PROGESTINS (Systemic)

Introduction

This monograph includes information on the following:1) Hydroxyprogesterone b; 2) Levonorgestrel; 3) Medrogestone a; 4) Medroxyprogesterone ; 5) Megestrol; 6) Norethindrone; 7) Norgestrel b; 8) Progesterone.

Hydroxyprogesterone caproate¾Hydroxyprogesterone
Medroxyprogesterone acetate¾Medroxyprogesterone
Megestrol acetate¾Megestrol
Norethindrone¾Norethisterone
BAN:

Hydroxyprogesterone caproate¾Hydroxyprogesterone
Medroxyprogesterone acetate¾Medroxyprogesterone
Megestrol acetate¾Megestrol
Norethindrone¾Norethisterone
VA CLASSIFICATION (Primary)
Hydroxyprogesterone¾HS103
Levonorgestrel¾HS103/HS104
Medrogestone¾HS103
Medroxyprogesterone¾HS103/; HS104
Megestrol¾HS103/
Norethindrone¾HS103/
Norgestrel¾HS103/
Progesterone¾HS103
Commonly used brand name(s):Alti-MPA4; Amen4; Apo-Megestrol5; Aygestin6; Colprone3; Crinone8; Curretab4; Cycrin4; Depo-Provera4; Depo-Provera Contraceptive Injection4; Gen-Medroxy4; Gesterol 508; Gesterol LA 2501; Hy/Gestrone1; Hylutin1; Megace5; Megace OS5; Micronor6; NORPLANT System2; Nor-QD6; Norlutate6; Novo-Medrone4; Ovrette7; PMS-Progesterone8; Plan B2; Pro-Span1; Prodrox1; Prometrium8; Provera4; Provera Pak4.
Another commonly used name for norethindrone is norethisterone.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Progestational agent¾Hydroxyprogesterone; Medrogestone; Medroxyprogesterone (oral); Norethindrone; Norgestrel; Progesterone.

Antianoretic¾Megestrol.

Anticachectic¾Megestrol.

Antineoplastic¾Medroxyprogesterone (parenteral); Megestrol.

Contraceptive (systemic)¾Levonorgestrel; Medroxyprogesterone (parenteral); Norethindrone (base); Norgestrel.

Diagnostic aid (estrogen production)¾Hydroxyprogesterone; Medroxyprogesterone (oral); Progesterone (parenteral).

Infertility therapy adjunct¾Progesterone (vaginal).

Ovarian hormone therapy agent adjunct¾Medroxyprogesterone (oral); Progesterone (oral).

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Amenorrhea, secondary (treatment)

Dysfunctional uterine bleeding (treatment) or

Menses, induction of (treatment)¾Hydroxyprogesterone, medrogestone, oral medroxyprogesterone, norethindrone acetate, and parenteral progesterone are indicated in the treatment of menstrual disorders 41, 74 , including secondary amenorrhea and dysfunctional uterine bleeding (DUB) caused by hormonal imbalance in the absence of organic pathology 59, 65, 69, 74, 80, 81, 82, 83, 97, 100.

Progesterone oral capsules * and progesterone vaginal gel are indicated in the treatment of secondary amenorrhea. The 8% strength of vaginal gel is used only if the patient fails to respond to treatment with the 4% progesterone vaginal gel 244.

Hydroxyprogesterone is also indicated for the production of a secretory endometrium and desquamation 97.

The uterus must be sufficiently primed with endogenous or exogenous estrogen for the progestins to produce a secretory-like endometrium and endometrial shedding after progestin use ends 22, 69, 97, 100, 229.

Withdrawal bleeding usually occurs 3 to 7 days after discontinuation of the progestin for women with an intact uterus. 74, 226

Anorexia (treatment)

Cachexia (treatment) or

Weight loss, significant (treatment)¾ Megestrol suspension is indicated in the treatment of anorexia, cachexia, unexplained significant weight loss (loss of 10% or more of base-line body weight) associated with acquired immunodeficiency syndrome (AIDS) 66, 67, 166, 167.

[Megestrol tablets are indicated in the treatment of anorexia, cachexia, and unexplained significant weight loss associated with cancer] 67.

Assisted reproductive technologies, in females or

[Corpus luteum insufficiency (treatment)] *¾Progesterone vaginal gel is indicated to replace the progesterone hormone in female patients whose infertility is due to partial or complete ovarian failure. Progesterone vaginal gel is indicated to supplement endogenous progesterone for luteal phase progesterone deficiency. Extemporaneously prepared [progesterone suppositories] * have also been used for these indications. 244

Carcinoma, breast (treatment)¾Megestrol and [oral and parenteral medroxyprogesterone] are indicated in the treatment of breast carcinoma; [medroxyprogesterone] is indicated for use in postmenopausal women only 67, 68, 73, 74, 139, 149, 151, 158, 159, 160, 161, 162, 176.

It is used as adjunctive or palliative therapy in the treatment of advanced (inoperable, recurrent, or metastatic) hormonally dependent carcinoma 67, 73.

Carcinoma, endometrial (treatment) ¾[Oral] or parenteral medroxyprogesterone 10, 74, 202, 214 , and megestrol are indicated for the treatment of endometrial carcinoma 67, 68, 72, 73, 74, 154.

It is used as adjunctive and/or palliative therapy in the treatment of advanced (recurrent or metastatic) hormonally dependent carcinoma 67, 73.

Carcinoma, prostate (treatment)¾[Megestrol] is indicated in the treatment of hormonally dependent and advanced prostate carcinoma as palliative therapy 67.

Carcinoma, renal (treatment)¾Parenteral medroxyprogesterone is also indicated in the treatment of metastatic renal carcinoma 72, 73, 172, 173, 182 as adjunctive and/or palliative therapy when used in the treatment of advanced (recurrent or metastatic) hormonally dependent carcinoma 67, 73.

Contraception, emergency postcoital (prophylaxis)¾Levonorgestrel, oral 254

Endometriosis (treatment)¾Norethindrone acetate, [parenteral medroxyprogesterone], and [oral medroxyprogesterone] * are indicated in the treatment of endometriosis 5, 65, 73, 82, 83, 186, 191.

Estrogen production, endogenous 47, 48, 97 (diagnosis)¾Hydroxyprogesterone, [oral medroxyprogesterone], and [parenteral progesterone] are indicated as a test for endogenous estrogen production and can be used to determine whether low levels of estrogen are present if withdrawal bleeding does not occur after a progestin challenge in menopausal women before estrogen-progestin ovarian hormone therapy is considered. However, determination that serum gonadotropins are elevated is the standard way to confirm menopause. 47, 48, 97, 186, 229, 230, 231, 232, 234

[Hyperplasia, endometrial (treatment)] * or

Hyperplasia, endometrial, estrogen-induced (prophylaxis)¾Megestrol and oral medroxyprogesterone have been used to treat endometrial hyperplasia without atypia, which is usually not a precursor of carcinoma. Complex atypical hyperplasia (previously called adenomatous hyperplasia) is usually best treated surgically, but in some high risk patients or when future pregnancy is desired, high continuous doses of progestins have been used. 216, 217, 218, 219, 220, 236, 237

For prevention, [oral medroxyprogesterone], 186 [norethindrone] *, medrogestone, and [oral progesterone] can be used to oppose the effects of estrogen on the endometrium in menopausal women 245 who take estrogens for ovarian hormone therapy (OHT), also called hormone replacement therapy (HRT) and estrogen replacement therapy (ERT). All menopausal patients receiving progestins do not have recognized endometrial shedding; there is frequently amenorrhea after several months of treatment with estrogen-progestin regimens. 189, 202 The optimal or recommended length for estrogen replacement after menopause has not been established. 17, 100, 165, 232 Studies have shown that administration of a progestin for a minimum of 10 to 14 61, 165 days of an estrogen cycle in women with an intact uterus is required for major reduction of endometrial hyperplasia and endometrial carcinoma 12, 82, 155, 165 compared with an estrogen-only cycle. Other dosing regimens for estrogens and progestins, including low continuous daily dosing, are also used. 188, 189, 223, 224 Progestins without estrogens may be used for debilitating menopausal symptoms in patients who have breast cancer and are candidates for progestin therapy but cannot take estrogens. 187

Pregnancy, prevention of¾Levonorgestrel, parenteral medroxyprogesterone, norethindrone (base), and norgestrel are indicated for the prevention of pregnancy 57, 63, 71, 73, 84, 86, 88, 90, 96.

Progestin-only oral contraceptives are also called minipills and progestin-only oral pills (POPs) 249.

