



Progestational Agents Therapeutic Class Review (TCR)

August 3, 2018

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MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
hydroxyprogesterone caproate (Makena®) ¹	generic, AMAG/Lumara	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
hydroxyprogesterone caproate* ²	generic, ANI	<ul style="list-style-type: none"> ■ Treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); ■ Management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance and in the absence of organic pathology, such as submucous fibroids or uterine cancer; ■ Test for endogenous estrogen production; ■ Production of secretory endometrium and desquamation
medroxyprogesterone injection (Depo-Provera®) ³	Pfizer	Adjunctive therapy and palliative treatment of inoperable, recurrent, and metastatic endometrial or renal carcinoma
medroxyprogesterone tablet (Provera®) ⁴	generic, Pfizer	<ul style="list-style-type: none"> ■ Treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer; ■ To reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving daily oral conjugated estrogens 0.625 mg tablets
norethindrone acetate tablet (Aygestin®) ⁵	generic, Teva	Treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer Limitation of Use: Aygestin is not intended, recommended, or approved to be used with concomitant estrogen therapy in postmenopausal women for endometrial protection
progesterone capsule (Prometrium®) ⁶	generic, Virtus	<ul style="list-style-type: none"> ■ For use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets; ■ For use in secondary amenorrhea
progesterone in oil for injection ⁷	generic	Treatment of amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer
progesterone vaginal gel (Crinone®) ⁸	Actavis	<ul style="list-style-type: none"> ■ For progesterone supplementation or replacement as part of an Assisted Reproductive Technology (ART) treatment for infertile women with progesterone deficiency; ■ For the treatment of secondary amenorrhea

* Approved via abbreviated new drug application (ANDA); reference product is Delalutin®, which has been discontinued. This formulation is not considered therapeutically equivalent to Makena.

The use of Depo-subQ Provera 104® (medroxyprogesterone acetate injectable suspension 104 mg/0.65 mL), indicated for the prevention of pregnancy in women of child bearing potential and for the management of endometriosis-associated pain, will not be addressed in this therapeutic class review.⁹

OVERVIEW

Progestins are a group of steroid hormones. Progesterone is naturally occurring and is secreted by the corpus luteum of the ovary, the placenta, and, in small amounts, by the adrenal cortex and testes. It prepares the inner lining of the uterus for pregnancy and, if pregnancy occurs, it maintains the uterus through the pregnancy and prevents ovulation during pregnancy. Progesterone is administered orally, vaginally, and by injection.

Medroxyprogesterone (Depo-Provera, Provera), norethindrone (Aygestin), and hydroxyprogesterone caproate (Makena, generic by ANI) are synthetic progestins administered orally and/or by injection. Medroxyprogesterone is also used to treat endometrial and renal cell carcinomas. Hydroxyprogesterone caproate (Makena) is only used to reduce the risk of preterm birth in women with singleton pregnancies who have a history of singleton spontaneous preterm birth, while hydroxyprogesterone caproate by ANI Pharmaceuticals carries other indications. These agents are not considered therapeutically equivalent by the Food and Drug Administration (FDA). FDA-approval of Makena was based on data with earlier available hydroxyprogesterone caproate agents (e.g., Delalutin).¹⁰

Progestins are used to treat conditions such as secondary amenorrhea, abnormal uterine bleeding, endometriosis, endometrial hyperplasia, and endometrial carcinoma. They are also used during assisted reproductive technology (ART) therapy and for the prevention of preterm birth.

Amenorrhea (Secondary)

Amenorrhea is the absence or abnormal cessation of menses. Primary and secondary amenorrhea identifies the occurrence of amenorrhea before or after menarche, respectively.¹¹ The National Institutes of Health (NIH) define secondary amenorrhea as absence of menses for 6 or more months.¹² Secondary amenorrhea can be due to abnormal levels of follicle stimulating hormone (FSH), hyperprolactinemia, anatomic conditions (e.g., Asherman syndrome), and hyperandrogenic states (e.g., ovarian tumor, polycystic ovary syndrome). The majority of cases are due to polycystic ovary syndrome (PCOS), hypothalamic amenorrhea, hyperprolactinemia, or ovarian failure. Treatment depends on the cause of the amenorrhea. Normal monthly menses usually return after the condition is adequately treated.

Functional disorders of the hypothalamus are the most common reason for chronic amenorrhea and can be attributed to weight changes, undernutrition, excessive exercise, and severe anxiety.¹³ Chronic debilitating disease can also lead to anovulation and amenorrhea. Women with hypothalamic amenorrhea are at increased risk for osteoporosis. Unless the primary cause can be easily corrected, cyclic estrogen-progestin therapy or oral contraceptives are warranted to prevent excessive bone loss.

