td>11.9</td>
<td>19.6</td>
<td>-7.7 (-11.8%, -3.5%)</td>
</tr>
</tbody>
</table>

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

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 followed in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated 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 who met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.

15 HOW SUPPLIED/STORAGE AND HANDLING

Makena auto-injector (NDC 64011-301-03) is supplied as 1.1 mL of 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: 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.

16 PATIENT COUNSELING INFORMATION

Advising patients to read the FDA-approved patient labeling (Patient Information) is required. Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient not to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or a change in the color or viscosity of the injection site (see Adverse Reactions (6.1)).

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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 an 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
- 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).

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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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