The following table presents the results of studies examining contraceptive failure rates calculated using the life-table method. The first column lists the contraceptive method used. The second column indicates the percentage of women experiencing an accidental pregnancy in the first year of use of a contraceptive method while using the method perfectly under clinical conditions. The range of failure rates in the clinical trials may be explained by interstudy variations in study design or patient population characteristics, such as motivation, fecundity, or socioeconomic factors (including education). The third column indicates contraceptive failure rates in the first year of contraceptive use under clinical conditions for typical couples who start using a method (not necessarily for the first time). Failure rates among adolescents may be higher due to poorer compliance than in other age groups. 53, 54, 55

Method used	Failure rate range (over 12 months) in clinical studies (%)	Typical first year failure rate (%)
None	78-94	85
Spermicides a	0.3-37	21
Periodic abstinence b	13-35	20
Withdrawal	7-22	19

Cervical cap with spermicide	6-27	18
Diaphragm with spermicide	2-23	18
Condom without spermicide	2-14	12
IUD		
Progesterone-releasing	1.9-2	2
Copper-T 200	3-3.6	
Copper-T 200Ag c	0-1.2	
Copper-T 220C d	0.9-1.8	
Copper-T 380A	0.5-0.8	0.8
Copper-T 380S	0.9	
Oral contraceptive		3
Estrogen and progestin	0-6	
Progestin only	1-10	0.5
Progestin injection		
Medroxyprogesterone (90-day)	0-0.3	0.3
Levonorgestrel (subdermal)		
Six implants	0-0.09	0.09
Two rods	0-0.2	0.3
Sterilization		
Female e	0-8	0.4
Male	0-0.5	0.15

a Spermicides studied include creams, foams, gels, jellies, and suppositories. 53, 54

b Methods studied include calendar, ovulation method, symptothermal (cervical mucus method supplemented by basal body temperature post-ovulation). 53, 54

c Life table method rate is unavailable for Copper-T 200Ag and the Pearl method rate at 12 months was reported; these methods at 12 months are considered comparable. 50, 51, 52

d Copper-T 220C is manufactured with copper sleeves instead of copper wire; often used as a control in clinical studies. 55

e Methods studied include culdotomy laparoscopy, minilaparotomy, electrocoagulation, laparotomy, tubal diathermy and/or use of rings or clips. 53, 54

[Polycystic ovary syndrome (treatment)] *¾Medroxyprogesterone is used in the treatment of endometrial hyperplasia and its consequences in syndromes, such as polycystic ovary syndrome. 35, 122

[Puberty, precocious (treatment)] *¾Parenteral medroxyprogesterone is accepted therapy for use in the treatment of precocious puberty but has been replaced by other treatment modalities. 35, 122

Unaccepted

There is no evidence that progesterone is effective in the treatment of premenstrual syndrome. 4, 86, 178

Progestins are no longer recommended for use as pregnancy tests because of possible teratogenic effects with synthetic progestins; also, other tests available are quicker and easier to perform. 67, 68, 69, 70, 71, 72, 73, 82

With the exception of progesterone in patients who are progesterone deficient, progestins have no proven value in the treatment of threatened abortion and are no longer recommended for such use. 32, 39, 40, 66, 68, 69, 82

Unlike oral medroxyprogesterone, parenteral medroxyprogesterone is not recommended by the manufacturer for treatment of secondary amenorrhea or dysfunctional uterine bleeding. 72, 73

Megestrol is not recommended for prophylactic use to avoid weight loss. 66

Levonorgestrel used for emergency postcoital contraception is not recommended for routine use as a contraceptive 254.

Levonorgestrel used for emergency postcoital contraception is not effective in terminating an existing pregnancy 254.

* Not included in Canadian product labeling.

Pharmacology

Mechanism of action/Effect:

Progestins enter target cells by passive diffusion and bind to cytosolic (soluble) receptors that are loosely bound in the nucleus. The steroid receptor complex initiates transcription, resulting in an increase in protein synthesis.
Progestins are capable of affecting serum concentrations of other hormones, particularly estrogen. Estrogenic effects are modified by the progestins, either by reducing the availability or stability of the hormone receptor complex or by turning off specific hormone-responsive genes by direct interaction with the progestin receptor in the nucleus. 68 In addition, estrogen priming is necessary to increase progestin effects by upregulating the number of progestin receptors and/or increasing progesterone production, causing a negative feedback mechanism that inhibits estrogen receptors. 119

Depending on the progestin and its dose, progestin may demonstrate varying degrees of progestational effects. Also, other hormonal effects, such as estrogenic-, 83, 90, 97 anabolic-, 67, 69, 74, 83, 90, 97 androgenic-, 67, 69, 74, 83, 90, 97 or glucocorticoid-inducing or suppressing 67, 74, 97 effects are demonstrated to different degrees and depend on the progestin type and dose. 33, 67 For example, an androgenic effect may be expressed by 19-nor derivatives of testosterone but not by other progestins.

The androgenic effects of norethindrone are minor to moderate; norethindrone acetate is twice as potent as norethindrone. Norgestrel and levonorgestrel have androgenic effects if unopposed by estrogens. 33, 40, 221, 238, 239 Rare cases of adrenal suppression have been reported in patients using megestrol 67.

While the progestational effects dominate, the other effects can become important when choosing the appropriate progestin or monitoring side effects. Progestins are not used exclusively for other than their progestational effects, as the other effects are highly variable and unreliable.
Progestational agents¾Progestins produce significant antiproliferative changes in the endometrium. 12, 100 As progestin levels fall after estrogen priming in the second half of the menstrual cycle, uterine bleeding may occur 226, 246.

Depending on the estrogen-progestin regimen, the progestin dose may be sufficient to cause amenorrhea 246.

Antianoretic or anticachectic¾The mechanism that produces weight gain has not been fully elucidated; 66, 110, 166 however, megestrol appears to have appetite-stimulant and metabolic effects that result in weight gain while causing minimal fluid retention. 110, 111 The underlying cause of wasting should be treated concurrently to optimize management of catabolism. 110, 166, 167

Antineoplastic¾The mechanism has not been fully elucidated; however, several mechanisms may be involved that are dependent on the type and dose of progestin. 115, 149 In certain doses, progestins can produce a diminished response to endogenous hormones in tumor cells by decreasing the number of steroid hormone receptors (estrogen, progesterone, androgen, and glucocorticoid); the degree of variation of response is tissue- and progestin-dependent. 150, 156 The suppression of the growth of hormone-sensitive cells may be due to a direct cytotoxic effect or antiproliferative effects on cell cycle growth and an increased terminal cell differentiation. 150, 154, 235 At higher doses, some progestins compete for the glucocorticoid receptor, resulting in suppressed adrenal production of estradiol and androstenedione. 150, 156 Still-higher progestin doses are able to completely suppress the hypothalamic-pituitary-adrenal axis (HPA axis), an effect that is important in the treatment of estrogen- or testosterone-sensitive tumors. 40, 115, 149, 152

Contraceptive (systemic)¾Inhibition of the secretion of gonadotropins from the anterior pituitary prevents ovulation and follicular maturation and is one of the contraceptive actions of levonorgestrel, parenteral medroxyprogesterone, norethindrone, 193 and norgestrel. These effects do not occur with low-dose oral medroxyprogesterone, which is not used for contraception. In some patients using low-dose progestin-only contraceptives, particularly norethindrone (base) and levonorgestrel subdermal implants, ovulation is not suppressed consistently from cycle to cycle. The contraceptive effect of the progestin is achieved through other mechanisms that result in interference with fertilization and implantation in the luteal cycle, such as thickening of the cervical mucus and changes in the endometrium 71, 81, 84, 86, 88, 90, 117, 118.

In males, medroxyprogesterone suppresses the Leydig cell function. 13, 74

Other actions/effects:

Progestins increase body temperature, stimulate the respiratory center, and, in some cases, may provide pain relief. 156, 157 The mechanism by which progesterone and medroxyprogesterone mediate

thermogenic effects is not clear. It has been suggested that progesterone influences neurotransmitters and neuropeptides in the brain, notably endogenous opioids, interleukin-1, and serotonin, 59, 81, 100, 119 that raise body temperature. 74 Also, medroxyprogesterone may reduce hypercapnia in certain patients by stimulating the respiratory center. 74 Pain relief from high-dose progestins may be due in part to an anti-inflammatory action. 34

Locally the progestins relax the uterine smooth muscle, sustain pregnancy, decrease the immune response, and, acting with estrogen, stimulate breast tissue growth. 81

Some progestins cause sodium and water retention. Progesterone doses of 50 to 100 mg may produce a moderate catabolic effect and transient increase in sodium chloride excretion. 59 In addition, use of some progestins may result in dose-related adverse effects on carbohydrate and lipid metabolism. 72, 97, 165

Progestins influence bone density. When progestins have been used without estrogen, a positive effect has been shown in postmenopausal women and a possible negative effect in premenopausal women; the latter may depend on the degree to which a progestin can reduce ovarian estrogen production, a dose-dependent effect. When progestins have been used sequentially with continuously administered estrogen, a synergistic protective effect on bone density has been shown. Specifically, placebo-controlled studies of postmenopausal women showed that medroxyprogesterone decreased the rate of cortical bone loss but did not protect trabecular areas of the skeleton, such as the spine, equally from bone loss in all studies. 5, 6, 62, 103, 163, 164, 191, 192 A low-dose combination of continuously administered estrogen and sequentially administered progestin therapy showed protective effects against bone loss that were similar to those of higher doses of estrogen therapy alone. This effect may be due to an increase of progestin receptors caused by estrogen, to an antagonistic effect of progestin binding to glucocorticoid receptors, or to a stimulatory effect of progestin acting on progestin receptors within osteoblasts. 5, 6, 14, 62, 163, 164, 200, 210 Additional studies are needed to confirm and fully characterize these results. 188

Other health benefits of progestational hormone therapy may include less painful menstruation, less menstrual blood loss and anemia, 14, 148 fewer pelvic infections, and lower incidence of uterine cancers. 12, 14, 90, 97, 155, 165, 177, 200

Precautions to Consider

Carcinogenicity

The benefit of lowering the incidence of endometrial hyperplasia and endometrial cancer by adding progestin to an estrogen regimen in ovarian hormone therapy to counter estrogen's effect on the uterus is established. 11, 12, 20, 22, 97, 100, 120, 155, 165

Medroxyprogesterone¾

Long-term studies in humans using parenteral medroxyprogesterone for contraception have found no increase in the overall risk of ovarian, liver, breast, or cervical cancer and have found a prolonged, protective effect of reducing the risk of endometrial cancer 11, 12, 123 for at least 8 years. 11 The possible protective effect may be lessened with concomitant use of estrogen; however, the lifetime risk for developing endometrial cancer is not increased in women with a uterus who take estrogen plus a progestin for 10 to 20 years. 22, 61 In the short-term, the initial risk of breast cancer with parenteral

medroxyprogesterone exposure may be increased in the first 4 years after initial exposure in women under 35 years of age. The risk lessens with duration of use and results in no overall increase of risk for developing breast cancer. 11

Studies of monkeys administered doses of 3, 30, and 150 mg per kg (mg/kg) of body weight every 90 days for 10 years produced undifferentiated carcinoma of the uterus in a few monkeys dosed at 150 mg/kg. No uterine malignancies were reported in monkeys taking other doses or in the control monkeys; no uterine abnormalities were produced in similar studies of rats after 2 years. 74 The relevance of these findings to humans is not known.

