CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21945Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

MAKENA™ (hydroxyprogesterone caproate injection) for intramuscular use.
Initial U.S. Approval: 1956

----------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.
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----------

- Administer intramuscularly at a dose of 250 mg (1 mL) once weekly
- 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 (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

5 mL multidose vial (250 mg/mL) contains 1250 mg hydroxyprogesterone caproate. (3)

----------CONTRAINDICATIONS----------

- Current or history of thrombosis or thromboembolic disorders (4)
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions (4)
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy (4)
- Cholestatic jaundice of pregnancy (4)
- Liver tumors, benign or malignant, or active liver disease (4)
- Uncontrolled hypertension (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic disorders: Discontinue if thrombosis or thromboembolism occurs (5.1)
- Allergic reactions: Consider discontinuing if allergic reactions occur (5.2)
- Decreased glucose tolerance: Monitor prediabetic and diabetic women receiving Makena (5.3)
- Fluid retention: Monitor women with conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction (5.4)
- Depression: Monitor women with a history of clinical depression; discontinue Makena if depression recurs (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions reported in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group are injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ther-Rx Corporation at 1-877-567-7676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Metabolism of drugs metabolized by CYP1A2, CYP2A6 and CYP2B6 may be increased if used with Makena. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Controlled studies show no increase in congenital anomalies, including genital abnormalities in male or female infants, from exposure during pregnancy to hydroxyprogesterone caproate. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised 2/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

- Administer intramuscularly at a dose of 250 mg (1 mL) once weekly (every 7 days) by a healthcare provider
- Begin treatment between 16 weeks, 0 days and 20 weeks, 6 days of gestation
- Continue administration once weekly until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first

2.2 Preparation and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Makena is a clear, yellow solution. Do not use if solid particles appear or if the solution is cloudy.

Instructions for administration:

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. Applying pressure to the injection site may minimize bruising and swelling.

Discard any unused product 5 weeks after first use.

3 DOSAGE FORMS AND STRENGTHS

Makena (250 mg/mL) is a sterile solution of hydroxyprogesterone caproate in castor oil for injection. Each 5 mL multidose vial contains 1250 mg hydroxyprogesterone caproate.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders

Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

5.2 Allergic Reactions

Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

5.3 Decrease in Glucose Tolerance

A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

5.4 Fluid Retention

Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

5.5 Depression

Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

5.6 Jaundice

Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

5.7 Hypertension

Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

6 ADVERSE REACTIONS

For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions (5).*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first.[1] *[See Clinical Studies (14.1).]*

Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	**Makena n/N**	**Control n/N**
Miscarriage (< 20 weeks)[1]	5/209	0/107
Stillbirth (≥ 20 weeks)[2]	6/305	2/153

[1] N = Total number of subjects enrolled prior to 20 weeks 0 days
[2] N = Total number of subjects at risk ≥ 20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	**Makena N=310 %**	**Control N=153 %**
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1] Other than delivery admission.

Common Adverse Reactions:
The most common adverse reaction was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥ 2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥ 2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial, 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 embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Makena.

Drugs Metabolized by CYP1A2, CYP2A6 and CYP2B6

The metabolism of drugs metabolized by CYP1A2 (such as theophylline, tizadine, clozapine), CYP2A6 (such as acetaminophen, halothane, nicotine) and CYP2B6 (such as efavirenz, bupropion, methadone) may be increased during treatment with Makena *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies of Makena use in women during the first trimester of pregnancy. Data from a vehicle (placebo)-controlled clinical trial of 310 pregnant women who received Makena at weekly doses of 250 mg by intramuscular injection in their second and third trimesters[1], as well as long-term (2-5 years) follow-up safety data on 194 of their infants[2], did not demonstrate any teratogenic risks to infants from in utero exposure to Makena.

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 Makena.

Makena administration produced embryolethality in rhesus monkeys but not in cynomolgus monkeys exposed to 1 and 10 times the human dose equivalent every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either species.

8.2 Labor and Delivery

Makena is not intended for use to stop active preterm labor. The effect of Makena in active labor is unknown.

8.3 Nursing Mothers

Discontinue Makena at 37 weeks of gestation or upon delivery. Detectable amounts of progestins have been identified in the milk of mothers receiving progestin treatment. Many studies have found no adverse effects of progestins on breastfeeding performance, or on the health, growth, or development of the infant.