Polycystic ovary syndrome (PCOS) is the most common cause of hyperandrogenic chronic anovulation, in which there is a higher androgen and estrogen levels and lower levels of progesterone.¹⁴ The diagnostic criterion for PCOS includes chronic anovulation, hyperandrogenism, and polycystic ovaries.^{15,16} The primary treatment for PCOS is weight loss through diet and exercise, which can lower androgen levels, improve hirsutism, normalize menses, and decrease insulin resistance characteristic of PCOS. Use of oral contraceptives or cyclic progestational agents can help maintain a normal endometrium. The optimal cyclic progestin regimen to prevent endometrial cancer is unknown, but a monthly 10- to 14-day regimen is recommended. Patients with ovarian failure should be offered

estrogen and progestin treatment to promote and maintain secondary sexual characteristics and to reduce the risk of osteoporosis.^{17,18}

Dopamine agonists, such as bromocriptine and cabergoline, are the preferred treatment of hyperprolactinemia with or without a pituitary tumor.¹⁹

Abnormal Uterine Bleeding (AUB)

According to the American Congress of Obstetricians and Gynecologists' (ACOG) Committee on Gynecologic Practice, the etiologies of acute AUB should be classified based on the PALM–COEIN system: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, and Not otherwise classified.²⁰ Hormonal management is considered first-line medical treatment for patients with acute AUB without known or suspected bleeding disorders. Treatment options include intravenous conjugated equine estrogen, combined oral contraceptives (OCs), and oral progestins. A study comparing OCs and progestins found that bleeding stopped within a median time of 3 days in 88% of women who took OCs and 76% of women who took medroxyprogesterone acetate. In addition, antifibrinolytic drugs, such as tranexamic acid, are effective treatments for patients with chronic AUB. Once the acute episode of bleeding has been controlled, long-term maintenance treatment of chronic AUB may be considered and include levonorgestrel intrauterine system, OCs (monthly or extended cycles), progestin therapy (oral or intramuscular), tranexamic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs).

ACOG also states that continuous combined hormonal contraception, depot medroxyprogesterone acetate (DMPA), and the levonorgestrel intrauterine system may be considered for long-term menstrual suppression (reaffirmed in [2018](#)).²¹

Uterine fibroids, also called leiomyomas or myomas, are benign growths that can be located inside, on the outer surface, or within the wall of the uterus.^{22,23} Fibroids most commonly occur in women 30 to 40 years of age, but can occur at any age and are more common in African American women than Caucasian women. Symptoms include abdominal or lower back pain, changes in menstruation, and AUB. Miscarriages and infertility can occur. Fibroids can be treated with oral contraceptives, gonadotropin-releasing hormone (GnRH) agonists, progestin therapy, surgery (e.g., myomectomy, hysterectomy, magnetic resonance imaging-guided ultrasound surgery, endometrial ablation, uterine artery embolization).

Endometrial hyperplasia is an increase in growth of the endometrium, most often caused by excess estrogen without progesterone.^{24,25} Women present with AUB, most often after menopause, or during perimenopause.²⁶ Mild or simple hyperplasia may resolve spontaneously or with hormone therapy and is associated with a very small risk of becoming cancerous. If left untreated, simple atypical hyperplasia may become cancerous in about 8% of cases, and complex atypical hyperplasia (CAH) has a risk of becoming cancerous in up to 29% of cases. The choice of treatment for endometrial hyperplasia is dependent on patient age, the presence of cytologic atypia, the desire for future childbearing, and surgical risk. Endometrial hyperplasia without atypia responds well to progestin therapy, via oral, vaginal, injectable, or intrauterine route. However, women with atypical hyperplasia should be treated with hysterectomy unless other factors preclude surgery.

Assisted Reproductive Technology (ART)

According to the Centers for Disease Control and Prevention (CDC), ART includes all fertility treatments in which both eggs and sperm are handled.²⁷ In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman. ART does not include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved.

Several medications, such as gonadotropin releasing hormone, GnRH agonists and antagonists, gonadotropins, and human chorionic gonadotropin (hCG), are used as part of an ART regimen, each having an important role of a stimulating cycle.²⁸

Luteal deficiency, inadequate levels of or response to progesterone, is common in older women and in women with abnormal ovulation. Progesterone has been used widely in an attempt to improve implantation and fertility.²⁹ Progesterone therapy has been used in the treatment of luteal phase deficiency, for the treatment of recurrent miscarriages, and in women undergoing *in vitro* fertilization and related procedures. Progesterone is used routinely in most *in vitro* fertilization programs after egg retrieval to support the lining of the uterus. The theoretical basis for progesterone use rests on the assumption that a high level of estrogen requires more progesterone to create an adequate uterine environment, and some of the progesterone producing potential of the ovary may be diminished after oocyte retrieval. In an early study on *in vitro* fertilization, pregnancy rates improved once progesterone was utilized.