Tumorigenicity

Tumorigenicity/Mutagenicity

Hydroxyprogesterone, levonorgestrel, medrogestone, norgestrel, norethindrone, and progesterone¾
Studies have not been done 59, 65, 80, 81, 85, 86, 88, 90, 96, 97, 100.

Medroxyprogesterone¾
Studies in humans have not been done 69, 70, 71, 72, 73, 74, 76, 77, 78, 79.

Mammary nodules, some of which were malignant in the high-dose group, developed in a number of beagles given doses of 3 or 75 mg/kg of medroxyprogesterone every 90 days for 7 years 74.

In studies of monkeys, doses of 3, 30, or 150 mg/kg of medroxyprogesterone given every 90 days for 10 years produced transient mammary nodules in the 3 and 30 mg/kg groups, with none reported in the 150 mg/kg group during the study; hyperplastic nodules had developed in 3 monkeys that had been administered 30 mg/kg of medroxyprogesterone; no breast abnormalities were produced in rats after 2 years 74.

Caution is warranted in applying these results of animal studies of progestins to their use in humans because of the hormonal differences between species. Also, humans and beagles metabolize medroxyprogesterone differently, and beagles are particularly susceptible to this type of breast tumor and develop these tumors spontaneously without progestin use. 36, 49, 123, 201

There was no mutagenic response in the Ames and micronucleus tests 69, 74.

Megestrol¾
Studies in humans have not been done 67, 68.

Studies of female dogs given megestrol for up to 7 years showed an increased incidence of both benign and malignant tumors; 2-year studies of female rats demonstrated an increased incidence of pituitary tumors. These effects were not found in monkey studies. 66, 68

Pregnancy/Reproduction

Fertility¾Progestins cause a decrease in quantity and/or change the quality of cervical mucus and may interfere with sperm function, fertilization, and subsequently, the occurrence of pregnancy. This effect

depends on the dose and type of the progestin. High-dose or long-term use of progestins may cause a delayed return to fertility. 69, 72, 74, 83, 90, 194

Levonorgestrel subdermal implants¾

After removal, 40% of those women wanting to conceive did so by 3 months; 76% conceived within 1 year, percentages are similar to normal pregnancy rates. 133, 138

Medroxyprogesterone¾

It has been reported that of the women who discontinued parenteral medroxyprogesterone to become pregnant, 68% conceived within 12 months, 83% conceived within 15 months, and 93% conceived within 18 months after discontinuation (range, 4 to 31 months; median 10 months). 36, 71 The return of fertility is a function of the uptake and metabolism of parenteral medroxyprogesterone; follicular activity has been reported to return 3 to 37 days after parenteral medroxyprogesterone is nondetectable in serum, whereas, luteal function is delayed by 14 to 102 days. 37, 38, 71

Animal studies with medroxyprogesterone have reported no impairment of fertility in first- or second-generation studies. 74

Megestrol¾

Studies in humans have not been done. 66

Studies of rats given megestrol in doses of 0.05 to 12.5 mg per kg of body weight (mg/kg), which are lower than the human dose of 13.3 mg/kg, resulted in impaired reproductive capability of male offspring produced from megestrol-treated females; similar results were found in studies of dogs. 66

Progesterone¾

Progesterone has been used successfully with assisted reproductive technologies to support embryo implantation and to maintain pregnancy if needed. 194, 195

Pregnancy¾Progestins, in general, should be withheld during pregnancy. 202 Progestins cross the placenta. Although many studies fail to demonstrate an increase in teratogenicity when progestins are given in the first trimester, the possibility that genital abnormalities may appear in male and female fetuses exposed to progestins during that period has been suggested by some studies. The low number of abnormalities reported include an increased risk of hypospadias in male fetuses exposed to intrauterine progesterone and virilization of the female fetus' external genitalia when exposed to ethisterone and norethindrone. 39 There is some controversy about the reliability of these reports. The significant concentration of endogenous natural progesterone produced during pregnancy is devoid of teratogenic effects. 2, 21, 24, 25, 26, 27, 28, 29, 30, 31, 39, 59

Ectopic pregnancy is possible with contraception failure because some progestin-only contraceptives reduce ectopic pregnancy risk substantially, but prevent ectopic pregnancy less effectively than intrauterine pregnancy. 71, 90, 232 For progestin-only oral contraceptives, the ectopic pregnancy rate reported is 4.1 per 100 pregnancies. 177 The rate of ectopic pregnancy for a set of levonorgestrel subdermal implants is 1.3 per 1000 woman-years. This is lower than those for women not using any contraceptive method (2.7 to 3 ectopic pregnancies per 1000 woman-years). However, the risk may increase with longer duration of use of levonorgestrel subdermal implants and increased weight of the user; risk does not increase in women of normal weight. 88, 138, 148, 194

Hydroxyprogesterone and progesterone¾

Use is generally not recommended during pregnancy, unless prescribed in the treatment of female infertility due to progesterone deficiency. Hydroxyprogesterone and progesterone have been used to prevent habitual or threatened abortion within the first few months of pregnancy. There are no adequate and well-controlled studies in humans to document that such use is effective during the first 4 months of pregnancy in preventing miscarriage; use is generally limited to certain cases of hormonal imbalance. Progesterone has been used successfully with assisted reproductive technologies to support embryo implantation and maintain pregnancy. 194, 195 Progesterone may be used to treat corpus luteum deficiency in early pregnancy. Progesterone replacement or supplementation does not appear to be efficacious when a hormone imbalance does not exist. 194 In addition, the progesterone's effects on the uterus may delay the spontaneous miscarriage of a defective ovum. 2, 3, 32, 58, 80, 81, 97

FDA Pregnancy Category D. 97

Levonorgestrel, norethindrone, and norgestrel¾

Use is not recommended during pregnancy. Virilization of the female fetus has been reported with norethindrone in a few cases, but a causal relationship has not been conclusively proven. 88

FDA Pregnancy Category X. 82, 86, 88, 90, 96

Medroxyprogesterone¾

Use is not recommended in pregnancy. Studies in humans have shown that medroxyprogesterone may decrease intrauterine growth. 194 Polysyndactyly in the offspring of women who had used parenteral medroxyprogesterone during pregnancy was reported in a few case-reports; this effect has not been seen in major studies. 71, 195 Furthermore, there has been no evidence of problems associated with growth and development in children exposed in utero to medroxyprogesterone and followed to adolescence. 71

In studies of pregnant beagles given doses of 1, 10, and 30 mg/kg of body weight per day for 6 months, clitoral hypertrophy appeared in the female pups of the high-dose group; no abnormalities were reported in the male pups. No abnormalities were detected in the treated female pups' offspring. Caution is warranted in transferring this information to humans because beagle dogs metabolize medroxyprogesterone differently than do humans. 74, 238

Medroxyprogesterone, parenteral¾FDA Pregnancy Category X. 71, 74, 97

Note:

An FDA pregnancy category has not been assigned for medroxyprogesterone tablets.

Megestrol¾

Use is not recommended during pregnancy. Risk-benefit must be carefully considered. 66, 67, 68

Studies in pregnant rats given high doses of megestrol decreased fetal birth weight, produced fewer live births, and resulted in reversible feminization of some male fetuses. 66, 68

Megestrol suspension¾FDA Pregnancy Category X. 66

Megestrol tablets¾FDA Pregnancy Category D. 68

Breast-feeding

Progestins are distributed into breast milk in variable amounts and, depending on the progestin and dose, may increase or decrease quantity or quality or have no effect on breast milk. 141, 142 The effect on the nursing infant has not been determined for many progestins.
No adverse effects on breast milk's quantity or quality 71, 84, 88, 141, 142, 143, 144, 145, 177 have been seen with progestin-only contraceptives, 195, 211, 212 or specifically, when norethindrone or medroxyprogesterone was used for contraception within 5 days postpartum or after the establishment of lactation. 14, 84 Progestin-only contraceptives are recommended in breast-feeding women when oral contraception is desired. The manufacturers and distributors of levonorgestrel subdermal implants and parenteral medroxyprogesterone for contraception recommend that their initial use for contraception begin at 6 weeks postpartum for exclusively breast-feeding mothers. 88, 70, 188, 212 Additionally, no adverse effects have been reported in a study of 71, 84, 141 nursing infants exposed to parenteral medroxyprogesterone and followed through puberty or in another study of 80 nursing infants exposed to levonorgestrel subdermal implants 6 weeks after delivery and followed for 3 years. 71, 88, 141, 212

Progestins used in very high doses are not recommended for use by nursing mothers. 58, 59, 66, 68, 69, 71, 72, 73, 74, 80, 81, 82, 86, 90, 96, 99, 100

Pediatrics

No information is available on the relationship of age to the effects of progestins in pediatric patients. Safety and efficacy have not been established. 59, 66, 68, 82, 97 Serious adverse effects have not been reported in small children who ingested large doses of oral contraceptives. 90, 148

Adolescents

Safety and efficacy of progestin-only contraceptives are expected to be the same in postpubertal adolescents as they are in adults. However, special counseling for medication compliance and prevention of sexually transmitted diseases (STDs) is needed. Studies have shown that adolescents tend to have a higher failure rate with the use of any type of contraceptive that requires strict compliance, such as oral progestins for contraception, and its use is not generally recommended in this age group. 189 Although parenteral medroxyprogesterone and levonorgestrel subdermal implants do not require daily compliance, readministration of their doses after 3 months (13 weeks) and after 5 years, respectively, is important. Furthermore, none of the progestin contraceptives protect against STDs, which are significant risk-factors for this age group. 45, 46

