

Progesterone

Drug Description

Progesterone is a naturally occurring progestin. In the body, it is synthesized in the ovaries, testes, placenta, and adrenal cortex. Progesterone is primarily used to treat amenorrhea, abnormal uterine bleeding, or as a contraceptive. Progesterone is also used to prevent early pregnancy failure in women with corpus luteum insufficiency, including women undergoing assisted reproductive technology (ART). Additionally, the use of progesterone for preterm delivery prophylaxis is being investigated. Preliminary data indicate that progesterone may be effective in preventing preterm delivery in high-risk women, especially those with a history of preterm delivery [33440]; however, the optimal dosage and route have not been determined. The American College of Obstetricians and Gynecologists (ACOG) Committee recommends that if progesterone is to be used for the prevention of preterm delivery, it should only be used in women with a history of spontaneous birth at < 37 weeks gestation, until more data supporting its use in other high-risk women are available.[33439] A study in support of the use of vaginal progesterone in women with a short cervix has been published.[33438] Progesterone is available commercially as an intramuscular injection, an intravaginal gel, an intravaginal insert, oral capsules, or a powder for use in extemporaneous preparations (e.g., vaginal suppositories). A progesterone-releasing IUD (Progestasert®) that was inserted once yearly has been discontinued. Progesterone was approved by the FDA in 1939. In May 1998, micronized progesterone capsules for oral administration were approved for secondary amenorrhea; they received a second indication in December 1998 for the prevention of endometrial hyperplasia in postmenopausal women with an intact uterus taking estrogen replacement therapy. In May 1997, a progesterone vaginal gel (Crinone®) was approved for progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) program for infertile women; a second intravaginal gel, Prochieve™, was released to the US market in 2002. A vaginal insert, Endometrin®, for progesterone supplementation as part of an ART program in infertile women was approved in June 2007.

Revision Date: 12/7/2009 10:07:00 AM

Classifications

Genitourinary Agents

Vaginal Agents

Hormones and Hormone Modifiers

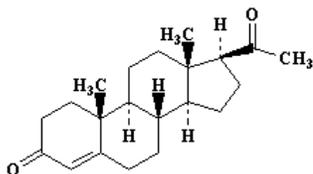
Progestins

Brand Names

- Crinone
 - Endometrin
 - First-Progesterone MC 10
 - First-Progesterone MC 5
 - First-Progesterone VGS 100
 - First-Progesterone VGS 200
 - First-Progesterone VGS 25
 - First-Progesterone VGS 400
 - First-Progesterone VGS 50
 - Gesterone
 - Gestrin
 - Prochieve
 - Prometrium
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Chemical Structures

Progesterone
 $C_{21}H_{30}O_2$



Mechanism of Action

Mechanism of Action: Endogenous progesterone is responsible for inducing secretory activity in the endometrium of the estrogen-primed uterus in preparation for the implantation of a fertilized egg and for the maintenance of pregnancy. It is secreted from the corpus luteum in response to luteinizing hormone. The hormone increases basal body temperature, causes histologic changes in vaginal tissues, inhibits uterine contractions, inhibits pituitary secretion, stimulates mammary alveolar gland tissues, and precipitates withdrawal bleeding in the presence of estrogen. The administration of progesterone to women with adequate estrogen production transforms the uterus from a proliferative to a secretory phase.

The primary contraceptive effect of exogenous progestins involves the suppression of the midcycle surge of LH. The exact mechanism of action, however, is unknown. At the cellular level, progestins diffuse freely into target cells and bind to the progesterone receptor. Target cells include the female reproductive tract, the mammary gland, the hypothalamus, and the pituitary. Once bound to the receptor, progestins slow the frequency of release of gonadotropin releasing hormone (GnRH) from the hypothalamus and blunt the pre-ovulatory LH surge, thereby preventing follicular maturation and ovulation. Overall, progestin-only contraceptives prevent ovulation in 70–80% of cycles, however, the clinical effectiveness ranges 96–98%. This suggests that additional mechanisms may be involved. Other actions of progestins include alterations in the endometrium that can impair implantation and an increase in cervical mucus viscosity which inhibits sperm migration into the uterus. Progesterone administered via IUD suppresses proliferation of endometrial tissue. Following removal of the IUD, the endometrium rapidly returns to a normal cyclic pattern and can support pregnancy. Progesterone has minimal estrogenic and androgenic activity.

Revision Date: 12/7/2009 10:07:00 AM

Pharmacokinetics

Pharmacokinetics:

Progesterone is administered orally (Prometrium micronized soft gelatin capsules), intramuscularly, intravaginally (Crinone gel, Prochieve gel), or as a component of an intrauterine device (IUD). Vaginal suppositories are also compounded for use, however, pharmacokinetic data is unavailable. Once in the systemic circulation, progesterone is extensively (96–99%) bound to cortisol binding globulin, sex hormone binding globulin, and albumin. The drug is metabolized hepatically to pregnanediol and conjugated with glucuronic acid. The plasma elimination half-life ranges 5–20 minutes. The metabolites are excreted primarily in the urine (50–60%). About 10% is eliminated via the bile and feces.