Carcinoma

Endometrial cancer is the most common gynecologic malignancy. It is the fourth most common cancer in women in the United States (U.S.).³⁰ It occurs most often in postmenopausal women, but can also occur prior to menopause.³¹ Risk factors include obesity, anovulatory menstrual cycles, diabetes, hypertension, and women with Lynch II syndrome. In addition, women with endometrial cancer are at a 19% to 25% greater chance of concurrent primary ovarian cancer.³² Prevalence is higher in Caucasian compared to Asian or African American women. Women present with AUB. Approximately 10% of postmenopausal bleeding will lead to a diagnosis of endometrial cancer.

ACOG recommends that most women with endometrial cancer should undergo complete surgical resection of all disease with exceptions being determined after consultation with a specialist such as a gynecologic oncologist.³³ Adjuvant radiation therapy in select individuals with stage I or II carcinomas can reduce the risk of local recurrence but does not affect overall survival. Women who desire to maintain their fertility may be treated with progestin therapy with complete intrauterine evaluation approximately every 3 months to document response. Hysterectomy should be recommended for women who do not desire future fertility.

The National Comprehensive Cancer Network (NCCN) uterine neoplasm guidelines (2.2018) recommend hysterectomy as primary treatment for endometrial carcinoma; hormone therapy can be considered in highly select patients, such as those with grade 1 endometrial hyperplasia who desire fertility preservation and in patients with endometrial stromal sarcoma.³⁴ Hormone therapy for recurrent, metastatic, or high-risk disease includes megestrol with alternating tamoxifen, progestational agents alone, aromatase inhibitors, fulvestrant, or tamoxifen alone. No particular drug

is preferred. Therapy with progestational agents has shown good response for asymptomatic or low-grade disseminated metastases, especially in patients with estrogen receptors (ER)/progesterone receptor (PR)-positive disease.

Endometriosis

Endometriosis is a condition in which tissue that normally grows inside the uterus begins to grow outside the uterus. It is one of the most common gynecological diseases, and its primary symptoms include pain and infertility.³⁵

In their 2010 management of endometriosis guidelines (**reaffirmed in 2018**), ACOG states that significant short-term improvement in endometrial pain may be experienced after conservative surgical treatment (Level A).³⁶ Medical suppressive therapy, such as oral contraceptives (OCs) or gonadotropin-releasing hormone (GnRH) agonists, improves pain symptoms; however, recurrence rates are high after the medication is discontinued (Level A). ACOG recommends the following: after failure of OCs and NSAIDs, empiric therapy with a 3-month course of a GnRH agonist (Level B); in patients with known endometriosis and dysmenorrhea, OCs and oral norethindrone or depot medroxyprogesterone acetate (DMPA) are effective compared with placebo and are equivalent to other more costly regimens (Level B); long-term (at least 24 months) OC use is effective in reducing endometrioma recurrence, as well as a reduction in the frequency and severity of dysmenorrhea (Level B). **In 2018, elagolix, the first of a new class of medications, GnRH receptor antagonists, was FDA-approved to treat endometriosis-related pain.**³⁷

Preterm Birth

Preterm birth, defined as birth of an infant prior to 37 week of gestation, affects nearly 1 of every 10 infants born in the U.S. each year.³⁸ Preterm-related causes of death accounted for **17% in 2015** of all infant deaths. There is a higher risk of serious disability or death the earlier the baby is born. Many organ systems, including the brain, lungs, and liver, need the final weeks of pregnancy to develop fully. Preterm birth is also a leading cause of long-term neurological disabilities in children. Women who have had a previous preterm birth are at increased risk for a subsequent premature birth. In addition, although most African American women give birth at term, on average, African American women are about 50% more likely to have a premature baby compared to Caucasian women.

Progestational agents have been studied in small controlled trials since the 1960s with mixed results. A meta-analysis published in 1990 restricted to placebo-controlled trials using hydroxyprogesterone caproate reported positive results in reduction of preterm labor, preterm birth, and birth weight under 2,500 grams.³⁹

The FDA originally approved hydroxyprogesterone caproate under the trade name of Delalutin® in 1956 based on safety data; the indications section of the original label stated that Delalutin appears to be useful in conditions generally responding to progestogens and listed habitual and threatened abortion as one such condition. In 1973, the FDA removed the pregnancy-related indications from the product label and in 2000, the manufacturer withdrew Delalutin from the market for reasons other than safety.⁴⁰ In 2015, the FDA approved a generic hydroxyprogesterone caproate formulation by ANI pharmaceuticals listing Delalutin as the reference product. Unlike Makena, which is also hydroxyprogesterone caproate, it is not approved for preterm labor.

PHARMACOLOGY^{41,42,43,44}

Progesterone is a naturally occurring steroid hormone, synthesized by the ovaries and adrenal cortices in non-pregnant women. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. For approximately 10 to 12 days of the menstrual cycle, under the effect of luteinizing hormone, the corpus luteum secretes progesterone, which stimulates the endometrium to develop into secretory tissue. If fertilization occurs, progesterone supports implantation of the ovum and maintains the pregnancy. If a fertilized ovum is not implanted, progesterone and estrogen levels decline sharply, resulting in menstrual bleeding.