Geriatrics

No information is available on the relationship of age to the effects of progestins in geriatric patients. 59, 97

Dental

Increased concentrations of progestins increase the normal oral flora growth rate, leading to an increase in inflammation of the gingival tissues and increased bleeding. A strictly enforced program of teeth

cleaning by a professional, combined with plaque control by the patient, will minimize severity. 124, 125

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Aminoglutethimide

(may significantly lower the serum concentrations of oral and parenteral 186, 188 medroxyprogesterone by an undetermined mechanism; it has been suggested that aminoglutethimide may decrease the intestinal absorption of oral medroxyprogesterone 69, 71, 72, 73, 74, 126, 127)

>> Hepatic enzyme inducing medications, such as
Carbamazepine or
Phenobarbital or
Phenytoin or
Rifabutin or 197, 198

Rifampin

(decreased efficacy of some progestins, including levonorgestrel subdermal implants, has been suggested to be caused by enhanced metabolism of the progestins by these drugs 84, 86, 88, 90, 121, 128, 129, 147, 183)
(phenytoin and rifampin increase the serum concentrations of sex hormone-binding globulin [SHBG]; this significantly decreases the serum concentration of free drug for some progestins 84, 86, 88, 90, 121, 128, 129, 147, 199 , which is a special concern in patients using progestins for contraception)
(drug interaction data are not available for rifabutin, but because its structure is similar to that of rifampin, similar precautions with its use with progestins may be warranted. Megestrol has been shown not to affect the pharmacokinetics of rifabutin; whether rifabutin changes megestrol pharmacokinetics has not been studied 67, 197, 198)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

Biopsy

(pathologist should be notified of relevant specimens 66, 72, 73, 74, 82, 86)

Glucose tolerance test 59, 72, 73, 74, 82, 86, 90, 131, 137

(varies with progestin and dose, glucose tolerance may be increased or decreased)

Metyrapone 59, 73, 74, 82, 97

(lower response than normally expected)

With laboratory test values

Apolipoprotein A and

High-density lipoproteins (HDL) and

Total cholesterol and

Triglycerides

(serum concentrations may be increased or decreased and may differ depending on type of progestin, dose, dosing, and duration of therapy. In general, all progestins will lower triglyceride and total cholesterol concentrations. Parenteral medroxyprogesterone, in low doses, produces no significant decrease in HDL cholesterol concentrations; oral doses may blunt an estrogen-induced increase of HDL. In contrast, 19-nor-testosterone-derived progestins significantly lower HDL cholesterol as well as total cholesterol 14, 16, 17, 18, 19, 90, 130, 137, 163, 194, 200)

Apolipoprotein B and

Low-density lipoproteins (LDL) 14, 71, 72, 86, 88, 90, 130, 137, 148

(serum concentrations may be increased and may differ depending on type of progestin, dose, dosing, and duration of therapy 16, 17, 18, 19, 130)
(LDL concentrations increased initially in some studies and then returned to normal or below normal baseline levels when progestins were given for a year. Additionally, serum estrogen concentrations seemed to influence the cyclicality and degree to which LDL concentration increased; progestins affected the values to a lesser extent when estrogen levels were normal 16, 17, 18, 19, 60)

Clotting factors II, VII, VIII, IX, and X and 59, 81, 97, 105, 130

Prothrombin 81, 105

(serum concentrations may be increased although studies have not shown consistent results; no change in clotting factors has been reported with parenteral medroxyprogesterone for contraception 43, 71, 72, 81, 82, 86, 90, 130, 188)

Gonadotropin and 188

Sex hormone-binding globulin (SHBG)

(serum concentration may be decreased 20, 71, 72, 74, 86, 88, 90, 133)

Liver function tests 71, 72, 73, 74, 81, 82, 86, 97

(values may be increased; if abnormal with parenteral medroxyprogesterone use, liver tests may be repeated 4 to 6 months after its discontinuation 59, 71, 72, 73)

T3-uptake

(values may be decreased because of increase in thyroid-binding globulin [TBG]; free T4 concentration is unaltered 59, 71, 72, 81, 82, 86, 90, 97)

T4, total

(unaffected by most progestins but concentrations are slightly decreased with levonorgestrel; free T4 concentration is unaltered 88, 133, 197)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, these medications should not be used when the following medical problems exist

>> Allergy to peanuts for oral or parenteral progesterone 245

>> Breast malignancies or tumors, known or suspected 59, 72, 73, 74, 81, 83, 86, 188, 197

(may worsen conditions in some nonresponsive patients; however, some progestins are used for palliative treatment in select patients 11, 68, 71, 73, 86, 88)

>> Hepatic disease, acute, including benign or malignant liver tumors

(metabolism of 19-nor derivatives of testosterone-type progestins may be impaired; also, progestins may worsen the condition 81, 88, 200)

Hypersensitivity to progestins 72, 73, 74, 83, 86, 245

>> Pregnancy, known or suspected 81

(use of synthetic progestins during pregnancy may result in virilization of a female fetus and, in a small number of cases, increase the risk of hypospadias in a male fetus 29, 30, 32, 59)
(use for pregnancy diagnosis is contraindicated 59, 66, 68, 71, 72, 73, 74, 81, 83, 86, 88)

>> Thrombophlebitis or thromboembolic disease, active

(the large doses of progestins used to treat breast and prostate cancer have been associated with a slight risk of thrombogenic conditions; mechanism is unclear and may be due to underlying condition. Problems have not been associated with low doses used for contraception, including parenteral

medroxyprogesterone, progestin-only oral contraceptives, and levonorgestrel subdermal implants 66, 71, 72, 73, 74, 82, 86, 88, 90, 105, 111, 123, 130, 132, 135, 190)

>> Urinary tract bleeding, undiagnosed or 59, 72, 74, 81

>> Uterine or genital bleeding, undiagnosed

(use of a progestin may delay diagnosis by masking underlying conditions, including cancer 72, 73, 74, 81, 83, 86, 88, 100, 202)

Risk-benefit should be considered when the following medical problems exist

Asthma or

Cardiac insufficiency, significant or

Epilepsy or

Hypertension or

Migraine headaches or

Renal dysfunction, significant

(fluid retention may be caused by some progestins, especially in high doses, and may aggravate these conditions 59, 71, 73, 74, 81, 82, 86, 88, 90, 100)

CNS disorders, such as depression or convulsions, history of

(progestins, such as levonorgestrel, medroxyprogesterone, or norethindrone, may make these conditions worse. Cases of convulsions have been reported with use of parenteral medroxyprogesterone; however, a clear association has not been established 59, 71, 73, 74, 82, 88, 90.

In one small study of 14 women with uncontrolled seizures, medroxyprogesterone reduced their seizure frequency by 30% 14.

However, use of many medications for seizure control reduce the contraceptive efficacy of many contraceptives 14)

Diabetes mellitus

(high doses of progestins may alter carbohydrate metabolism by an unknown mechanism, producing a mild decrease in glucose tolerance in some patients. New-onset diabetes mellitus and exacerbation of preexisting diabetes mellitus have been reported in patients taking high or chronic doses of megestrol 67.

Progestin-only oral contraceptives do not usually affect carbohydrate metabolism, but may occasionally affect lipid metabolism 185, 189, 195, 199, 200, 249.

No clinical significance on fasting blood glucose is seen in nondiabetics receiving low doses of oral progestins for contraception 71, 72, 74, 82, 86, 90, 131, 177)
(levonorgestrel's effects on carbohydrate metabolism appear to be minimal for nondiabetics but are considered inconclusive for prediabetics and diabetics 88)
(parenteral medroxyprogesterone may decrease glucose tolerance for some patients by an undetermined mechanism; it has been used with caution for contraception in diabetics 131, 137)

Hepatic disease or dysfunction, history of

(metabolism of progestins, specifically androgenic progestins, may be impaired and contribute to the hepatic condition 71, 72, 73, 74, 83, 86, 88, 199, 200)

Hyperlipidemia

(some progestins, specifically androgenic progestins, might increase LDL and lower HDL levels and aggravate problems in controlling hyperlipidemia 88, 90, 130, 197, 200, 235)

Significant risk factors for low bone mineral content

(the overall effect on bone density for progestins has yet to be established and may depend on type of progestin, dose, and gender and age of patient. A retrospective cross-sectional study has reported that women using parenteral medroxyprogesterone for contraception had bone density measurements lower than the control group of premenopausal women but higher than the control group of postmenopausal women. Specifically, medroxyprogesterone may temporarily increase the loss of trabecular bone and additionally increase the risk of osteoporosis. The greatest bone loss is evident in the early years of use, is usually reversible, and possibly reflects other factors, such as hypoestrogenism, when progestin is used alone. A prospective study has reported that the use of oral medroxyprogesterone alone for treatment of menopausal symptoms showed a protective effect against loss of bone; other studies, particularly those in which a progestin was combined with estrogen, have also shown a protective effect 5, 6, 14, 71, 123, 163, 188, 210)

>> Thromboembolic disorders, including cerebrovascular disease, pulmonary embolism, retinal thrombosis, history of or

Thrombophlebitis, history of

(the large doses of progestins used to treat breast and prostate cancer have been associated with a slight risk of thrombogenic conditions; mechanism is unclear and may be due to the underlying condition. Problems have also occurred with megestrol 67, 134.