8.4 Pediatric Use

Makena is not indicated for use in children. Safety and effectiveness in pediatric patients less than 16 years of age have not been established. A small number of women under age 18 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 Geriatric Use

Makena is not intended for use in postmenopausal women. Safety and effectiveness in postmenopausal women have not been established.

8.6 Renal Impairment

No studies have been conducted to examine the pharmacokinetics of Makena in patients with renal impairment.

8.7 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

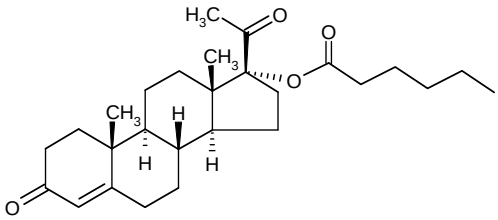
There have been no reports of adverse events associated with overdosage of Makena in clinical trials. In the case of overdosage, the patient should be treated symptomatically.

11 DESCRIPTION

The active pharmaceutical ingredient in Makena is hydroxyprogesterone caproate.

The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17[(1-oxohexyl)oxy]. It has an empirical formula of $C_{27}H_{40}O_4$ 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:



Makena is a clear, yellow, sterile, non-pyrogenic solution for intramuscular injection. Each 5 mL multidose vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Makena.

12.3 Pharmacokinetics

Absorption: Peak serum levels of hydroxyprogesterone caproate appeared after 3-7 days in non-pregnant female subjects following a single intramuscular injection of 1000 mg hydroxyprogesterone caproate. Based on pharmacokinetic analysis of five non-pregnant female subjects who received a single intramuscular administration of 1000 mg hydroxyprogesterone caproate, the mean (±SD) C_{max} is estimated to be 27.8 (±5.3) ng/mL, and the T_{max} is estimated to be 4.6 (±1.7) days. The elimination half-life of hydroxyprogesterone caproate was 7.8 (±3.0) days. Once-weekly intramuscular administration of 1000 mg hydroxyprogesterone caproate to non-pregnant women resulted in trough concentration of 60.0 (±14) ng/mL after 13 weeks. The pharmacokinetics of the 250 mg dose of hydroxyprogesterone caproate has not been evaluated.

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

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

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

Specific Populations

Renal Impairment: The effect of renal impairment on the pharmacokinetics of Makena has not been evaluated.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Makena has not been evaluated.

Drug Interactions

Cytochrome P450 (CYP) enzymes: An in vitro study using human liver microsomes and CYP isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. The clinical implication of this in vitro metabolic acceleration is not well understood.

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

The metabolic induction potential of hydroxyprogesterone caproate has not been evaluated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Hydroxyprogesterone caproate has not been adequately evaluated for carcinogenicity.

No reproductive or developmental toxicity or impaired fertility was observed in a multigenerational study in rats. Makena administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F_0) dams, their developing offspring (F_1), or the latter offspring's ability to produce a viable, normal second (F_2) generation.

14 CLINICAL STUDIES

14.1 Clinical Trial to Evaluate Reduction of Risk of Preterm Birth

In a multicenter, randomized, double-blind, vehicle (placebo)-controlled clinical trial, the safety and effectiveness of Makena for the reduction of the risk of spontaneous preterm birth was studied in women with a singleton pregnancy (age 16 to 43 years) who had a documented history of singleton spontaneous preterm birth (defined as delivery at less than 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes).[1] At the time of randomization (between 16 weeks, 0 days and 20 weeks, 6 days of gestation), an ultrasound examination had confirmed gestational age and no known fetal anomaly. Women were excluded for prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease, or maternal/obstetrical complications (such as current or planned cerclage, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either Makena (N=310) or vehicle (N=153) at a dose of 250 mg administered weekly by intramuscular injection starting between 16 weeks, 0 days and 20 weeks, 6 days of gestation, and continuing until 37 weeks of gestation or delivery. Demographics of the Makena-treated women were similar to those in the control group, and included: 59.0% Black, 25.5% Caucasian, 13.9% Hispanic and 0.6% Asian. The mean body mass index was 26.9 kg/m^2.

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 4.