•Route-Specific Pharmacokinetics

Oral Route

After oral administration, progesterone is significantly absorbed with peak serum concentration occurring within 3 hours. The absolute bioavailability, however, is not known.

Intramuscular Route

The absorption of progesterone following intramuscular injection is rapid, and the effects last for about 24 hours.

Other Route(s)

Vaginal Route

Following intravaginal administration of progesterone gel, absorption is prolonged with an absorption half-life of approximately 25–50 hours.

Intrauterine Route

Intrauterine devices release progesterone at an average rate of 65 mcg/day by membrane controlled diffusion. Local absorption of progesterone into the uterine epithelium readily occurs. Systemic absorption from an IUD is clinically insignificant.

Revision Date: 12/7/2009 10:07:00 AM

Indications

- amenorrhea
- contraception
- corpus luteum insufficiency †
- dysfunctional uterine bleeding
- early pregnancy failure †
- estrogen replacement therapy
- infertility
- premenstrual syndrome (PMS) †
- preterm delivery prophylaxis †

† non-FDA-approved indication

For the treatment of amenorrhea:

Intravaginal dosage (micronized gel):

Adult females: Administer the 4% or 8% gel PV every other day up to a total of 6 doses. Use the 8% gel for women who fail to respond to the 4% gel. Note that dosage increases from the 4% gel can only be accomplished by using the 8% gel. Increasing the volume of gel administered does not increase the amount of progesterone absorbed.

Intramuscular dosage:

Adult females: 5–10 mg IM once daily for 6–8 days, usually started 8–10 days prior to the anticipated first day of menstruation. If the endometrium has been proliferative, withdrawal bleeding will generally occur within 48–72 hours following cessation of progesterone therapy. Cycles may return to normal after a single course of therapy.

Oral dosage (micronized capsules, e.g., Prometrium):

Adult females: For the treatment of secondary amenorrhea, 400 mg PO as a single dose in the evening for 10 days.

For the prevention of endometrial hyperplasia associated with conjugated estrogen replacement therapy in postmenopausal women who have an intact uterus:

Oral dosage (micronized capsules, e.g., Prometrium):

Adult females with an intact uterus: 200 mg PO given as a single dose in the evening for 12 sequential days of every 28-day cycle of daily estrogen therapy.

For the treatment of dysfunctional uterine bleeding secondary to hormonal imbalance:

Intramuscular dosage:

Adult females: 5–10 mg IM once daily for 6 days. If estrogen therapy is administered concomitantly, progesterone is usually administered after 2 weeks of estrogen therapy. Alternatively, a single dose of 50–100 mg IM may be given.

For the treatment of infertility or for the prevention of early pregnancy failure† (e.g., miscarriage) in women with corpus luteum insufficiency†:

NOTE: The optimal dose and route of progesterone administration has not been determined. Vaginal progesterone is often used preferentially over the intramuscular formulation secondary to comparable efficacy and decreased side effects (e.g., pain at the injection site, sterile abscess formation).[33327]

Intramuscular dosage†:

Adult females: 12.5 mg IM once daily at onset of ovulation. Two weeks therapy is usually sufficient, but may be continued for up to the 11th week of gestation.

Vaginal dosage (extemporaneously compounded suppositories)†:

Adult females: 25–100 mg PV 1–2 times per day, initiated within several days of ovulation.

Treatment is usually continued if the patient is pregnant to roughly the 11th week of gestation.

•to supplement or replace progesterone in women with infertility and corpus luteum insufficiency (e.g., progesterone deficiency) as part of an Assisted Reproductive Technology (ART) treatment program:

Intramuscular dosage†:

Adult females: 25–100 mg IM once daily starting at oocyte retrieval and continuing during the luteal phase or until 10–12 weeks gestation.[33326]

Vaginal dosage (Endometrin vaginal insert):

Adult females: 100 mg administered vaginally 2–3 times/day starting the day after oocyte retrieval and continuing for up to 10 weeks total duration. Efficacy in women 35 years of age and older has not been established; the appropriate dosage in this age group has not been determined.

Vaginal dosage (micronized gel):

Adult females: 90 mg (8% gel) PV once daily. In women with partial or complete ovarian failure, a dose of 90 mg intravaginally twice daily is recommended. If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10–12 weeks of gestation.

For the treatment of symptoms associated with premenstrual syndrome (PMS)†:

Oral dosage (micronized capsules, e.g., Prometrium):

Adults: Initially, 300 mg PO four times per day has been used; then adjusted to patient response; however, progesterone efficacy for PMS is questionable. In one study, alprazolam was superior to progesterone or placebo overall. Progesterone was better than alprazolam for physical symptoms; alprazolam was better for controlling mood. Progesterone was administered from day 18 of the cycle to the first day of menses with a taper on the first 2 menstrual days. Dosing was flexible; patients could receive up to twelve 300 mg capsules/day if necessary. The actual dose taken during the third treatment cycle was 1760 mg/day PO. The authors concluded that progesterone was ineffective for PMS.[24639]

For contraception in primarily parous women who have no history of pelvic inflammatory disease:

Intrauterine device dosage (Progestasert IUD):

Adult females: The 38 mg T-shaped system IUD is inserted into the uterus. Replace the IUD once every twelve months.