Progesterone also controls the estrogen-primed endometrial glands by decreasing the number of estrogen receptors and regulates mitosis in fully differentiated endometrial cells, thus preventing endometrial cancer.

Hydroxyprogesterone caproate (Makena, generic by ANI), medroxyprogesterone (Depo-Provera, Provera), and norethindrone acetate (Aygestin) are oral and/or synthetic progestins.

Medroxyprogesterone decreases endometriosis-related pain by suppressing serum estradiol concentrations and possibly by having a direct action on the lesions of endometriosis.

When use as a contraceptive agent, progestins slow the frequency of release of GnRH from the hypothalamus and blunt the pre-ovulatory surge of luteinizing hormone, thereby preventing follicular maturation and ovulation. Overall, progestin-only contraceptives prevent ovulation in 70% to 80% of cycles; however, the clinical effectiveness ranges are 96% to 98%.

The mechanism by which hydroxyprogesterone prevents preterm delivery is not fully understood.

PHARMACOKINETICS^{45,46,47,48,49,50,51,52,53,54,55}

Despite the extensive serum protein binding, progesterone has a relatively short half-life of about 5 minutes. Because of the poor oral absorption of progesterone and its susceptibility to rapid first-pass metabolism in the liver, a variety of oral, injectable, and implantable synthetic analogs, hydroxyprogesterone caproate, medroxyprogesterone, and norethindrone have been developed.

Progesterone capsules (Prometrium) are an oral dosage form of micronized progesterone which has increased oral bioavailability.

Drug	Tmax	Half-life	Excretion (%)
hydroxyprogesterone caproate (Makena)	4.6 days	7.8 days	Urine: 30 Feces: 50
hydroxyprogesterone caproate	3 to 7 days	nr	Urine: not specified Feces: not specified
medroxyprogesterone injection (Depo-Provera)	3 weeks	50 days	Urine: primary
medroxyprogesterone tablet (Provera)	2-4 hr	11-17 hr	Urine: primary
norethindrone acetate tablet (Aygestin)	2 hr	9 hr	Urine: not specified Feces: not specified
progesterone capsule (Prometrium)	1.5-2.3 hr	nr	Urine: primary Bile/Feces: minor
progesterone in oil for injection	8 hr	nr	Urine: primary Bile/Feces: minor
progesterone vaginal gel (Crinone)	5-7 hr	5-20 min	Renal: 50-60 Bile/Feces: 10

nr = not reported; Tmax = time to maximum serum concentration

CONTRAINDICATIONS/WARNINGS^{56,57,58,59,60,61,62,63}

All agents in this review are contraindicated in patients with undiagnosed vaginal bleeding, current or history of carcinoma of the breast or genital organs, impaired liver function, current or history of thromboembolic disorders, or hypersensitivity to any of the drug components. Progesterone capsules (Prometrium) should not be used in patients with peanut allergy. Allergic reactions, including urticaria, pruritus, and angioedema, have been reported with use of hydroxyprogesterone (Makena) or with other products containing castor oil.

Medroxyprogesterone (Depo-Provera, Provera), norethindrone (Aygestin), and progesterone (Prometrium) are contraindicated in women with known or suspected pregnancy. Medroxyprogesterone tablets (Provera), progesterone in oil, and progesterone vaginal gel (Crinone) should not be used in women with a missed abortion.

Hydroxyprogesterone (Makena) should be avoided in those with cholestatic jaundice of pregnancy or uncontrolled hypertension. Limited evidence suggests that among women with hypertension, those who used progestin-only oral or injectable contraceptives had a small increased risk for cardiovascular events than did women who did not use these methods.⁶⁴

Women who use medroxyprogesterone injection (Depo-Provera) may experience significant loss of bone mineral density (BMD) which is greater with increasing duration of use and may not be completely reversible.⁶⁵ In a controlled clinical study, adult women using medroxyprogesterone depot (150 mg every 3 months) for up to 5 years as a contraceptive (not an indication for the 400 mg/mL injection), showed spine and hip BMD mean decreases of 5% to 6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first 2 years of use. Full recovery of bone loss in adolescents and adult women at 60 months and 24 months after drug discontinuation, respectively, was not evident. It is unknown if its use during adolescence or early adulthood, a critical time of bone growth, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. Medroxyprogesterone injection 150 mg for contraceptive use is not included in this review.

Prescribing information for progesterone capsules (Prometrium) includes a boxed warning against its combination use with estrogens for the prevention of cardiovascular disease or dementia citing the Women's Health Initiative (WHI) substudy that reported increased risks of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens 0.625 mg combined with medroxyprogesterone acetate 2.5 mg, as compared to placebo. In addition, this substudy also demonstrated an increased risk of invasive breast cancer. Progestins with estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Patients with risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (e.g., personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately. Progestin therapy should be discontinued immediately if manifestations of thrombotic disorders occur.

