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 medinfoUS@covispharma.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 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 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)

Indications and Usage

- for nonsteroidal anti-inflammatory drugs (NSAIDs) and other medicines that may cause decreased glucose tolerance: Monitor prediabetic and diabetic women receiving NSAIDs and other medicines that may cause decreased glucose tolerance.
- for hypertension, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- for decreased glucose tolerance: Monitor prediabetic and diabetic women receiving NSAIDs and other medicines that may cause decreased glucose tolerance.
- for depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)
- for thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- for allergic reactions: Consider discontinuing if allergic reactions occur (5.2)

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%]. (6.1)

Overdosage

- No specific treatment is required. If overdose occurs, discontinue Makena and institute supportive measures. Consult a Poison Control Center for additional information.

Preparation and Administration

- For subcutaneous injection, use only if solution is clear and colorless. Solutions that are discolored should not be used.
- Make sure the needle is sterile before use.
- Only administer Makena to 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.

2.1 Dosing

- Makena single- and multi-dose vials: Administer subcutaneously using auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Makena auto-injector: Administer subcutaneously using auto-injector at a dose of 275 mg (1.1 mL) once weekly, in the back of either upper arm (2.1)
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation (2.1)
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Dosage and Administration

1. Dosage and Administration

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 for intramuscular use only and are for use in the upper outer quadrant of the gluteus maximus. The injection site is 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 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. Apply 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 utricaria 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 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 who used Makena as an intramuscular injection. In the second study, injection site pain occurred in 20/39 (52%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

5.2 Postmarketing Experience

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

6.1  Clinical Trials Experience

Two clinical studies were conducted to examine the pharmacokinetics of Makena. Administration of hydroxyprogesterone caproate exists as white to practically white crystals or powder with a melting point of 120°-124°C.

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

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

### Pharmacokinetics

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

### Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

For all three groups, peak concentration (Cmax) and area under the curve (AUC(0-7 days)) of the mono-hydroxylated metabolites were approximately 3-fold lower than the respective parameters for the intact progesterone. While di-hydroxylated 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 multiple hydroxylated metabolites. The relative activity and significance of these metabolites are not known.

### Clinical Studies

13 Clinical studies

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

### How Supplied/Storage and Handling

Makena 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) with the preservative benzyl alcohol NF (2% v/v).

### General Information

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising.

### Storage

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

### Adverse Reactions

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

### Table 5

<table>
<thead>
<tr>
<th>Group</th>
<th>Cmax (mg/mL)</th>
<th>T1/2 (days)</th>
<th>AUC(0-7 days) (mg·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (N=3)</td>
<td>5.0 (1.1)</td>
<td>0.0 (0.9)</td>
<td>13.9 (3.7)</td>
</tr>
<tr>
<td>Group 2 (N=8)</td>
<td>12.5 (3.9)</td>
<td>1.0 (0.9-1.9)</td>
<td>266.9 (253.0)</td>
</tr>
</tbody>
</table>

*Reienow as median (range) of 7 days.*

Hydroxyprogesterone caproate is predominantly mediated by CYP3A4 and CYP3A5. The in vitro data indicate that the metabolism of hydroxyprogesterone caproate is predominately mediated by CYP3A4 and CYP3A5. The elimination half-life of hydroxyprogesterone caproate, as evaluated from 4 patients in the study, was 16.4 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±2.1) days.

### Drug Interactions

Cytochrome P450 (CYP) enzymes: An in vitro inhibition study using human liver microsomes and CYP substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in vitro studies in humans who were administered hydroxyprogesterone caproate, the conjugated metabolites include sulfated, glucuronidated, and acetylated products. In vivo data indicate that the metabolism of hydroxyprogesterone caproate is predominately mediated by CYP3A4 and CYP3A5. In vivo data indicate that the conjugate that is retained during metabolism of hydroxyprogesterone caproate.

Excretion: Both conjugated and unconjugated 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.

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*Four of the 310 Makena-treated subjects had lost both follow-up and stillbirth or neonatal status could not be determined.*

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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).
- migraines headaches.
- asthma.
- heart problems.
- kidney problems.
- depression.
- high blood pressure.

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

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

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

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

What are the possible side effects of MAKENA?
MAKENA may cause serious side effects, including:
- Blood clots. Symptoms of a blood clot may include:
  - leg swelling
  - redness in your leg
  - a spot on your leg that is warm to the touch
  - leg pain that gets worse when you bend your foot

Call your healthcare provider right away if you get any of the symptoms above during treatment with MAKENA.
- Allergic reactions. Symptoms of an allergic reaction may include:
  - hives
  - itching
  - swelling of the face

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

The most common side effects of MAKENA include:
- pain, swelling, itching or a hard bump at the injection site
- hives
- itching
- nausea
- diarrhea

Call your healthcare provider if you have the following at your injection site:
- increased pain over time
- oozing of blood or fluid
- swelling

Other side effects that may happen more often in women who receive MAKENA include:
- Miscarriage (pregnancy loss before 20 weeks of pregnancy)
- Stillbirth (fetal death occurring during or after the 20th week of pregnancy)
- Hospital admission for preterm labor
- Preeclampsia (high blood pressure and too much protein in your urine)
- Gestational hypertension (high blood pressure caused by pregnancy)
- Gestational diabetes
- Oligohydramnios (low amniotic fluid levels)

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

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

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

How should I store MAKENA?
- MAKENA auto-injector for subcutaneous use:
  - Store the auto-injector at room temperature between 68°F to 77°F (20°C to 25°C).
    - Do not refrigerate or freeze.
    - Protect the auto-injector from light.
    - Store the auto-injector in its box.
- MAKENA vial for intramuscular use:
  - Store the vial at room temperature between 68°F to 77°F (20°C to 25°C).
    - Do not refrigerate or freeze.
    - Protect the vial from light.
    - Store the vial in its box in an upright position.

Keep MAKENA and all medicines out of the reach of children.

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

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

What are the ingredients in MAKENA?
Active ingredient: hydroxyprogesterone caproate
Inactive ingredients: castor oil and benzyl benzoate. 5 mL multi-dose vials also contain benzyl alcohol (a preservative).

Distributed by: AMAG Pharmaceuticals, Inc. 
Makeena 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