For preterm delivery prophylaxis†:

NOTE: The American College of Obstetricians and Gynecologists (ACOG) Committee recommends that if progesterone is to be used for the prevention of preterm delivery, it should only be used in women with a history of spontaneous birth at < 37 weeks gestation; in addition, the ideal formulation or whether it should be used in other high-risk women is not yet known.[33439]

Vaginal dosage (extemporaneously compounded suppositories)†:

Adult females: Limited data suggest that 100 mg PV once daily at night during weeks 24–34 gestation may be effective. Compared to placebo (n=70), the use of progesterone (n=72) decreased the incidence of preterm birth at < 37 weeks gestation (28.5% for placebo vs. 13.8% for progesterone, P=0.03) and at < 34 weeks gestation (18.6% for placebo vs. 2.8% for progesterone, P=0.002) in high-risk women.[33441]

•for preterm delivery prophylaxis† in women with a short cervix (<= 15 mm in length):

Vaginal dosage (micronized capsules Utrogestan):

NOTE: Utrogestan capsules are not commercially available in the U.S.

Adults females: Limited data suggest 200 mg PV once daily at bedtime starting at 24 weeks gestation and continuing through 33 weeks 6 days gestation may be effective in preventing preterm birth in women with a short cervix. Women undergoing routine ultrasonography at 20—25 weeks gestation and found to have a cervical length of ≤ 15 mm were eligible for participation in this study. Spontaneous birth before 34 weeks gestation was 19.2% in the progesterone group and 34.4% in the placebo group (n=125 for both groups; RR 0.56, 95% CI 0.36—0.86). Neonatal morbidity or mortality was not different between the 2 groups.[33438]

Maximum Dosage Limits

•Adults

Dependent on indication for therapy, and dosage route/formulation selected.

•Elderly

Dependent on indication for therapy, and dosage route/formulation selected.

•Adolescents

Dependent on indication for therapy, and dosage route/formulation selected.

•Children

Not indicated in prepubescent females.

Patients with Hepatic Impairment Dosing

Progesterone is considered contraindicated for use in patients with significant hepatic disease.

Patients with Renal Impairment Dosing

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

†non-FDA-approved indication

Revision Date: 4/12/2010 11:07:00 AM

Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Oral Administration

- Administer progesterone with or without food; evening dosing is suggested.

Injectable Administration

- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Intramuscular Administration:

- Administer intramuscularly. Never administer intravenously.
- Shake vial thoroughly prior to withdrawing dose into the syringe.

Intramuscular injection:

- Injections cause irritation at the injection site.
- Inject deeply into a large muscle mass. Aspirate prior to injection to avoid injection into a blood vessel. Rotate sites of injection.

Intravaginal Administration

Intravaginal gel (Crinone, Prochieve):

- Use disposable applicators supplied by the manufacturer.
- Instruct patient on proper administration. The Patient Information Sheet contains special instructions for using the applicator at altitudes above 2500 feet in order to avoid a partial release of the gel before vaginal insertion.

Intravaginal suppositories (Endometrin):

- Use disposable applicators supplied by the manufacturer.
- Patients should be instructed to place the thin end of the applicator filled with the insert well into the vagina while standing, sitting, or lying on her back with her knees bent. The plunger on the applicator should be pushed to release the insert. Discard the applicator after each use.

Extemporaneous Compounding-Vaginal:

Extemporaneous Intravaginal Suppositories preparation:

- One compounding formula that has been used is as follows:
 - 710 mg (0.71 grams) progesterone powder
 - 33.7 grams polyethylene glycol 400
 - 22.3 grams polyethylene glycol 6000
 - This formulation makes 28 suppositories containing 25 mg progesterone per suppository.

Other Administration Route(s)

Intrauterine device (IUD) Administration

NOTE: This drug is discontinued in the US.

- The system can be inserted into the uterus at any time during the menstrual cycle by a trained health-care professional. The preferred time for insertion is at the end of a menstrual cycle or within 2 days to reduce the risk of inserting when there is an undiagnosed pregnancy.

Intrauterine device (Progestasert):

- Replace every 12 months.
- The retrieval threads should be visible.

Revision Date: 12/7/2009 10:10:00 AM

Contraindications / Precautions

Absolute contraindications are italicized

- | | |
|---|---|
| <ul style="list-style-type: none"> B <i>breast cancer</i> • <i>cervical cancer</i> • <i>hepatic disease</i> • <i>incomplete abortion</i> • <i>myocardial infarction</i> • <i>peanut hypersensitivity</i> • <i>stroke</i> • <i>thromboembolic disease</i> • <i>thrombophlebitis</i> • <i>uterine cancer</i> • <i>vaginal bleeding</i> • <i>vaginal cancer</i> • asthma • breast-feeding B cardiac disease • children | <ul style="list-style-type: none"> B dementia • depression • diabetes mellitus • driving or operating machinery • ectopic pregnancy • elderly • hyperlipidemia • infection • inflammation • intravenous administration • migraine • pregnancy • renal disease • seizure disorder • visual disturbance |
|---|---|

Progesterone injection formulations are for intramuscular use only. Never administer via intravenous administration.