Discontinue norethindrone, medroxyprogesterone, and progesterone pending examination if there is a sudden partial or complete loss of vision, sudden onset of proptosis, diplopia, or migraine, or diagnosis of papilledema or retinal vascular lesion.

Because progestins may cause fluid retention, women with conditions which might be impacted by fluid retention, such as epilepsy, migraine, and cardiac or renal dysfunction, should be carefully monitored.

Patients who have a history of clinical depression should be carefully observed. Progestin therapy should be discontinued if depression recurs to a serious degree.

Norethindrone or progesterone therapy may have adverse effects on lipid and carbohydrate metabolism.

Laboratory test results, such as those of hepatic function, coagulation tests, and thyroid tests, may be affected by progestin therapy. Physicians should be aware of progestin therapy when assessing laboratory test results. Pretreatment and annual physical examination should include appropriate monitoring of blood pressure, breasts, abdomen, pelvic organs, and relevant laboratory tests.

Progestins may decrease glucose tolerance; additional monitoring may be required in diabetic patients.

DRUG INTERACTIONS^{66,67,68,69,70,71,72,73,74}

No drug-drug interaction studies have been conducted with hydroxyprogesterone (Makena, generic by ANI), medroxyprogesterone tablet (Provera), norethindrone (Aygestin), or progesterone gel (Crinone).

The metabolism of drugs metabolized by CYP1A2 (e.g., acetaminophen, halothane, nicotine) and CYP2B6 (e.g., efavirenz, bupropion, methadone) may be increased during treatment with hydroxyprogesterone.

Data suggest that ketoconazole or other known inhibitors of the CYP3A4 enzyme may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown. Agents that induce CYP3A4 may decrease the plasma concentrations of contraceptive hormones, such as medroxyprogesterone injection (Depo-Provera), and may decrease the effectiveness of hormonal contraceptives.

Use of vaginal progesterone products (Crinone) with vaginal products, such as vaginal antifungals, may alter progesterone absorption. Concurrent use is not recommended.

ADVERSE EFFECTS^{75,76,77,78,79,80,81,82}

Common adverse effects reported during progestin therapy includes: breast enlargement/tenderness, change in menstrual flow, amenorrhea, headache/migraine, changes in body weight, cholestatic jaundice, melasma, acne, urticaria, abnormalities of liver tests (e.g., aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), mood swings, nausea, and insomnia.

In clinical studies, the most common adverse events reported with intramuscular (IM) hydroxyprogesterone (Makena) use was injection site pain (34.8% versus 32.7% in the control group) and injection site swelling (17.1% versus 7.8% in the control group). The most common adverse reaction reported with the subcutaneous (SC) formulation (and higher than with the IM injection) was injection site pain (10% to 34%). In addition, certain pregnancy-related fetal and maternal complications or events were numerically increased in hydroxyprogesterone-treated subjects as to control subjects, including miscarriages and still births, admission for preterm labor, preeclampsia or hypertension, gestational diabetes, and oligohydramnios.

SPECIAL POPULATIONS^{83,84,85,86,87,88,89,90}

Pediatrics

Progesterone (Prometrium, Crinone), medroxyprogesterone tablets (Provera), hydroxyprogesterone (generic by ANI), medroxyprogesterone injection (Depo-Provera), and norethindrone (Aygestin) are not indicated for use in children.

Safety and effectiveness of the use of hydroxyprogesterone (Makena) in pediatric patients less than 16 years of age have not been established.

Medroxyprogesterone injection (Depo-Provera) has been associated with loss of bone mineral density, a particular concern in the pediatric population.

Pregnancy

Medroxyprogesterone (Depo-Provera, Provera), norethindrone (Aygestin), and oral progesterone (Prometrium) are contraindicated in women with known or suspected pregnancy.

Previously, hydroxyprogesterone (Makena) was Pregnancy Category B, but its labeling was updated in compliance with the Pregnancy and Lactation Labeling Rule (PLLR). Clinical trial data has not shown a difference in adverse developmental outcomes in children of hydroxyprogesterone caproate-treated women; however, data are insufficient to determine a drug-associated risk as none of the treated women received the drug during the first trimester of pregnancy. Data on use of hydroxyprogesterone (generic by ANI) are not available within its prescribing information.

Progesterone vaginal gel (Crinone) has been used to support embryo implantation and maintain pregnancies through its use as part of Assisted Reproductive Technology (ART) treatment regimens in 2 clinical studies.

Hepatic Impairment

The pharmacokinetics of norethindrone (Aygestin), medroxyprogesterone injection (Depo-Provera), and progesterone (Crinone, Prometrium) have not been evaluated; these agents are contraindicated in patients with markedly impaired liver function or liver disease.