Table 4 Proportion of Subjects Delivering at < 37, < 35 and < 32 Weeks Gestational Age (ITT Population)

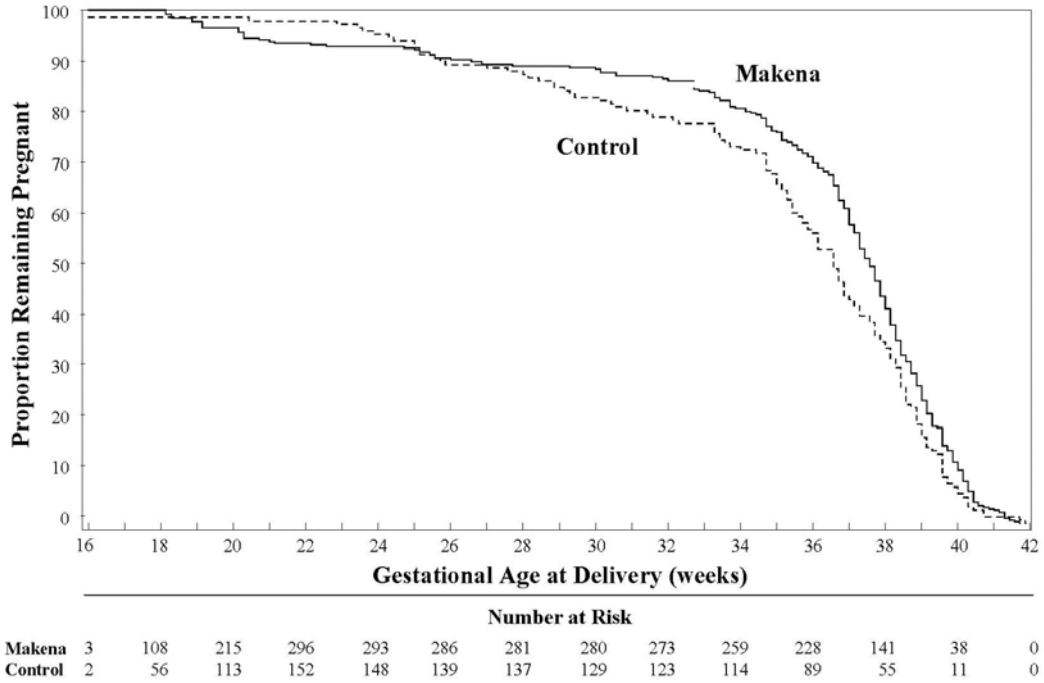
Delivery Outcome	Makena[1] (N=310) %	Control (N=153) %	Treatment difference and 95% Confidence Interval[2]
<37 weeks	37.1	54.9	-17.8% [-28.0%, -7.4%]
<35 weeks	21.3	30.7	-9.4% [-19.0%, -0.4%]
<32 weeks	11.9	19.6	-7.7% [-16.1%, -0.3%]

[1] Four Makena-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18^4, 22^0, 34^3 and 36^4 weeks).
[2] Adjusted for interim analysis.

Compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at < 37 weeks. The proportions of women delivering at < 35 and < 32 weeks also were lower among women treated with Makena. The upper bounds of the confidence intervals for the treatment difference at < 35 and < 32 weeks were close to zero. Inclusion of zero in a confidence interval would indicate the treatment difference is not statistically significant. Compared to the other gestational ages evaluated, the number of preterm births at < 32 weeks was limited.

After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7% of control subjects; see Figure 1.

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



The rates of fetal losses and neonatal deaths in each treatment arm are displayed in Table 5. 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 5 Fetal Losses and Neonatal Deaths

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

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

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

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

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

14.2 Infant Follow-Up Safety Study

Infants born to women enrolled in this study, and who survived to be discharged from the nursery, were eligible for participation in a follow-up safety study. Of 348 eligible offspring, 79.9% enrolled: 194 children of Makena-treated women and 84 children of control subjects. The primary endpoint was the score on the Ages & Stages Questionnaire (ASQ), which evaluates communication, gross motor, fine motor, problem solving, and personal/social parameters. The proportion of children whose scores met the screening threshold for developmental delay in each developmental domain was similar for each treatment group.[2]

15 REFERENCES

[1] Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med.* 2003;348(24):2379-85.

[2] Northen A, Norman G, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate. *Obstet & Gynecol.* 2007;110:865-872.