Hormonal contraceptives have been associated with the development of hepatic tumors. Although this is believed to be an estrogen-mediated effect, progesterone is contraindicated in patients with *hepatic disease* or hepatic dysfunction.

Progesterone is contraindicated in *undiagnosed abnormal vaginal bleeding* or *incomplete abortion*. Hormones can cause irregular menstrual bleeding in most women. In general, these irregularities diminish with continuing use. Women should be counseled regarding irregular menstrual bleeding.

Progesterone is contraindicated in patients with pre-existing *breast cancer* or cancer of reproductive organs, such as *cervical cancer*, *uterine cancer*, or *vaginal cancer*, except as palliative therapy in selected patients. Although progestins reduce the risk of endometrial cancer in patients receiving estrogen replacement therapy, it is unclear whether progestins added to estrogen therapy reduce the risk of breast cancer in postmenopausal women.[23505]

Progesterone should be used cautiously in patients with hyperlipidemia. Although hyperlipidemia is associated with estrogen-progestin combinations, the effects of progestin-only oral contraceptives on serum lipids have not been studied. Serum lipoproteins (HDL and LDL) should be monitored during therapy with progesterone.

Prometrium micronized progesterone capsules are classified in FDA pregnancy category B. In general, several studies of women exposed to progesterone during pregnancy have not demonstrated a significant increase in fetal malformations. A single case of cleft palate has been reported in an infant exposed to micronized progesterone in utero. Rare cases of fetal death have been reported in women administered micronized progesterone in early pregnancy, but causality has not been established. Crinone progesterone vaginal gel may be used to support early pregnancy as part of an Assisted

Reproductive Technology (ART) program; if pregnancy occurs, the gel is typically continued for 10–12 weeks until placental production of progesterone is adequate to support the pregnancy. Similarly, Endometrin vaginal inserts are used for up to 10 weeks in ART. Progesterone should only be used during early pregnancy under the observation of an ART specialist, although *other formulations of progesterone are contraindicated for use in pregnancy and suspected pregnancy as they are classified as FDA pregnancy category X*, data suggest that progesterone may be effective in preventing preterm delivery, especially in high-risk populations.[33438] [33440] The American College of Obstetricians and Gynecologists (ACOG) Committee recommends that if progesterone is to be used, it should only be used in women with a history of spontaneous birth at < 37 weeks gestation; in addition, the ideal formulation or whether it should be used in other high-risk women is not yet known.[33439] Progesterone should not be used if there is ectopic pregnancy, during cases of missed abortion, or during diagnostic tests for pregnancy.

In general, the American Academy of Pediatrics considers progesterone to be compatible with breast-feeding. Detectable amounts of progestins have been identified in the milk of nursing mothers; in general the presence of progestins in the milk are not expected to have adverse effects on lactation production. However, the effects of progestins present in breast milk on the nursing infant have not been determined. The administration of any medication to nursing mothers should take into account the benefit of the drug to the mother and the potential for risk to the breast-fed infant.

The safety and effectiveness of progesterone in children have not been established. The safety and efficacy of progesterone have only been established in females of reproductive age. Use of progesterone in female children before menarche is not usually indicated, and its safety and efficacy in this population is not established.

Progesterone is contraindicated in patients with a history of *thrombophlebitis* or *thromboembolic disease* (including *stroke* and *myocardial infarction*). Although thromboembolic disease is believed to be an estrogen-related effect, studies have shown that patients receiving hormonal contraceptives or hormonal replacement therapy regimens containing progestins may have a higher risk of venous thromboembolic (VTE) disease. Because of the higher risk of thromboembolic disease in tobacco smoking women, women should be advised not to smoke, particularly if they are over the age of 35 years. Hormonal contraceptives and hormone replacement therapies should also be used cautiously in patients with history of coronary artery disease, progestin intolerance, or cerebrovascular disease.

Progesterone should be used cautiously in patients with diabetes mellitus. Although the effects appear to be minimal during therapy with progestins, altered glucose tolerance secondary to decreased insulin sensitivity has been reported during hormonal contraceptive therapy.

Progesterone should be prescribed cautiously in patients with asthma, congestive heart failure, nephrotic syndrome or other renal disease, or cardiac disease. Hormonal contraceptives can cause fluid retention and may exacerbate any of the above conditions.

Progesterone should be used cautiously in patients with a history of major depression, migraine, or seizure disorder. Progestins may exacerbate these conditions in some patients. Some cases of seizures following administration of progestins have been reported.

An intrauterine device containing progesterone should not be used if there is any infection or inflammation in the female reproductive tract. There is a risk of infection progressing to pelvic inflammatory disease. Exposure to sexually transmitted disease also increases this risk.

Prometrium (progesterone) capsules should not be used in patients with *peanut hypersensitivity*. This product is formulated with peanut oil.