Hydroxyprogesterone caproate (Makena, generic by ANI) and medroxyprogesterone tablet (Provera) are extensively metabolized in the liver. Hepatic impairment may reduce the elimination of these products.

Renal Impairment

The safety and effectiveness of progestational agents have not been established in patients with renal insufficiency.

DOSAGES^{91,92,93,94,95,96,97,98}

Drug	Dosage	Availability
hydroxyprogesterone caproate (Makena)	<p>Preterm birth (intramuscular [IM]): Administer 250 mg (1 mL) IM every 7 days in the upper outer quadrant of the gluteus maximus 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;</p> <p>Preterm birth (subcutaneous [SC]): Administer 275 mg (1.1 mL) SC in the back of either upper arm 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</p>	<p>Multidose vial for IM use: 5 mL (250 mg/mL)</p> <p>Single-dose vial (preservative-free) for IM use: 1 mL (250 mg/mL)</p> <p>Auto-injector (preservative-free) for SC use: 275 mg/1.1 mL (brand only)</p>
hydroxyprogesterone caproate	<p>Adenocarcinoma: 1,000 mg or more IM repeated 1 or more times per week (1 to 7 g per week) until relapse or lack of objective response at 12 weeks</p> <p>Amenorrhea:</p> <ul style="list-style-type: none"> ▪ One-time dosage: 375 mg IM initiated at any time ▪ Cyclic Therapy: 20 mg estradiol valerate on day 1 followed by 250 mg hydroxyprogesterone caproate IM on day 14 with estradiol valerate 5 mg administered 2 weeks following the hydroxyprogesterone caproate injection as part of a 28-day cycle; repeat every 4 weeks for 4 cycles; initiate 4 days following desquamation or 21 days following hydroxyprogesterone caproate injection if no bleeding <p>Production of secretory endometrium and desquamation:</p> <ul style="list-style-type: none"> ▪ One-time dosage: 375 mg IM initiated at any time ▪ Cyclic Therapy: 20 mg estradiol valerate on day 1 followed by 250 mg hydroxyprogesterone caproate IM on day 14 with estradiol valerate 5 mg administered 2 weeks following the hydroxyprogesterone caproate injection as part of a 28-day cycle; repeat every 4 weeks until cyclic therapy no longer required; initiate 4 days following desquamation or 21 days following hydroxyprogesterone caproate injection if no bleeding <p>Testing for Endogenous Estrogen Production: 250 mg IM x 1 dose; may repeat after 4 weeks for confirmation</p> <p>All injections should be administered IM into the outer quadrant of the gluteal muscle</p>	<p>Multidose vial: 5 mL (250 mg/mL)</p>
medroxyprogesterone injection (Depo-Provera)	<p>Endometrial or renal carcinoma: Initially 400 mg to 1,000 mg per week given IM; If improvement is noted within a few weeks or months and the disease appears stabilized, it may be possible to maintain improvement with as little as 400 mg per month</p> <p>Only for IM use</p>	<p>Vial: 2.5 mL suspension (400 mg/mL)</p>

Dosages (continued)

Drug	Dosage	Availability
medroxyprogesterone tablet (Provera)	<p>Secondary Amenorrhea: 5 mg to 10 mg for 5 to 10 days</p> <p>AUB: 5 mg to 10 mg for 5 to 10 days beginning on the calculated 16th or 21st day of the menstrual cycle</p> <p>Endometrial Hyperplasia: 5 or 10 mg daily for 12 to 14 consecutive days per month, in postmenopausal women receiving daily 0.625 mg conjugated estrogens, either beginning on the 1st day of the cycle or the 16th day of the cycle</p>	Tablets: 2 mg, 5 mg, 10 mg
norethindrone acetate tablet (Aygestin)	<p>Secondary amenorrhea and AUB: 2.5 to 10 mg orally daily for 5 to 10 days</p> <p>Endometriosis: Initial 5 mg daily for 2 weeks; dosage should be increased by 2.5 mg per day every 2 weeks until 15 mg per day is reached; continue therapy for 6 to 9 months or until annoying breakthrough bleeding demands temporary termination</p>	Tablets: 5 mg
progesterone capsule (Prometrium)	<p>Secondary Amenorrhea: 400 mg at bedtime for 10 days</p> <p>Endometrial Hyperplasia: 200 mg orally at bedtime for 12 days sequentially per 28-day cycle, to a postmenopausal woman with a uterus who is receiving daily conjugated estrogens tablets</p>	Capsules: 100 mg, 200 mg
progesterone in oil for injection	<p>Amenorrhea: 5 to 10 mg are given for 6 to 8 consecutive days</p> <p>AUB: 5 mg to 10 mg daily for 6 doses; bleeding may be expected to cease within 6 days</p>	Multidose vial: 10 mL (50 mg/mL)
progesterone vaginal gel (Crinone)	<p>Assisted Reproductive Technology:</p> <ul style="list-style-type: none"> ▪ For progesterone supplementation – progesterone 8% 90 mg administered vaginally once daily ▪ For progesterone replacement – progesterone 8% 90 mg administered vaginally twice daily ▪ If pregnancy occurs, treatment may be continued until placental autonomy is achieved, up to 10 to 12 weeks <p>Secondary Amenorrhea: progesterone 4% administered every other day for up to a total of 6 doses;</p> <p>For women who fail to respond, progesterone 8% administered every other day for up to 6 doses may be instituted</p>	Single use disposable applicators: 4% (45 mg), 8% (90 mg)

Hydroxyprogesterone acetate (Makena) should only be administered by a healthcare professional.