Problems have not been associated with low doses used for contraception, including parenteral medroxyprogesterone, progestin-only oral contraceptives, or levonorgestrel subdermal implants for patients with a history of thromboembolic disorders or thrombophlebitis 66, 71, 72, 73, 74, 82, 86, 88, 105, 111, 123, 130, 132, 135)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Breast examinations

(should be performed routinely, especially with prolonged progestin use 61)

Papanicolaou (Pap) test and

Physical examination

(as determined by physician, with special attention being given to abdomen, breast and pelvic organs 61 ; pre- and post-inspection of site of insertion and removal of levonorgestrel subdermal implants with annual inspection of implantation site during use 71, 72, 73, 86, 194)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Amenorrhea stopping of menstrual periods) 59, 71, 73, 74, 81, 82, 86, 88, 130, 146, 148, 246; breakthrough menstrual bleeding or metromenorrhagia medium to heavy uterine bleeding between regular monthly periods) 59, 66, 67, 68, 71, 73, 74, 81, 82, 86, 88, 100, 113, 146; hyperglycemia dry mouth); frequent urination); loss of appetite); unusual thirst)¾16% with high doses of megestrol 115; menorrhagia increased amount of menstrual bleeding occurring at regular monthly periods) 71, 82, 88, 90; spotting light uterine bleeding between regular monthly periods)¾17% for levonorgestrel subdermal implants or oral progestins for contraception 59, 71, 74, 81, 82, 86, 88, 100, 146

Note: For all progestins, if abnormal uterine bleeding is persistent (longer than 10 days at a time) or recurring (heavier than normal menses occurring longer than 10 months after beginning therapy or more often than monthly), malignancy should be considered as a cause of the bleeding. 61, 71, 72, 194

For progestins used for cycle control or as part of ovarian hormone therapy: Breakthrough uterine bleeding is not as prevalent as it is with progestin-only contraceptives; therefore, any unexpected uterine bleeding that persists for 3 to 6 months should be investigated. 194, 246

For oral progestins for contraception: Breakthrough menstrual bleeding or spotting is common. 90, 232

For parenteral medroxyprogesterone: Amenorrhea increases with duration of use (12 months¾55% and 24 months¾68%). 71, 73 Breakthrough menstrual bleeding occurs in 90% of users. 232

For levonorgestrel subdermal implants: After 1 year of use of levonorgestrel subdermal implants, total uterine blood loss decreases from baseline levels of 31 mL per month to 24 mL per month. 148

Amenorrhea occurs in 9.4 to 15% of users of the subdermal implants and breakthrough menstrual bleeding occurs in 28% of users, persisting throughout treatment. 232, 240

Incidence less frequent

Galactorrhea unexpected or increased flow of breast milk); 73, 74, 86, 88; mental depression 59, 71, 72, 73, 74, 81, 82, 86, 146; skin rash 66, 68, 71, 73, 82, 86, 88
Incidence rare

Adrenal suppression or insufficiency or hypotension 249 dizziness); nausea or vomiting); unusual tiredness or weakness)¾may occur during chronic megestrol treatment or on its withdrawal 67; Cushing's syndrome backache); filling or rounding out of the face); irritability); menstrual irregularities); mental depression); unusual decrease in sexual desire or ability in men); unusual tiredness or weakness)¾may occur during chronic megestrol treatment 67; thromboembolism or thrombus formation (headache or migraine 86, 88; loss of or change in speech, coordination, or vision 71; pain or numbness in chest, arm, or leg 73, 74; shortness of breath, unexplained 67, 68, 71)¾severe and sudden, with high doses of progestins for noncontraceptive uses 111, 112, 115, 149

Note: It is not clear if the thromboembolism or thrombus formation associated with use of progestins in high doses is due to the treatment or to the underlying condition that is being treated, such as cancer 190, 196.

Thrombophlebitis, pulmonary embolism, and heart failure have occurred with use of megestrol; fatalities occurred in some cases 68.

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain or cramping 71, 86, 88, 146; diarrhea¾ 5% for oral levonorgestrel for postcoital contraception; dizziness ; drowsiness 249¾for progesterone only; edema bloating or swelling of ankles or feet); 68; fatigue¾17% for oral levonorgestrel for postcoital contraception; headache, mild¾up to 24% with levonorgestrel subdermal implants 67, 68, 71, 73, 74, 81, 86, 88, 146, 148; mood changes ¾up to 16% for levonorgestrel subdermal implants 146, 201; nausea ¾23% for oral levonorgestrel for postcoital contraception; nervousness 71, 73, 74, 81, 86, 88; ovarian enlargement or ovarian cyst formation (abdominal pain)¾10% for levonorgestrel subdermal implants 148, 177; pain, redness, or skin irritation at the site of injection or implantation¾ including local skin color change and residual lump 73, 88; unusual tiredness or weakness 66, 71, 73, 74, 81; unusual or rapid weight gain 59, 67, 68, 71, 73, 74, 81, 82, 86, 88, 100, 139, 140; vomiting¾5% for oral levonorgestrel for postcoital contraception 254

Note: For parenteral medroxyprogesterone for contraception: Average weight gain is 2.5 to 7.5 kilograms (kg) after 1 to 6 years of use. 71

Ovarian enlargement or ovarian cyst formation occurring with levonorgestrel subdermal implants is almost always transient and rarely requires surgery. 148, 177, 239

For oral levonorgestrel for postcoital contraception: If vomiting occurs within one hour of taking a dose of levonorgestrel, the dose may have to be repeated 254.

Incidence less frequent

Acne 71, 73, 74, 86, 88, 146, 148; breast pain or tenderness 67, 73, 74, 86, 88; hot flashes 71, 73, 74, 146, 148; insomnia (trouble in sleeping) 71, 73, 74; libido decrease (loss of sexual desire) 66, 71, 81, 86; loss or gain of body, facial, or scalp hair 67, 68, 71, 73, 74, 86, 88, 146; melasma (brown spots on exposed skin, which may persist after treatment stops) 59, 73, 81, 82, 86; nausea¾subsides in 3 months for low dose progestins for contraception 66, 68, 71, 73, 74, 81, 86, 88, 90, 100

Those indicating need for medical attention if they occur after medication is discontinued

Adrenal suppression or insufficiency or hypotension 249 dizziness); nausea or vomiting); unusual tiredness or weakness)¾may occur on withdrawal of chronic megestrol treatment; delayed return of fertility in females stopping of menstrual periods); unusual menstrual bleeding, continuing)

Note: Progestin-only oral contraceptives and progestins used for ovarian hormone therapy have not been shown to cause adrenal suppression or insufficiency or delayed return of fertility 249.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Progestins¾For Noncontraceptive Use (Systemic) or Progestins¾For Contraceptive Use (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Allergy to peanuts, for oral or parenteral progesterone, or history of hypersensitivity to progestins
Carcinogenicity¾Studies are ongoing and have not been done with all progestins. Use of progestins with estrogens in ovarian hormone therapy lowers the incidences of endometrial hyperplasia and endometrial cancer. Significantly, a prolonged (8-year) study in women using injectable medroxyprogesterone for contraception has found a protective effect against endometrial cancer. Long-term studies of parenteral medroxyprogesterone have found no increase in overall risk of breast, ovarian, liver, or cervical cancer. Women 35 years of age or younger may have an increased risk of breast cancer during the first four years following initial use
Pregnancy¾With the exception of hydroxyprogesterone and progesterone, use is not recommended during pregnancy. When progestins are used in doses for contraception, ectopic pregnancy is possible, although rare. Alternative methods of contraception should be used by fertile and sexually active females when high dose progestins are used for noncontraceptive purposes, such as in treatment of cancer; physician should be told immediately if pregnancy is suspected
Breast-feeding¾Progestins are distributed into breast milk in variable amounts; high doses may increase or decrease the quantity or quality of breast milk while low doses have no effect on breast milk and are recommended for use in breast-feeding women needing contraception; adverse effects in the nursing infant have not been reported

Use in adolescents¾Adolescents tend to have a greater risk for sexually transmitted diseases (STDs) and have a higher failure rate for oral progestins for contraception because of compliance problems. Adolescents who are at increased risk for STDs or those failing to comply with strict dosing schedule for contraceptives (a strict 24-hour dose regimen for oral medications or replacement doses for contraceptive injection and implants) may be better served with another form of contraception
Dental¾May predispose patient to increased bleeding and inflammation of the gingival tissues; teeth cleaning and plaque control should minimize severity
Other medications, especially aminoglutethimide and hepatic enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, rifabutin, or rifampin
Other medical problems, especially active thrombophlebitis or thromboembolic disease; acute hepatic disease, including benign or malignant tumors; history of thromboembolic disease; known or suspected breast malignancy or tumor; known or suspected pregnancy; undiagnosed genital, uterine, or urinary tract bleeding
Proper use of this medication

Reading patient directions

>> Importance of not taking more or less medication than the amount prescribed

>> Proper dosing
Missed dose for noncontraceptive uses of progestins (except for progesterone capsules): Taking as soon as possible; not taking if almost time for next dose; not doubling doses
Missed dose for progesterone capsules: If 200 mg at bedtime is missed, taking 100 mg in the morning, then going back to regular dose schedule. If 300 mg a day is missed, not taking the missed doses, then going back to regular dose schedule
Missed dose for medroxyprogesterone injection for contraceptive use: If next injection is delayed longer than 13 weeks, using a back-up method of contraception and checking with physician about continuing the medication
Missed dose for progestin-only oral contraceptives: If one or more tablets are missed or if dose is delayed by 3 hours or more, taking the missed dose as soon as remembered, continuing your regular dosing schedule, and using a backup method, such as condoms or spermicides, for the next 48 hours if planning to have sexual intercourse. A dose that is 3 hours late is considered a missed dose
>> Proper storage
For contraception use

Caution that progestins do not protect against sexually transmitted diseases, including human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)

For levonorgestrel subdermal implants

Insertion procedure by a health care professional takes 15 minutes under local anesthesia

>> Caring for insertion site requires removing pressure dressing in 24 hours, leaving steristrips (sterile tape) on incisions for 3 days, keeping covered and dry, taking care not to bump site or to lift heavy objects for 24 hours, and expecting some swelling and bruising at site of insertion