Progesterone may cause transient dizziness in some patients. Use caution when driving or operating machinery.

Estrogen/progestin combination therapy has been found to fail to prevent mild cognitive impairment (memory loss) and to increase the risk of dementia in women 65 years and older. The WHIMS study, an ancillary study of the WHI trial to assess the effects of estrogen/progestin therapy on cognitive function in elderly women (65 years of age or older), found that patients receiving either active treatment or placebo had similar rates of developing mild cognitive impairment. Patients receiving estrogen/progestin combination therapy were more likely than patients receiving placebo to be diagnosed with dementia. The applicability of this finding to women who use estrogen alone or to the typical user of HRT (i.e., younger, symptomatic women taking hormone replacement therapy to relieve menopausal symptoms) is unclear. Administration of estrogen/progestin combination therapy should be avoided in women 65 years of age and older and estrogen/progestin combination therapy should not be used to prevent or treat dementia or preserve cognition (memory).[27451]

Hormonal contraceptives have been associated with retinal thrombosis. Although this effect is generally believed to be related to estrogen, patients should be monitored carefully for the development of ocular lesions. Progesterone therapy should be discontinued if any unexplained visual disturbance occurs.

Pregnancy / Breast-feeding

Prometrium micronized progesterone capsules are classified in FDA pregnancy category B. In general, several studies of women exposed to progesterone during pregnancy have not demonstrated a significant increase in fetal malformations. A single case of cleft palate has been reported in an infant exposed to micronized progesterone in utero. Rare cases of fetal death have been reported in women administered micronized progesterone in early pregnancy, but causality has not been established. Crinone progesterone vaginal gel may be used to support early pregnancy as part of an Assisted Reproductive Technology (ART) program; if pregnancy occurs, the gel is typically continued for 10–12 weeks until placental production of progesterone is adequate to support the pregnancy. Similarly, Endometrin vaginal inserts are used for up to 10 weeks in ART. Progesterone should only be used during early pregnancy under the observation of an ART specialist, although *other formulations of progesterone are contraindicated for use in pregnancy and suspected pregnancy as they are classified as FDA pregnancy category X*, data suggest that progesterone may be effective in preventing preterm delivery, especially in high-risk populations.[33438] [33440] The American College of Obstetricians and Gynecologists (ACOG) Committee recommends that if progesterone is to be used, it should only be used in women with a history of spontaneous birth at < 37 weeks gestation; in addition, the ideal formulation or whether it should be used in other high-risk women is not yet known.[33439] Progesterone should not be used if there is ectopic pregnancy, during cases of missed abortion, or during diagnostic tests for pregnancy.

In general, the American Academy of Pediatrics considers progesterone to be compatible with breast-feeding. Detectable amounts of progestins have been identified in the milk of nursing mothers; in general the presence of progestins in the milk are not expected to have adverse effects on lactation production. However, the effects of progestins present in breast milk on the nursing infant have not been determined. The administration of any medication to nursing mothers should take into account the benefit of the drug to the mother and the potential for risk to the breast-fed infant.

Revision Date: 4/12/2010 11:17:00 AM

Interactions

Level 1 - Severe

- Bosentan

Level 2 - Major

- Barbiturates
- Bexarotene
- Carbamazepine
- Ethotoin
- Fosphenytoin
- Phenytoin
- Rifabutin
- Rifampin
- Rifapentine

Level 3 - Moderate

- Aprepitant, Fosaprepitant
- Sodium Iodide I-131

Level 4 - Minor

- Bromocriptine
- Cimetidine
- Clarithromycin
- Danazol
- Diltiazem
- Doxorubicin
- Erythromycin
- Fluconazole
- food
- Itraconazole
- Ketoconazole
- Verapamil
- Voriconazole

Vaginal preparations of progesterone (e.g., Crinone, Endometrin, and Prochieve) should not be used with other intravaginal products (e.g., vaginal antifungals) as concurrent use may alter progesterone release and absorption from the vagina. The manufacturer of Crinone and Prochieve indicates that other intravaginal products can be used as long as 6 hours has lapsed either before or after vaginal administration of progesterone.[10173] [10174]

Drugs that can induce hepatic enzymes can accelerate the rate of metabolism of hormones including hormonal contraceptives. Pregnancy has been reported during therapy with estrogens, oral contraceptives, or progestins in patients receiving phenytoin concurrently.[5503] Women taking both hormones and hepatic enzyme-inducing drugs should report breakthrough bleeding to their prescribers. An alternate or additional form of contraception should be considered in patients prescribed concomitant therapy with enzyme-inducing anticonvulsants, or higher-dose hormonal

regimens may be indicated where acceptable or applicable. The alternative or additional contraceptive agent may need to be continued for one month after discontinuation of the interacting medication. Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on phenytoin, with dose adjustments made based on clinical efficacy.

