

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 hydroxyprogesterone caproate injection-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the hydroxyprogesterone caproate injection-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation 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 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 progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

8.4 Pediatric Use
Hydroxyprogesterone caproate injection 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 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)*].

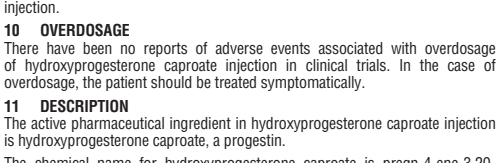
8.6 Hepatic Impairment
No studies have been conducted to examine the pharmacokinetics of hydroxyprogesterone caproate injection in patients with hepatic impairment. Hydroxyprogesterone caproate injection is extensively metabolized and hepatic impairment may reduce the elimination of hydroxyprogesterone caproate injection.

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

11 DESCRIPTION
The active pharmaceutical ingredient in hydroxyprogesterone caproate injection is hydroxyprogesterone caproate, a progestin.

The chemical name for hydroxyprogesterone caproate is pregn-4-ene-3,20-dione, 17[(1 α -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° to 124°C.

The structural formula is:



Hydroxyprogesterone caproate injection is a clear, yellow, sterile, non-pyrogenic solution for intramuscular injection. Each 1 mL single-dose vial contains hydroxyprogesterone caproate, 250 mg/mL (25% w/v), in a preservative-free solution containing castor oil (30.6% v/v) and benzyl benzoate (46% 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 hydroxyprogesterone caproate injection.

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 20 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

Group (N)	C _{max} (ng/mL)	T _{max} (days) ^a	AUC _(0-7 days) ^b (ng•hr/mL)
Group 1 (N=6)	5.0 (1.5)	5.5 (2.0 to 7.0)	571.4 (195.2)
Group 2 (N=8)	12.5 (3.9)	1.0 (0.9 to 1.9)	1269.6 (285.0)
Group 3 (N=11)	12.3 (4.9)	2.0 (1.0 to 3.0)	1268.0 (511.6)

Blood was drawn daily for 7 days (1) starting 24 hours after the first dose between Weeks 16 to 20 (Group 1), (2) after a dose between Weeks 24 to 28 (Group 2), or (3) after a dose between Weeks 32 to 36 (Group 3)

^aReported as median (range)
^bt = 7 days

For all three groups, peak concentration (C_{max}) and area under the curve (AUC_(0-7 days)) of the mono-hydroxylated metabolites were approximately 3 to 8-fold lower than the respective parameters for the parent drug, hydroxyprogesterone caproate. While di-hydroxylated and tri-hydroxylated metabolites were also detected in human plasma to a lesser extent, no meaningful quantitative results could be derived 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 (±3.6) days. The elimination half-life of the mono-hydroxylated metabolites was 19.7 (±6.2) days.

In a single-dose, open-label, randomized, parallel design bioavailability study in 120 healthy post-menopausal women, comparable systemic exposure of hydroxyprogesterone caproate was seen when hydroxyprogesterone caproate injection 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 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 to 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 isoform-selective substrates indicated that hydroxyprogesterone caproate increased the metabolic rate of CYP1A2, CYP2A6, and CYP2B6 by approximately 80%, 150%, and 80%, respectively. However, in another *in vitro* study using human hepatocytes under conditions where the prototypical inducers or inhibitors caused the anticipated increases or decreases in CYP enzyme activities, hydroxyprogesterone caproate did not induce or inhibit CYP1A2, CYP2A6, or CYP2B6 activity. Overall, the findings indicate that hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related 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 CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.

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. Hydroxyprogesterone caproate administered intramuscularly, at gestational exposures up to 5 times the recommended human dose, had no adverse effects on the parental (F₁) dams, their developing offspring (F₂), or the latter offspring's ability to produce a viable, normal second (F₃) 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 hydroxyprogesterone caproate injection for the reduction of 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). 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 eclampsia, hypertension requiring medication, or a seizure disorder).

A total of 463 pregnant women were randomized to receive either hydroxyprogesterone caproate injection (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 hydroxyprogesterone caproate injection-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/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)

Delivery Outcome	Hydroxyprogesterone Caproate Injection 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%]

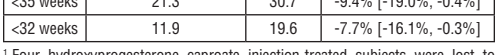
¹ Four hydroxyprogesterone caproate injection-treated subjects were lost to follow-up. They were counted as deliveries at their gestational ages at time of last contact (18¹, 22², 34³ and 36⁴ weeks).

² Adjusted for interim analysis.

Compared to controls, treatment with hydroxyprogesterone caproate injection 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 hydroxyprogesterone caproate injection. 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 hydroxyprogesterone caproate injection-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 6. Due to the higher rate of miscarriages and stillbirths in the hydroxyprogesterone caproate injection arm, there was no overall survival difference demonstrated in this clinical trial.

Table 6 Fetal Losses and Neonatal Deaths

Complication	Hydroxyprogesterone Caproate Injection 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)
<i>Antepartum stillbirth</i>	5 (1.6)	1 (0.6)
<i>Intrapartum stillbirth</i>	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 hydroxyprogesterone caproate injection-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 hydroxyprogesterone caproate injection, n=107 for control) enrolled at <20 weeks gestation.

A composite neonatal morbidity/mortality index evaluated adverse outcomes in live births. 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 hydroxyprogesterone caproate injection 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 hydroxyprogesterone caproate injection-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.

16 HOW SUPPLIED/STORAGE AND HANDLING
Hydroxyprogesterone caproate injection, USP (NDC 0517-1791-01) is supplied as 1 mL of a sterile preservative-free clear yellow solution in a single-dose glass vial.

Each 1 mL vial contains hydroxyprogesterone caproate, 250 mg/mL (25% w/v), in castor oil (30.6% v/v) and benzyl benzoate (46% v/v).

Single unit carton: Contains one 1 mL single-dose vial of hydroxyprogesterone caproate injection containing 250 mg of hydroxyprogesterone caproate.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature]. Do not refrigerate or freeze.

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

17 PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Counsel patients that hydroxyprogesterone caproate 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:
American Regent, Inc.,
Shirley, NY 11967

novaplus[†] RQ1084-00
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Call your healthcare provider right away if you get any of the symptoms above during treatment with hydroxyprogesterone caproate injection.

- **Decrease in glucose (blood sugar) tolerance.** Your healthcare provider will need to monitor your blood sugar while taking hydroxyprogesterone caproate injection 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 hydroxyprogesterone caproate injection 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 hydroxyprogesterone caproate 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 hydroxyprogesterone caproate injection. 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 hydroxyprogesterone caproate injection?

- 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 hydroxyprogesterone caproate injection and all medicines out of the reach of children.

General information about the safe and effective use of hydroxyprogesterone caproate injection.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use hydroxyprogesterone caproate injection for a condition for which it was not prescribed. Do not give hydroxyprogesterone caproate injection to other people, even if they have the same symptoms you have. It may harm them.

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

What are the ingredients in hydroxyprogesterone caproate injection?

Active ingredient: hydroxyprogesterone caproate
Inactive ingredients: castor oil and benzyl benzoate.

Manufactured by:
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Shirley, NY 11967

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For more information, go to www.americanregent.com or call American Regent at the toll free number 1-800-734-9236.

This Patient Information has been approved by the U.S. Food and Drug Administration

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