>> Full contraceptive protection begins within 24 hours when insertion is done within 7 days of the beginning of the menstrual period; otherwise, another birth control method must be used during the rest of the first menstrual cycle; protection ends immediately after removal

>> Removal procedure may be done at any time by a health care professional. After 5 years of use the subdermal implants should be removed and, if desired, a new set of subdermal implants can be inserted at this time; the removal procedure takes 20 minutes or longer under local anesthesia; rarely, some difficult cases may require skin healing after an unsuccessful attempt

For levonorgestrel tablets

The medicine may be taken any time during the menstrual cycle

For medroxyprogesterone for contraception

>> Importance of receiving an injection by a health care professional every 3 months (13 weeks)

Stopping use by simply not receiving the injection

Full contraceptive protection begins immediately after initial injection without need for additional birth control methods if given within the first 5 days of a normal menstrual period, within the first 5 days postpartum if not breast-feeding, and, if exclusively breast-feeding, at the sixth postpartum week. Protection continues when an injection is given every 3 months (13 weeks)

For oral progestins for contraception

>> Compliance with therapy, taking medication at the same time each day at 24-hour intervals

When switching from estrogen and progestin oral contraceptives, the first dose of the progestin-only oral contraceptive should be taken the next day after the last active tablet of the oral estrogen and progestin oral contraceptive is administered. The placebo (inactive) tablets of the 28-day cycle can be discarded
Also, when switching, full protection begins within 48 hours if the dose is taken on the first day of the menstrual period; if treatment is begun at other times, a back-up method should be used for 3 weeks as a conservative approach

A chance of pregnancy is increased for each missed dose

For noncontraception use

Caution in taking combination therapy; taking each medication at the right time

Precautions while using this medication

>> Regular visits to health care professional

>> Caution when driving or doing things requiring alertness because the medication may cause dizziness; for progesterone capsules, dizziness or drowsiness may occur 1 to 4 hours after ingestion

Checking with doctor immediately if uterine bleeding (spotting or breakthrough menstrual bleeding) continues longer than 3 months or if menstruation is delayed by 45 days

>> Contacting doctor immediately if pregnancy is suspected or a menstrual period is missed

If scheduled for laboratory tests, tell physician if taking progestins; certain blood tests may be affected

Possibility of dental problems, such as tenderness, swelling, or bleeding of gums; checking with dentist if there are questions about care of teeth or gums or if tenderness, swelling, or bleeding of gums occurs; patient should follow good cleaning procedures, such as regular brushing and flossing of teeth, massaging gums, and having dentist clean teeth regularly

For contraceptive use

>> Using a second method of birth control when taking medications that reduce effectiveness of progestins

If vomiting occurs for any reason shortly after taking the progestin-only oral contraceptive pill, do not take another dose, resume your normal dosing schedule and use an additional backup method for 48 hours

If vomiting occurs within 1 hour of taking either dose of the levonorgestrel tablets for emergency contraception, contact your physician to discuss whether the dose should be repeated

For noncontraceptive use

>> Advisability of using contraceptive methods while taking progestins for noncontraceptive uses if fertile and sexually active

For progesterone (vaginal) dosage form: Avoiding use of other vaginal products for 6 hours before and for 6 hours after administering progesterone vaginally to ensure its complete absorption 244

Side/adverse effects

Signs of potential side effects, especially amenorrhea; breakthrough menstrual bleeding or metromenorrhagia; hyperglycemia; menorrhagia; spotting; galactorrhea; mental depression; skin rash; adrenal suppression or insufficiency or hypotension (megestrol only); Cushing's syndrome (megestrol only), or thromboembolism or thrombus formation

General Dosing Information

For all progestins

The cyclical administration of progestins is based on an assumed menstrual cycle of 28 days. 82, 83

Onset of the female menopause may be masked by the use of progestins. 97, 202

Follicular atresia may be delayed, allowing the growth and development of follicles that clinically may appear to be ovarian cysts, especially with levonorgestrel subdermal implants. In most cases, enlarged follicles disappear spontaneously, but, rarely, they may rupture, causing abdominal pain and requiring surgical intervention. 88

Discontinue medication pending eye examination if there is sudden partial or complete loss of vision or sudden onset of proptosis (exophthalmos or abnormal protrusion of the eyeball), diplopia (seeing double), or migraine. Also, discontinue medication if examination reveals papilledema or if thrombotic disorder occurs or is suspected. 73, 74

The patient package insert is mandatory for progestational drugs to convey information regarding birth defects to premenopausal women unless childbearing is impossible. 39, 72, 87, 89, 91, 101 However, it is recommended that the patient package insert also be given to patients taking or using progestins for noncontraceptive purposes. 71, 90, 99

For contraception use

Although some progestin products protect against pregnancy, none protects against HIV infection or AIDS. 71

Another contraceptive method should be used and pregnancy should be ruled out before resuming use of hormonal contraceptives if two tablets or an injection is missed. 88, 194

For levonorgestrel subdermal implants

Insertion (usually a 15-minute procedure using local anesthesia) should be performed within the first 7 days of a normal menstrual period or immediately postabortion. Insertion is not recommended by the manufacturer in the first 6-weeks postpartum for breast-feeding women. 88, 194

All 6 implants are inserted subdermally in a fanlike pattern about 15 degrees apart (totaling 75 degrees) in the midportion of the upper arm (8 to 10 centimeters above the crease in the elbow). 88

Proper insertion technique for insertion or removal of subdermal implants reduces the incidence of hard-to-remove subdermal implants, expulsions, and improper placement of subdermal implants. Bruising and some scarring may occur with insertion or removal procedures. 88, 240 Insertion site complications at 1-year follow-up include 0.8% skin infection, 0.4% expulsion, and 4.7% local skin reaction; in approximately 41% of women with a skin infection, an expulsion of an implant resulted. 136

When an implant is expelled, a new subdermal implant may be inserted in the same incision, although any infection or unusual wound or incision site problems should heal before a new sterile subdermal implant is inserted. Other contraceptive methods should be used concurrently when fewer than 6 subdermal implants are in place. Also, if removal of all subdermal implants is not successful with the first attempt, the skin should be allowed to heal completely before a second attempt of removal. 88

Removal of the levonorgestrel implants (usually a 20-minute procedure) may occur on request at any time or at the end of the fifth year of use, and should be considered if prolonged immobilization is anticipated 88 or if persistent infection develops at the implantation site. 88, 136 Used subdermal

implants should be disposed of by using the Centers for Disease Control guidelines for biohazardous waste. 88

For oral levonorgestrel for postcoital contraception

The first dose (0.75 milligram) should be taken as soon as possible within 72 hours of intercourse 254.

The second dose must be taken 12 hours later 254.

Levonorgestrel may be taken at any time during the menstrual cycle 254.

Patients should be instructed to contact their health care if vomiting occurs within one hour of taking either dose of levonorgestrel to discuss whether the dose should be repeated 254

For oral progestins for contraception

When used as oral contraceptives, progestins are administered daily without interruption, regardless of menstrual cycle 90, 96.

When switching a patient from estrogen and progestin oral contraceptives, a new progestin-only oral contraceptive is begun on the 22nd day; the inactive or placebo tablets of the 28-day cycle should be discarded 249.

Full contraceptive protection begins within 48 hours if the first oral progestin dose is taken on Day 1 of the menstrual cycle. A back-up birth control method should be used for 3 weeks (a conservative approach) if the patient is started at any other time.
For parenteral medroxyprogesterone

The formulation of parenteral medroxyprogesterone for noncontraceptive use (400 mg/mL) should not be used for contraceptive uses, even if the proper dose (150 mg) is considered. Efficacy issues arose and resulted in discontinuation of a clinical trial conducted by the manufacturer using a lower volume dose than that used in the formulation of medroxyprogesterone for contraception. 14, 188 Dose adjustment is not necessary for body weight but it is reported that plasma concentration and duration decreased by a mean of 3.3 picograms/mL per kg increase of body weight because of its accumulation in fat cells; therefore, return to fertility may be especially prolonged in obese women. 37, 38, 71, 228

Injecting into the deltoid muscle as opposed to the gluteal muscle is recommended by some clinicians to lessen absorption problems that may occur because of rubbing the injection site while sitting. 231, 241, 243

For noncontraceptive uses

For women who are using progestins for other reasons besides contraception, concurrent contraceptive methods should be used if fertile and sexually active. 66, 188

Response rates are about 15 to 16% in patients using progestins for treating endometrial carcinoma with high-grade resistant tumors and may be significantly better with low-grade malignancy; response

rate decreases for tumors of increasing grade and in those tumors negative for both estrogen and progesterone receptors; median survival is approximately 9 to 10 months. 153, 154, 200

Response rates are approximately 5% and of short duration in patients using progestins for treating renal carcinoma; routine receptor assay is not helpful in predicting appropriate patients. 172, 173, 174, 175

Response rates of up to about 40% have been reported when high-dose oral medroxyprogesterone has been used to treat breast cancer. 188, 205, 206

Decisions to treat menopausal symptoms with hormones for a limited time (1 to 5 years) or to use hormones to prevent diseases in postmenopausal women for a longer period of time (10 to 20 years), or a lifetime, should be separate decisions. Counseling asymptomatic postmenopausal women about the benefits and risks of long-term estrogen and progestin ovarian hormone therapy to prevent disease and prolong life is complex. It is dependent on an individual's risk of breast cancer, osteoporosis, and coronary heart disease and whether a uterus is present (progestins are not needed when the uterus is absent). Adding a progestin to estrogen therapy may benefit postmenopausal women at risk for osteoporosis, slightly reduce estrogen's protective effect against coronary heart disease (women at more risk are provided the greatest benefit), and slightly increase the risk of breast cancer over that of non-users. Women should understand that the benefits and risks of preventive ovarian hormone therapy depend on their risk status. 17, 44, 60, 61, 213, 225, 227

For medroxyprogesterone

Re-establishment of menstrual cycle may be delayed (up to 18 months or longer) and is difficult to predict following the intramuscular administration of medroxyprogesterone. 73 Because of the prolonged action and the resulting difficulty in predicting the time of withdrawal bleeding following injection, parenteral medroxyprogesterone is not recommended for treatment of secondary amenorrhea or dysfunctional uterine bleeding; oral medroxyprogesterone is the preferred mode of therapy. 73, 194

For megestrol

The magnitude and rate of weight gain are highly dependent on megestrol dose and are significantly greater with higher doses. The greatest effect can be maintained at a lower dose of 400 mg a day in the second to fourth months when 800 mg a day is taken in the first month, although some studies have reported further benefit when the dose is not lowered. 111, 207, 208

Adrenal suppression may occur with normal dosing range; effects on HIV viral replication have not been determined. 66

For progesterone

For oral progesterone:
If only one dose of progesterone capsules is needed, it should be taken at bedtime to minimize the side effect of dizziness or drowsiness experienced by patients within 1 to 4 hours after taking 200 mg progesterone 245.