Drugs that can induce hepatic enzymes can accelerate the rate of metabolism of hormones including hormonal contraceptives. Pregnancy has been reported during therapy with estrogens, oral contraceptives, or progestins in patients receiving phenytoin (the active metabolite of fosphenytoin) concurrently.[5265] [5503] Women taking both hormones and hepatic enzyme-inducing drugs should report breakthrough bleeding to their prescribers. An alternate or additional form of contraception should be considered in patients prescribed concomitant therapy with enzyme-inducing anticonvulsants, or higher-dose hormonal regimens may be indicated where acceptable or applicable. The alternative or additional contraceptive agent may need to be continued for one month after discontinuation of the interacting medication. Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on fosphenytoin, with dose adjustments made based on clinical efficacy.

Drugs that can induce hepatic enzymes can accelerate the rate of metabolism of hormones including hormonal contraceptives. Pregnancy has been reported during therapy with estrogens, oral contraceptives, or progestins in patients receiving phenytoin concurrently.[5503] A similar interaction may be expected with ethoin.[4741] Women taking both hormones and hepatic enzyme-inducing drugs should report breakthrough bleeding to their prescribers. An alternate or additional form of contraception should be considered in patients prescribed concomitant therapy with enzyme-inducing anticonvulsants, or higher-dose hormonal regimens may be indicated where acceptable or applicable. The alternative or additional contraceptive agent may need to be continued for one month after discontinuation of the interacting medication. Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on ethoin, with dose adjustments made based on clinical efficacy.

Estrogens and progestins are both susceptible to drug interactions with hepatic enzyme inducing drugs such as carbamazepine. Concurrent administration of carbamazepine with estrogens, oral contraceptives, or progestins may increase the hormone's elimination.[4754] [4743] [6300] Women taking both hormones and hepatic enzyme-inducing drugs should report breakthrough bleeding to their prescribers. If used for contraception, an alternate or additional form of contraception should be considered in patients prescribed hepatic enzyme inducing drugs, or higher-dose hormonal regimens may be indicated where acceptable or applicable as pregnancy has been reported in patients taking the hepatic enzyme inducing drug phenytoin concurrently with hormonal contraceptives. The alternative or additional contraceptive agent may need to be continued for 1 month after discontinuation of the interacting medication. Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on carbamazepine, with dose adjustments made based on clinical efficacy.

Estrogens and progestins are both susceptible to drug interactions with hepatic enzyme inducing drugs such as barbiturates. Concurrent administration of barbiturates with estrogens, oral contraceptives, non-oral combination contraceptives, or progestins may increase the hormone's elimination.[4722] [5326] [9794] [10173] Women taking both hormones and hepatic enzyme-inducing drugs should report breakthrough bleeding to their prescribers. If used for contraception, an alternate or additional form of contraception should be considered in patients prescribed hepatic enzyme inducing drugs. Higher-dose hormonal regimens may be indicated where acceptable or applicable as pregnancy has been reported in patients taking the hepatic enzyme inducing drug phenytoin concurrently with hormonal contraceptives. The alternative or additional contraceptive agent may need to be continued for 1 month after discontinuation of the interacting medication. Additionally, epileptic women taking both anticonvulsants and OCs may be at higher risk of folate deficiency secondary to additive effects on folate metabolism; if oral contraceptive failure occurs, the additive effects could potentially heighten the risk of neural tube defects in pregnancy.[5307] Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on barbiturates, with dose adjustments made based on clinical efficacy.

Estrogens and progestins are both susceptible to drug interactions with hepatic enzyme inducing drugs such as rifampin, rifabutin, or rifapentine. Concurrent administration of these drugs with estrogens, oral contraceptives, or progestins may increase the hormone's elimination.[4718] [4724] [9794] [10173] In addition, free estrogen-hormone concentrations are decreased because rifampin increases estrogen protein binding ability. Additionally, like other anti-infectives, rifampin indirectly inhibits the enterohepatic recirculation of estrogen through disruption of GI flora growth. Women taking both hormones and any of these drugs should report breakthrough bleeding to their prescribers; it is estimated that 70% of women taking oral contraceptives and rifampin experience menstrual abnormalities, and 6% become pregnant.[5212] [5239] If used for contraception, an alternate or additional form of contraception should be considered in patients prescribed rifampin, rifabutin, or rifapentine. Higher-dose hormonal regimens may be indicated where acceptable or applicable. The alternative or additional contraceptive agent may need to be continued for 1 month after discontinuation of the interacting medication. Patients taking these hormones for other indications may need to be monitored for reduced clinical effect while on rifampin, rifabutin, or rifapentine, with dose adjustments made based on clinical efficacy.

The metabolism of progesterone was inhibited by ketoconazole, a known inhibitor of cytochrome P450 3A4 hepatic enzymes.[6266] It has not been determined whether other drugs which inhibit CYP3A4 hepatic enzymes would have a similar effect. Other such drugs include cimetidine [5277], clarithromycin [4964], danazol [4718], diltiazem [5004], erythromycin [4718], fluconazole [4718], itraconazole [4718], troleandomycin, verapamil [4718] and voriconazole [4882]. This list is not inclusive of all drugs that inhibit CYP3A4.