For medroxyprogesterone injection (Depo-Provera), to ensure the patient is not pregnant at the time of the first injection, the first injection should be given only during the first 5 days of a normal menstrual period; only within the first 5 days postpartum if not breastfeeding; and, if exclusively breastfeeding, only at the sixth postpartum week. If the time interval between injections is greater than 13 weeks, the physician should determine that the patient is not pregnant before administering the drug.

Progesterone capsules (Prometrium) should be taken with a glass of water while in the standing position for women who experience difficulty swallowing.

When progesterone in oil injection is administered to treat secondary amenorrhea, if there has been sufficient ovarian activity to produce a proliferative endometrium, withdrawal bleeding is expected 48 to 72 hours after the last injection. This may be followed by spontaneous normal cycles. When used in combination with estrogen to treat abnormal uterine bleeding, the administration of progesterone is begun after 2 weeks of estrogen therapy. If menstrual flow begins during the course of injections of progesterone, they are discontinued.

It is important to note that, when using progesterone vaginal gel (Crinone), 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. Progesterone vaginal gel should not be used concurrently with other local intravaginal therapy. If other local intravaginal therapy is to be used concurrently, there should be at least a 6-hour period before or after progesterone administration.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed, and review of information sent by manufacturers. Search strategy included the agents in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There is a paucity of clinical studies for progestin therapy. Open-label studies were included for progesterone vaginal gel (Crinone) for use in women with amenorrhea and for ART.

Approval of hydroxyprogesterone caproate by ANI pharmaceuticals is based on data with Delalutin.⁹⁹

Amenorrhea (Secondary)

progesterone capsule (Prometrium) versus placebo

In a single-center, double-blind clinical study premenopausal women who experienced secondary amenorrhea for at least 90 days, were randomized to receive 10 days of oral progesterone 300 mg per day (n=20) or placebo (n=21).¹⁰⁰ Eighty percent of women in the progesterone group experienced withdrawal bleeding within 7 days of the last dose of progesterone, compared to 10% of women in the placebo group.

Endometrial Hyperplasia

medroxyprogesterone acetate tablets (Provera) plus conjugated estrogen versus conjugated estrogen only

In a 3-year, double-blind, placebo-controlled study 356 nonhysterectomized, postmenopausal women between 45 and 64 years of age were randomized to receive placebo (n=119), 0.625 mg conjugated estrogen only (n=119), or 0.625 mg conjugated equine estrogen plus cyclic oral medroxyprogesterone acetate 10 mg (n=118).¹⁰¹ Results showed a reduction in patients that experienced endometrial hyperplasia in the combination treatment group and the placebo group as compared to the estrogen-only group as reported by proportion of patients with no hyperplasia after three years (95% versus 97% versus 38%, respectively).

progesterone capsule (Prometrium) plus estrogen versus estrogen-only

In a randomized, double-blind clinical trial, 358 postmenopausal women, each with an intact uterus, received treatment for up to 36 months with progesterone 200 mg per day given orally for 12 days per 28-day cycle in combination with conjugated estrogens 0.625 mg per day (n=120); conjugated estrogens 0.625 mg per day only (n=119); or placebo (n=119). The majority of patients in the study were Caucasian.¹⁰² There was a significantly lower rate of hyperplasia in the combination treatment group versus the estrogen-only group throughout 36 months of treatment (6% combination product versus 64% estrogen alone). The discontinuation rates due to hyperplasia were also significantly lower for patients in the combination treatment group compared to the estrogen-only group (< 1% versus 37%, respectively).

The rate of secretory transformation was evaluated in a small multicenter, randomized, double-blind clinical study in estrogen-primed postmenopausal women.¹⁰³ Progesterone 400 mg per day administered orally for 10 days (n=22) induced complete secretory changes in the endometrium in 45% of women compared to 0% in the placebo group (n=23).