If a progesterone dose is taken in the morning, the patient should take it 2 hours after eating breakfast 245.

For vaginal progesterone:
Synthetic progestins are more potent than natural progesterone; i.e., 20 to 25 mg progesterone (intramuscular) has an effect equivalent to 100 mg progesterone (vaginal suppository) or 5 to 10 mg medroxyprogesterone (oral) or 50 mg medroxyprogesterone (intramuscular). 74, 184

Use of other vaginal products should be avoided for at least 6 hours before or 6 hours after administering progesterone vaginally to ensure its complete absorption 244.

For treatment of adverse effects

For megesterol¾
Reports of adrenal suppression or insufficiency have been reported in patients during treatment and at treatment discontinuation of high or chronic doses of megestrol, whereas Cushing's syndrome has been reported during treatment with high or chronic doses of megestrol 67.

Recommended treatment of adrenal insufficiency consists of the following:
· Laboratory evaluation for adrenal insufficiency 67.

· Physiologic replacement doses of a rapid-acting glucocorticosteroid 67.

HYDROXYPROGESTERONE

Summary of Differences

Category¾
Progestational agent; diagnostic aid.

Indications¾
Amenorrhea, dysfunctional uterine bleeding, induction of menses, and test for endogenous estrogen production.

Pharmacology/pharmacokinetics¾
More potent than progesterone with longer duration of action.
Synthetic 17-hydroxy derivative of progesterone with progestogenic, androgenic, and glucocorticoid effects.

Parenteral Dosage Forms

HYDROXYPROGESTERONE CAPROATE INJECTION USP

Usual adult and adolescent dose

Amenorrhea or
Dysfunctional uterine bleeding¾
Intramuscular, 375 mg. 97

Estrogen production, endogenous, diagnosis or
Menses, induction of¾
Intramuscular, 125 to 250 mg given on Day 10 of the menstrual cycle, repeated every seven days until suppression is no longer desired. 97

Note: Withdrawal bleeding usually occurs within three to seven days after discontinuing therapy.

Strength(s) usually available

U.S.¾125 mg per mL (Rx) 97

250 mg per mL (Rx)[Gesterol LA 250] [Hy/Gestrone] [Hylutin] [Prodrox] [Pro-Span] 8, 97

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Note: Castor or sesame oils are commonly used as the vehicle for intramuscular injection. 97

Include mandatory patient package insert (PPI) when dispensing to premenopausal patient unless reproduction is impossible. 97

LEVONORGESTREL

Summary of Differences

Category¾
Contraceptive.

Indications¾
Pregnancy prophylaxis.; contraception, emergency postcoital (prophylaxis)

Pharmacology/pharmacokinetics¾
19-nor derivative of testosterone; has progestational and androgenic effects.

Precautions¾
Breast-feeding¾Generally recommended for use 6 weeks postpartum in breast-feeding women but has been used 5 days postpartum after establishment of lactation.
Laboratory value alterations¾Serum T3 concentrations may be slightly elevated and T4 concentrations may be decreased; total serum T4 concentrations are unaffected.
Medical considerations/contraindications¾Levonorgestrel subdermal implants have not caused thrombogenic disorders, but caution may be necessary with use in patients with a history of thrombosis.

Caution is necessary in patients with a history of CNS disorders, such as depression or history of convulsions.

Side effects¾

Breakthrough menstrual bleeding or spotting, reduced amount of menstrual bleeding, and amenorrhea are predominant side effects. These bleeding irregularities may persist but are less problematic with time. Other side effects include ovarian enlargement or cysts (usually reversible with continued use), acne, headaches, and mood changes.

Additional Dosing Information

See also General Dosing Information.

Special training for insertion, removal, and disposal of levonorgestrel subdermal implants includes knowledge and familiarity of procedures by physician and patient.

Oral Dosage Form

LEVONORGESTREL TABLETS

Usual adult and adolescent dose

Contraception, emergency postcoital (prophylaxis) ¾

The first dose of 0.75 milligram should be taken as soon as possible within 72 hours of intercouse. The second dose must be taken 12 hours later. 254

Strength(s) usually available

U.S.¾0.75 milligram (Rx)[Plan B 254]

Subdermal Dosage Form

LEVONORGESTREL IMPLANTS

Usual adult and adolescent dose

Pregnancy, prevention of¾

Subdermally, one set of six implants surgically inserted every five years. 88

Strength(s) usually available

U.S.¾216 mg (Rx)[NORPLANT System 88]

Canada¾216 mg (Rx)[NORPLANT System 204]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store away from excess heat or moisture.

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patient unless reproduction is impossible. 88

MEDROGESTONE

Summary of Differences

Category¾
Progestational agent.

Indications¾
Secondary amenorrhea, dysfunctional uterine bleeding, induction of menses, and, in conjunction with estrogens, for endometrial shedding in menopausal women.

Pharmacology/pharmacokinetics¾
17-hydroxy derivative of progesterone; highly progestational, devoid of estrogenic, androgenic, glucocorticoid, or anti-androgenic effects.

Oral Dosage Forms

MEDROGESTONE TABLETS

Usual adult and adolescent dose

Amenorrhea, secondary or
Dysfunctional uterine bleeding or
Hyperplasia, endometrial, estrogen-induced, postmenopausal, prophylaxis or
Menses, induction of¾
Oral, 5 to 10 mg a day on Days 15 through 25 of monthly cycle. 100

Note: Withdrawal bleeding usually occurs within three to seven days after discontinuing therapy. 100

An optimum secretory transformation of an endometrium that has been adequately primed with either endogenous or exogenous estrogens (Days 5 to 25 of the menstrual cycle) may be reestablished with three or more cycles. 100

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾5 mg (Rx)[Colprone (scored) 100]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

MEDROXYPROGESTERONE

Summary of Differences

Category¾

Oral medroxyprogesterone used as a progestational agent, antineoplastic agent, and diagnostic aid (test for endogenous estrogen production). Parenteral medroxyprogesterone used as adjunct in antineoplastic therapy and indicated as contraceptive agent in a special parenteral formulation.

Indications¾

Oral and parenteral medroxyprogesterone indicated to treat breast carcinoma in postmenopausal women and endometrial hyperplasia in conditions such as polycystic ovary syndrome; however, only parenteral medroxyprogesterone is indicated for adjunct treatment of metastatic renal or endometrial carcinoma and endometriosis. Parenteral medroxyprogesterone is accepted therapy for precocious puberty, but has been replaced by other modalities. Unlike parenteral medroxyprogesterone, oral medroxyprogesterone is indicated for secondary amenorrhea, dysfunctional uterine bleeding, induction of menses, carcinoma, ovarian hormone therapy in menopause, and testing for endogenous estrogen production.

Unlike oral medroxyprogesterone, parenteral medroxyprogesterone is not recommended for treatment of secondary amenorrhea or dysfunctional uterine bleeding.

Pharmacology/pharmacokinetics¾

17-hydroxy derivative of progesterone with progestogenic, androgenic, and glucocorticoid effects.

Precautions¾

Fertility¾Luteal function may be delayed after cessation of parenteral medroxyprogesterone treatment for contraception, especially in obese females of reproductive age.

Pregnancy¾Use in pregnancy has produced problems in the fetus and is not recommended. Doses used for contraception have not appeared to produce problems for nursing infants after lactation is established.

Drug interactions¾Use of aminoglutethimide may lower serum concentrations of medroxyprogesterone and interfere with intestinal absorption of oral dose.

Medical considerations/contraindications¾Low dose parenteral medroxyprogesterone can be used with caution for contraception in women with diabetes mellitus. High doses (but not low doses) have rarely been associated with thromboembolic disorders or thrombophlebitis.

Side/adverse effects¾

Bloating or swelling of face, ankles, or feet more likely with higher doses.

Additional Dosing Information

See also General Dosing Information.

Re-establishment of menstrual cycle can be delayed and difficult to predict following the parenteral dose. Also, only the 150 mg/mL formulation and a 150-mg dose should be used for contraception; a special dose adjustment for the obese patient is not needed; however, contraceptive efficacy in patients over 90 kg has not been evaluated.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use or indications that are not included in U.S. product labeling.