Although specific studies have not been done with progesterone (including the progesterone intrauterine device, IUD), an alternative or additional non-hormonal method of birth control is recommended during aprepitant, fosaprepitant treatment and for 28 days after aprepitant treatment is discontinued to avoid potential for contraceptive failure.[7438]

Bromocriptine is used to restore ovulation and ovarian function in amenorrheic women (see Bromocriptine, Mechanism of Action).[5066] Progestins can cause amenorrhea and, therefore, counteract the desired effects of bromocriptine. Concurrent use is not recommended.

Food can increase the bioavailability of progesterone administered orally.[6266] Mean peak serum concentrations (C_{max}) were increased slightly when progesterone was administered with or 2 hours after a high fat breakfast relative to the fasting state. In contrast, when the capsules were administered 4 hours after the high fat breakfast, there was a significant increase in C_{max}. There was no effect on the time to maximum serum concentrations (T_{max}). The effects of food on the pharmacokinetics of progesterone showed high intra- and intersubject variability.

In a published study, progesterone was given intravenously to patients with advanced malignancies at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m²) by IV bolus. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed.[1954] Similar effects may occur with doxorubicin liposomal.

Based on an interaction with tamoxifen, bexarotene capsules may theoretically increase the rate of metabolism and reduce plasma concentrations of other substrates metabolized by CYP3A4, including progestins.[4791]

Bosentan is a significant inducer of CYP3A hepatic enzymes.[4718] [5226] Specific interaction studies have not been performed to evaluate the effect of coadministration of bosentan and hormonal contraceptives (oral contraceptives, estrogens, or progestins), including oral, injectable or implantable agents.[5226] Since many of these drugs are metabolized by CYP3A4 [4718], there is a possibility of contraceptive failure when bosentan is coadministered.[5226] Women should not rely on hormonal contraception alone when taking bosentan; bosentan is teratogenic and is contraindicated during pregnancy.[5226] Since many of these drugs are metabolized by CYP3A4, a reduction in hormone replacement efficacy is possible when bosentan is coadministered.[5226]

Progesterone is known to decrease the uptake of iodide into thyroid tissue.[8683] In order to increase thyroid uptake and optimize exposure of thyroid tissue to the radionucleotide sodium iodide I-131, consider withholding progesterone prior to treatment with sodium iodide I-131.

Revision Date: 7/29/2009 3:20:00 PM

Adverse Reactions

- abdominal pain
- acne vulgaris
- alopecia
- amenorrhea
- anorexia
- anxiety
- appetite stimulation
- arthralgia
- breakthrough bleeding
- breast enlargement
- cervicitis
- cholestasis
- constipation
- cough
- depression
- diarrhea
- dizziness
- drowsiness
- dysmenorrhea
- dyspareunia
- edema
- elevated hepatic enzymes
- hirsutism
- hyperglycemia
- hypertension
- infection
- injection site reaction
- irritability
- jaundice
- leukorrhea
- libido decrease
- libido increase
- mastalgia
- melasma
- menstrual irregularity
- musculoskeletal pain
- nausea
- nocturia
- perineal pain
- pruritus
- pulmonary embolism
- retinal thrombosis
- thromboembolism
- urticaria

- emotional lability
- erythema
- fatigue
- fluid retention
- galactorrhea
- headache
- hepatitis
- hepatoma
- uterine pain
- vaginal discharge
- vaginal irritation
- vaginitis
- vomiting
- weakness
- weight gain
- weight loss

The most common adverse reactions occurring during therapy with progesterone include menstrual irregularity, menstrual flow changes, and dysmenorrhea or amenorrhea. These effects may be indistinguishable from pregnancy. Progesterone also causes spotting, breakthrough bleeding, weight gain, nausea/vomiting, breast tenderness or mastalgia, and mild headache. These adverse effects occur less frequently with progestin-only OCs compared to combination OCs. Other reported adverse reactions during therapy include diarrhea, dizziness, alopecia, dermatitis, acne vulgaris, melasma, chloasma, pruritus, urticaria, anorexia, appetite stimulation, cough, libido decrease, libido increase, breast discharge, cervicitis, galactorrhea, musculoskeletal pain, weight loss, fatigue, hirsutism, abdominal pain, leukorrhea, unusual weakness, and vaginitis. Additional adverse reactions associated with the intravaginal gel include arthralgia, breast enlargement, constipation, drowsiness, dyspareunia, nocturia, perineal pain, and vaginal discharge. Adverse reactions associated with vaginal inserts include vaginal irritation, vaginal itching, vaginal burning, and vaginal discomfort.

Fluid retention and/or edema may occur in patients receiving progesterone. Patients with heart failure and/or renal disease may experience an exacerbation of their condition.

Patients receiving progesterone or other hormonal contraceptives can experience emotional lability. This adverse effect may be manifest as mental depression, anxiety, frustration, irritability, anger, or other emotional outbursts.

The insertion of an intrauterine device (IUD) containing progesterone may result in infection. The risk of infection is greatest within the first 20 days after insertion. Untreated infection may lead to pelvic inflammatory disease, which requires removal of the system and appropriate antibiotic treatment. The patient's partner may also require antibiotic treatment. Uterine pain may follow initial insertion of the progesterone IUD and usually responds to analgesic therapy. Pain should not persist for more than a few hours after IUD insertion.