16 HOW SUPPLIED/STORAGE AND HANDLING

Makena (NDC 64011-243-01) is supplied as 5 mL of a sterile solution in a multidose glass vial.

Each 5 mL vial contains hydroxyprogesterone caproate USP, 250 mg/mL (25% w/v), in castor oil USP (28.6% v/v) and benzyl benzoate USP (46% v/v) with the preservative benzyl alcohol NF (2% v/v).

Single unit carton: Contains one 5 mL multidose vial of Makena (250 mg/mL) containing 1250 mg of hydroxyprogesterone caproate.

Store at controlled room temperature [15°-30° C (59°-86° F)]. Use within 5 weeks after first use.

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Counsel patients that Makena injections may cause pain, soreness, swelling, itching or bruising. Inform the patient to contact her physician if she notices increased discomfort over time, oozing of blood or fluid, or inflammatory reactions at the injection site *[see Adverse Reactions (6.1)]*.

Manufactured by: Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403

Marketed by: Ther-Rx Corporation
St. Louis, MO 63044

Patient Information
Makena (mah-KEE-na)
(hydroxyprogesterone caproate injection) 250 mg/mL

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.

Makena is for women who:

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

How well does Makena work?

Makena was studied in women who were at risk for having a preterm baby because they had previously given birth to a preterm baby. In the main study, about 37 of 100 women who received Makena gave birth preterm (before 37 weeks of pregnancy), compared to about 55 of 100 women who did not receive Makena. Another study of Makena is going on to see whether Makena reduces 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.

It is not known whether Makena is safe and effective in women less than 16 years old.

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

Who should not receive Makena?

Makena should not be used if you:

- Have now or have had a history of blood clots or other blood clotting problems
- Have now or have had a history of breast cancer or other hormone-sensitive cancers
- Have unusual vaginal bleeding not related to your current pregnancy
- Have yellowing of your skin due to liver problems during your pregnancy
- Have liver problems, including liver tumors

- Have uncontrolled high blood pressure

What should I tell my healthcare provider before receiving Makena?

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. See the end of this patient leaflet for a complete list of the ingredients in Makena.
- Diabetes or prediabetes
- Epilepsy
- Migraine headaches
- Asthma
- Heart problems
- Kidney problems
- Depression
- High blood pressure

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription 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 medication.

How should I receive Makena?

- **Do not give yourself Makena injections.** A healthcare professional will give you the Makena injection into your hip area (upper outer area of the buttocks) once a week (every 7 days).
- 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 once weekly until week 37 of your pregnancy or when your baby is delivered, whichever happens first.

Makena comes in ready-to-use vials. There are 5 doses of medicine in each vial. Your healthcare professional should give you only **one dose** (1 mL) of Makena as prescribed each week.

Makena should be used within 5 weeks after the first use.

It is very important that you do not miss a dose of Makena and that you continue to receive the medicine once a week. If you miss a dose, talk to your healthcare provider for specific directions on how to get back on schedule.

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 touch
    - Leg pain that worsens 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.

- **Depression**
- **Yellowing of your skin and the whites of your eyes**

The most common side effects of Makena include:

- Pain, swelling, itching, bruising 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

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.

In a clinical study, certain complications or events associated with pregnancy occurred more often in women who received Makena compared to women who did not receive Makena, including:

- 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)

Call your healthcare provider for medical advice about side effects or pregnancy complications. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Makena?

- Store Makena at room temperature (59° to 86°F or 15° to 30°C)
- Store Makena in the original box to protect it from light
- Store the Makena box upright
- Makena should be used within 5 weeks after the first use
- **Keep Makena 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 mentioned in the Patient Information Leaflets. Do not take Makena for conditions for which it was not prescribed. Do not give Makena to other people, even if they have the same condition 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 for information about Makena that is written for healthcare professionals.

For more information, go to www.makena.com or call Ther-Rx Corporation Customer Service at the toll free number 1-877-567-7676.

To refill a prescription or to check on prescription status, call the Makena Care Connection at the toll free number 1-800-847-3418.

What are the ingredients in Makena?

Active ingredient: hydroxyprogesterone caproate

Inactive ingredients: castor oil, benzyl benzoate, and benzyl alcohol (a preservative)

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/s/

JULIE G BEITZ
02/03/2011