Preterm Births

hydroxyprogesterone caproate (Makena) versus placebo

A published multicenter, double-blind, placebo-controlled study conducted from September 1999 to February 2002 by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network was used as the pivotal trial in support of FDA approval for Makena.¹⁰⁴ This published study compared hydroxyprogesterone caproate prepared by a research pharmacy to placebo (castor oil). This product was not the currently marketed Makena product; rather, it was comparable to Delalutin. Four hundred and sixty-three women, 16 to 43 years of age, with a singleton pregnancy that were at risk for preterm delivery were enrolled. Eligibility criteria included a documented history of spontaneous preterm delivery in a previous singleton pregnancy which was defined as delivery prior to 37 weeks of gestation following spontaneous preterm labor or premature rupture of membranes. Exclusion criteria included known fetal anomaly, prior progesterone treatment or heparin therapy during the current pregnancy, a history of thromboembolic disease or maternal/obstetrical complications, such as current or planned cervical cerclage, hypertension requiring medication, or a seizure disorder. Participants were randomized to 250 mg hydroxyprogesterone caproate (n=310) or placebo (n=153) administered IM once weekly beginning at

16 to 20 weeks of gestation and continuing until 36 weeks 6 days of gestation or delivery, whichever came first. The women in the placebo group had more previous preterm deliveries than those in the hydroxyprogesterone caproate group (mean 1.6 versus 1.4; $p=0.007$). The primary outcome measure was adjusted to account for this difference using logistic regression. The primary outcome measure was the proportion of women delivering at < 37 weeks of gestation. Secondary outcomes included the proportion delivering at < 35 and < 32 weeks, prolongation of pregnancy, neonatal outcomes, and neonatal morbidity and mortality. The proportion delivering at < 37 weeks was 37.1% in the hydroxyprogesterone caproate group compared with 54.9% in the placebo group with a treatment difference of -17.8% (95% confidence interval [CI], -28 to -7.4). The proportion of women delivering at < 35 weeks was 21.3% in the hydroxyprogesterone caproate group versus 30.7% in the placebo group with a treatment difference of -9.4% (95% CI, -19 to -0.4) and for those delivering before 32 weeks was 11.9% versus 19.7% with a treatment difference of -7.7% (95% CI, -16.3 to -0.3). After adjusting for time in the study, more patients in the hydroxyprogesterone caproate group (7.5%) than in the placebo group (4.7%) delivered before 25 weeks of gestation. There was no overall survival difference shown in this trial. In the hydroxyprogesterone caproate-treated group, fewer infants weighed < 2,500 grams (27% versus 41%; $p=0.0029$). The composite neonatal morbidity/mortality index which included death, respiratory distress syndrome, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, proven sepsis, or necrotizing enterocolitis was lower in the hydroxyprogesterone caproate-treated group but the difference was not statistically significant.

A follow-up study evaluated surviving children of mothers who participated in the pivotal trial. A total of 278 (80%) of the 348 surviving children (194 from the hydroxyprogesterone caproate-treated group and 84 from the placebo-treated group) were included. The Ages and Stages Questionnaire was the primary outcome measure in this study. At a mean of 48 months of age, there were no significant differences between groups in the Ages and Stages Questionnaire scores, health status, physical exam, or genital anomalies. The gender-specific roles (measured using the Preschool Activities Inventory) were within the normal range for both groups.¹⁰⁵

The approval of SC hydroxyprogesterone caproate (Makena) was based on comparable pharmacokinetic data to the IM formulation.^{106,107}

SUMMARY

Progesterone, a naturally occurring hormone secreted by the ovaries, serves to prepare the inner lining of the uterus for implantation of a fertilized ovum, and, if pregnancy occurs, it maintains the uterus through the pregnancy and prevents ovulation during pregnancy. Progesterone is administered orally, vaginally, and by injection.

Progestins are used to treat conditions such as secondary amenorrhea, abnormal uterine bleeding, endometriosis, endometrial hyperplasia, and endometrial carcinoma. They are also used during Assisted Reproductive Technology (ART) therapy and for the prevention of preterm birth.

Progesterone vaginal gel (Crinone) is also indicated for progesterone supplementation or replacement as part of an ART treatment for infertile women with progesterone deficiency.

Medroxyprogesterone (Depo-Provera, Provera), norethindrone (Aygestin), and hydroxyprogesterone (Makena) are synthetic progestins administered orally and/or by injection. Medroxyprogesterone is also used to treat endometrial and renal cell carcinomas. Hydroxyprogesterone caproate (Makena

only) is used to reduce the risk of preterm birth in women with singleton pregnancies that have a history of singleton spontaneous preterm birth. Hydroxyprogesterone caproate (generic by ANI Pharmaceuticals) is also approved for uterine adenocarcinoma, amenorrhea, production of secretory endometrium and desquamation, and testing for endogenous estrogen production. It is not therapeutically equivalent to Makena.

All agents in this review are contraindicated in patients with undiagnosed vaginal bleeding, current or history of carcinoma of the breast or genital organs, impaired liver function, and current or history of thromboembolic disorders.

Adverse effects of progestin therapy include decreased bone mineral density and fluid retention. Patients with risk factors for arterial vascular disease and/or venous thromboembolism should be managed appropriately.

Good quality double-blind and head-to-head clinical studies of progestin products are lacking.

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