Thromboembolic disease is more common in hormonal contraceptive users than in non-users. Previously, thromboembolic disease such as deep venous thrombosis (DVT), appeared to be more related to estrogen therapy than to progestin therapy, however, there is some evidence that different types of progestins are associated with differing rates of venous thromboembolism. At usual doses, women receiving third generation progestins (e.g., desogestrel or gestodene) appear to have an increased risk of venous thromboembolic disease compared to women receiving previous generation progestins.[24588] [24654] The risk is even greater in women with genetic predisposition or family history for venous thromboembolic disease.[24655] Thromboembolism or thrombus formation has also been associated with high doses of progestins. Other rare adverse reactions that may occur during progestin therapy may include pulmonary embolism, retinal thrombosis, elevated blood pressure or hypertension, hepatoma, hepatitis (and elevated hepatic enzymes), cholestasis, jaundice, and hyperglycemia.

Intramuscular administration of progesterone often causes an injection site reaction. Adverse local reactions include erythema, irritation, pain, and swelling at the site of injection.

Revision Date: 2/10/2010 10:01:00 AM

How Supplied

Progesterone Bulk powder

Progesterone Micronized Powder for Compounding (00574-0430) (Paddock Laboratories Inc) **(off market)**

Progesterone Micronized Powder for Compounding (39822-6000) (X Gen Pharmaceuticals Inc)

Progesterone Milled Powder for Compounding (00574-0432) (Paddock Laboratories Inc) **(off market)**

Progesterone Wettable Microcrystalline Powder for Compounding (00574-0431) (Paddock Laboratories Inc)

Progesterone Wettable Powder for Compounding (39822-6100) (X Gen Pharmaceuticals Inc)

Progesterone Oil for injection

Progesterone 50mg/ml in Oil for Injection (63323-0261) (APP Pharmaceuticals)

Progesterone 50mg/ml in Oil for Injection (00574-0704) (Paddock



Laboratories Inc) (off market)

Progesterone 50mg/ml in Sesame Oil for Injection (40042-0050)
(PharmaForce, Inc.)

Progesterone 50mg/ml in Sesame Oil for Injection (00364-6683) (Schein
Pharmaceutical Inc) (off market)

Progesterone 50mg/ml in Sesame Oil for Injection (00591-3128) (Watson
Pharmaceuticals Inc) 

Progesterone Oral capsule

Prometrium 100mg Capsule (00032-1708) (Solvay Pharmaceuticals Inc) 

Prometrium 200mg Capsule (00032-1711) (Solvay Pharmaceuticals Inc) 

Progesterone Topical cream

First-Progesterone MC 10% Compounding Kit (65628-0031) (CutisPharma,
Inc) (off market)

First-Progesterone MC 5% Compounding Kit (65628-0030) (CutisPharma, Inc)
(off market)

Progesterone Vaginal gel

Crinone 4% Vaginal Gel (44087-0804) (Serono Inc) (off market)

Crinone 8% Vaginal Gel (44087-0818) (Columbia Laboratories Inc) (off
market)

Crinone 8% Vaginal Gel (55056-0818) (Columbia Laboratories Inc) (off
market) 

Crinone 8% Vaginal Gel (55056-0806) (Columbia Laboratories Inc)

Crinone 8% Vaginal Gel (44087-0818) (Serono Inc) (off market)

Crinone 8% Vaginal Gel (44087-0808) (Serono Inc) (off market) 

Crinone 8% Vaginal Gel (55056-0818) (WatsonPharma Inc)

Prochieve 4% Vaginal Gel (55056-0406) (Ascend Therapeutics, Inc.) (off
market) 

Prochieve 4% Vaginal Gel (55056-0406) (Columbia Laboratories Inc) (off
market) 

Prochieve 4% Vaginal Gel (55056-0406) (WatsonPharma Inc)

Prochieve 8% Vaginal Gel (55056-0806) (Columbia Laboratories Inc) (off
market) 

Prochieve 8% Vaginal Gel (55056-0818) (Columbia Laboratories Inc) (off
market) 

Prochieve 8% Vaginal Gel (55056-1601) (Columbia Laboratories Inc) (off
market)

Prochieve 8% Vaginal Gel (55056-1601) (WatsonPharma Inc)

Progesterone Vaginal insert

Endometrin 100mg Vaginal Insert (55566-6500) (Ferring Pharmaceuticals Inc)

Progesterone Vaginal Suppository

First-Progesterone VGS 100 Compounding Kit (65628-0062) (CutisPharma,
Inc)

First-Progesterone VGS 200 Compounding Kit (65628-0063) (CutisPharma,
Inc)

First-Progesterone VGS 25 Compounding Kit (65628-0060) (CutisPharma, Inc)

First-Progesterone VGS 400 Compounding Kit (65628-0064) (CutisPharma,
Inc)

First-Progesterone VGS 50 Compounding Kit (65628-0061) (CutisPharma, Inc)

Monitoring Parameters

- pap smear
- pelvic exam
- pelvic ultrasound
- pregnancy testing
- serum progesterone concentrations

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