



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Hydroxyprogesterone Caproate USP (17 α - hydroxy-progesterone)

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Coverage Position Number 5033

Table of Contents

Coverage Position.....	1
General Background	1
Coding/Billing Information	3
References.....	3

Hyperlink to Related Coverage Positions

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

CIGNA covers Hydroxyprogesterone Caproate as medically necessary for ANY of the following:

- the prevention of preterm labor in women with a prior history of preterm delivery before 37 weeks gestation but no current symptoms of preterm labor
- the treatment of amenorrhea
- the treatment of dysfunctional uterine bleeding
- the treatment of advanced (stage III, IV) endometrial carcinoma

General Background

Hydroxyprogesterone caproate is used for the treatment of amenorrhoea and for the treatment of dysfunctional uterine bleeding caused by fibroids or uterine cancer. The drug stimulates a proliferative endometrium into secretion as well as stimulates the growth of mammary alveolar tissues. Hydroxyprogesterone caproate's mechanism of action in endometrial cancer is not understood; however, the drug has antineoplastic activity.

Hydroxyprogesterone caproate, although an FDA-approved product, is no longer commercially available in the United States. It is generally administered as a deep IM injection; however, as all product formulations are exclusively available through individual pharmacy compounding, vaginal suppository

formulations have also been prepared. Its dose is based upon the indication of use where monthly injections are administered for amenorrhea and dysfunctional uterine bleeding. For adjuvant and palliative therapy in inoperable endometrial carcinoma, hydroxyprogesterone caproate is dosed weekly to daily, depending upon response. For its use in the prevention of preterm labor in high-risk women, hydroxyprogesterone caproate is generally administered by weekly IM injection between 16 weeks and 36 weeks gestation to only those women who have a history of preterm delivery but do not have present symptoms of preterm labor.

Hydroxyprogesterone caproate is a synthetic derivative of progesterone sharing the pharmacologic actions of all progestins. 17 α -hydroxyprogesterone (17-P) has minimal progestational activity; however, the esterified form, hydroxyprogesterone caproate has significant progesterone effects and a prolonged duration of action, from 7 to 14 days. The drug also has reported androgenic, estrogenic, and glucocorticoid activity.

Although progestins have been used in the first trimester of pregnancy to prevent habitual abortion or threatened abortion, their use is not without risk and adverse effects. All progestins, including hydroxyprogesterone caproate have potential teratogenic effects including female fetus masculinization. They have a pregnancy use category of D where studies have demonstrated fetal risk, but that use of the drug may outweigh potential risks.

More recent research interest and studies use hydroxyprogesterone caproate to prevent preterm labor during the second trimester when teratogenic risk is diminished. Preterm births occur in approximately one out of every eight pregnancies and result in significant morbidity and mortality. The precise mechanism for hydroxyprogesterone caproate in prevention of preterm labor and delivery is unknown, although it is understood that progesterone has beneficial effects towards the maintenance of pregnancy in general.

A recent large randomized placebo-controlled trial (Meis et al., 2003) examined 17-P therapy to prevent preterm birth in a high-risk group of pregnant women who had a documented history of previous spontaneous birth < 37 weeks gestation. A total of 459 women were enrolled between 16 and 20 weeks gestation to randomly receive weekly 250 mg 17-P injections or placebo. The trial was ended early when results showed a significant protection against recurrent preterm birth for women in the 17-P group. In looking at the outcomes of pregnancy measures as delivery before 37 weeks, delivery before 35 weeks, and delivery before 32 weeks, only 36.3 % of 17-P group women delivered before 37 weeks, whereas 54.9% of the placebo group had a frequency of delivery before 37 weeks. This achieved a statistical significance at $p < 0.001$.

Concerns over the high rate of preterm delivery in the control group relate to the overall risk of preterm labor from the entire group. The risk of preterm delivery increases with a decreasing gestational age of the prior preterm delivery. The study results showed a control group with a mean gestational age in the prior delivery of 31 weeks \pm 4.2 weeks. No gestational age distributions were provided for the prior delivery. Caution is required when extrapolating the results of this study into other populations.

A recent meta-analysis (Sanchez-Ramos et al., 2005) examined the trials using progestational agents, in general, and hydroxyprogesterone caproate, specifically. Compared to groups of pregnant women receiving a placebo, those receiving a progestational agent had lower rates of preterm delivery (26.2% versus 35.9%; OR 0.45, 95% CI 0.25–0.80). Similar results were obtained with patients receiving hydroxyprogesterone caproate as compared to placebo. (29.3% versus 40.9%; OR 0.45, 95% CI 0.22-0.93). Additionally, these 17-P treated women had lower frequencies of low-birth weight babies (less than 2500 g).

This clinical evidence work builds upon other published studies of smaller, yet randomized controlled trials with the use of progesterone vaginally on a daily basis to prevent preterm birth. As a consequence, the ideal formulation of progesterone and method of administration has yet to be determined. ACOG's 2003 Committee Opinion stresses that further studies are needed to evaluate the use of progesterone, in general, in patients with other high-risk obstetric factors, such as multiple gestations, short cervical length,

or positive cervicovaginal fetal fibronectin. Progesterone should only be used in the patient group of women with a documented history of previous spontaneous birth at less than 37 weeks gestation as unresolved issues remain, such as optimal drug and route of delivery and long-term safety of the progestational agents used.

Coding/Billing Information

Note: This section is currently unavailable.

References

1. ACOG Committee Opinion. Use of progesterone to reduce preterm birth. *Obstet Gynecol.* 2003; 102(5): 1115-6.
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3. Meis PJ, Klebanoff M, Thom, E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *NEJM.* 2003; 348(24):2379-85.
4. Meis PJ; Society for Maternal-Fetal Medicine. 17 hydroxyprogesterone for the prevention of preterm delivery. *Obstet Gynecol.* 2005; 105(5 Pt 1):1128-35.
5. Petrini JR, Callaghan WM, Klebanoff M et al. Estimated effect of 17-alpha-hydroxyprogesterone caproate on preterm birth in the United States. *Obstet Gynecol.* 2005; 105(2) 267-72.
6. Sanchez-Ramos, L, Kaunitz AM, Delke I. Progestational agents to prevent preterm birth: a meta-analysis of randomized controlled trials. *Obstet Gynecol.* 2005; 105(6): 273-279.

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