MEDROXYPROGESTERONE ACETATE TABLETS USP

Usual adult or adolescent dose

Amenorrhea, secondary¾
Oral, 5 to 10 mg a day for five to ten days, started any time during cycle. 56, 74, 78, 98

Dysfunctional uterine bleeding¾
Oral, 5 to 10 mg a day for five to ten days, commencing on the calculated Day 16 or Day 21 of the menstrual cycle. 69, 74, 78, 98

Menses, induction of¾
Oral, 10 mg daily for ten days starting on Day 16 of the menstrual cycle. 69, 74, 78, 98 If bleeding is controlled satisfactorily, two or more subsequent cycles of the treatment should be given. 74

[Hyperplasia, endometrial, estrogen-induced, postmenopausal, prophylaxis]¾There are several recommended dosing schedules

Oral, 5 to 10 mg medroxyprogesterone a day for ten or fourteen days beginning on Days 12 or 16 through Day 25, estrogen is taken on Day 1 through Day 25, and neither estrogen nor medroxyprogesterone is taken on the twenty-fifth day through the end of the month. 17, 20, 60, 61

Oral, 5 to 10 mg medroxyprogesterone a day taken on the first ten to fourteen days along with continuous estrogen dosing. 17, 20, 60, 61

Oral, 2.5 or 5 mg medroxyprogesterone a day taken continuously with continuous estrogen dosing. 17, 20, 60, 61, 224

Note: Other regimens may differ but also may be appropriate. 242 Withdrawal bleeding usually occurs within three to seven days after discontinuing therapy. 69, 74

[Carcinoma, breast, postmenopausal women]¾
Oral, 400 mg a day in divided doses. 9, 34, 74, 139, 151, 152, 158, 162

[Carcinoma, endometrial]¾
Initial: Oral, 200 to 400 mg a day for two to three months. 10, 74

Maintenance: Oral, 200 mg a day. 74

Note: Improvement may not be evident until eight to ten weeks following initiation of therapy for breast or endometrial carcinoma. However, treatment should be discontinued when there is rapid progression of the disease at any time during therapy. 74

[Endometriosis] *¾

Oral, 10 to 40 mg a day for six to nine months. 188, 191, 194, 238

[Estrogen production, endogenous, diagnosis]¾
Oral, 10 mg a day for five to ten days. Withdrawal bleeding will occur three to seven days following therapy if the uterus has been sufficiently primed with endogenous estrogen. 47, 48

[Hyperplasia, endometrial, treatment] *¾There are several recommended dosing schedules

Oral, 10 mg a day for three to six months. 232, 234

Oral, 10 mg a day for twenty-one days each month for three months. Then the dose is reduced to 10 mg a day for ten to fourteen days a month. 215, 216, 217, 218, 219, 220

Oral, 20 mg a day for thirty days every six months. 216, 217, 218, 219, 220

Note: Other regimens may differ but also may be appropriate. 242

Strength(s) usually available

U.S.¾2.5 mg (Rx)[Cycrin (scored) 76] [Provera (scored) 69] [Generic] 78

5 mg (Rx)[Cycrin (scored) 76] [Provera (scored) 69] [Generic] 78

10 mg (Rx)[Amen (scored)] [Curretab (scored) 98] [Cycrin (scored) 76] [Provera (scored) 69] [Generic] 78

Canada¾2.5 mg (Rx)[Alti-MPA 248] [Gen-Medroxy (scored) 251] [Novo-Medrone (scored) 250] [Provera 74]

5 mg (Rx)[Alti-MPA 248] [Gen-Medroxy (scored) 251] [Novo-Medrone (scored) 250] [Provera (scored) 74] [Provera Pak (scored) 252]

10 mg (Rx)[Alti-MPA 248] [Gen-Medroxy (scored) 251] [Novo-Medrone (scored) 250] [Provera (scored) 74]

100 mg (Rx)[Provera (scored) 74]

Note: Brand name Provera Pak contains 14 tablets in blister packaging 252.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. 69, 74, 76, 78

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patient unless reproduction is impossible. 69

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use or indications that are not included in U.S. product labeling.

MEDROXYPROGESTERONE ACETATE INJECTABLE SUSPENSION USP

Note: Formerly known as Sterile Medroxyprogesterone Acetate Suspension, USP 1.

Usual adult or adolescent dose

Carcinoma, endometrial or
Carcinoma, renal¾
Initial: Intramuscular, 400 mg to 1 gram once a week until improvement and stabilization occur. 72, 73

Maintenance: Intramuscular, 400 mg or more once a month. 72, 73, 188

[Carcinoma, breast]¾
Initial: Intramuscular, 500 mg a day for twenty-eight days. 34, 73, 159

Maintenance: Intramuscular, 500 mg two times a week. 73, 159

Note: Improvement may not be evident for eight to ten weeks of therapy for breast or endometrial carcinoma. However, treatment should be discontinued when there is rapid progression of the disease at any time during therapy. 73, 74

[Endometriosis]¾There are several recommended dosing schedules

Intramuscular, 50 mg once a week for at least six months. 73

Intramuscular, 100 mg every two weeks for at least six months. 73

Intramuscular, 150 mg every 3 months for at least six months. 194

Pregnancy, prevention of¾
Intramuscular, 150 mg every three months. 71

Note: Dosage does not need to be adjusted for body weight in patients weighing less than 90 kg, but dosage has not been studied in patients weighing more than 90 kg. 188 It is recommended that the first injection be given during the first five days after onset of a normal menstrual period; within five days postpartum if not breast-feeding, and if exclusively breast-feeding, at six weeks postpartum. 14, 71, 233 A physician should determine that a patient is not pregnant if more than thirteen weeks will elapse between injections. 14, 71, 188

Strength(s) usually available

U.S.¾150 mg per mL (Rx)[Depo-Provera Contraceptive Injection 71]

400 mg per mL (Rx)[Depo-Provera 72]

Note: Brand name Depo-Provera Contraceptive Injection is available in vials or as prefilled syringes 71.

Canada¾50 mg per mL (Rx)[Depo-Provera 73]

150 mg per mL (Rx)[Depo-Provera 73]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing. 71, 72, 73

Preparation of dosage form:

Should be shaken vigorously before administration 73.

Auxiliary labeling:

· Shake well. 71, 72, 73

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patient unless reproduction is impossible. 71, 72

MEGESTROL

Summary of Differences

Category¾
Antianoretic, anticachectic, antineoplastic.

Indications¾
Endometrial or breast carcinoma; anorexia, cachexia and significant weight loss, associated with cancer (tablets) and acquired immunodeficiency syndrome (AIDS) (suspension); and advanced prostate carcinoma. Not recommended for prophylactic avoidance of weight loss.

Pharmacology/pharmacokinetics¾
17-hydroxy derivative of progesterone; progestogenic, glucocorticoid, and anti-estrogenic effects.

Precautions¾
Fertility¾Impaired fertility shown in male offspring of megestrol-treated females in studies in rats and dogs.
Pregnancy¾Use is not recommended.

Additional Dosing Information

See also General Dosing Information.

Magnitude and rate of weight gain are dose-related; lower doses of 400 mg are recommended after the first month, although some results have shown weight gain continuing with 800 mg given continuously for 4 months.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use or indications that are not included in U.S. product labeling.

MEGESTROL ACETATE SUSPENSION

Usual adult and adolescent dose

Anorexia or
Cachexia or
Weight-loss, significant¾
For patients with AIDS: Oral, 800 mg a day the first month, then 400 or 800 mg a day for three more months. 66, 166, 167, 207, 208, 209

Strength(s) usually available

U.S.¾40 mg per milliliter (mL) (Rx)[Megace (alcohol 0.06%) (sucrose) 66]

Canada¾40 mg per milliliter (mL) (Rx)[Megace OS (alcohol 0.06%) (sucrose) 67]

Packaging and storage:

Store between 15 and 25 °C (59 and 77 °F). Protect from heat 66.

Store in a well-closed container.

Auxiliary labeling:

· Shake well. 66

Note: Include patient package insert (PPI) when dispensing.

MEGESTROL ACETATE TABLETS USP

Usual adult and adolescent dose

[Anorexia] or
[Cachexia]or
[Weight-loss, significant]¾
For patients with cancer: Oral, 400 to 800 mg a day as a single daily dose 67.

Carcinoma, breast¾
Oral, 160 mg a day as a single dose or in divided doses. 67, 68, 111, 149

Carcinoma, endometrial¾
Oral, 40 to 320 mg a day in divided doses. 67, 68

[Carcinoma, prostate, advanced]¾
Oral, 120 mg once a day with 0.1 mg diethylstilbesterol a day. 67, 116

Note: At least two months of continuous treatment is considered an adequate period for determining the efficacy of megestrol. 67, 68

[Hyperplasia, endometrial, treatment] *¾
Oral, 20 to 40 mg a day for 14 days or longer every month. 216, 217, 218, 219, 220

Strength(s) usually available

U.S.¾20 mg (Rx)[Megace (scored) 68] [Generic]

40 mg (Rx)[Megace (scored) 68] [Generic]

Canada¾40 mg (Rx)[Apo-Megestrol (scored) 247] [Megace (scored) 67]

160 mg (Rx)[Apo-Megestrol (scored) 247] [Megace 67]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Note: Include patient package insert (PPI) when dispensing.

NORETHINDRONE

Summary of Differences

Category¾
Indicated as a progestational agent (norethindrone base and acetate) and contraceptive agent (norethindrone base).

Indication¾
Norethindrone acetate indicated for secondary amenorrhea, dysfunctional uterine bleeding, induction of menses, and endometriosis. Norethindrone base is indicated for contraception while the acetate form is not.

Oral Dosage Forms

NORETHINDRONE TABLETS USP

Usual adult and adolescent dose

Pregnancy, prevention of¾
Oral, 350 mcg (0.35 mg) a day, starting on Day 1 of the menstrual cycle and continuing uninterrupted at the same time every day of the year, whether or not menstrual bleeding occurs. 90, 96

Strength(s) usually available

U.S.¾350 mcg (0.35 mg) (Rx)[Micronor 90] [Nor-QD 96]

Canada¾350 mcg (0.35 mg) (Rx)[Micronor 84]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patient unless reproduction is impossible.

NORETHINDRONE ACETATE TABLETS USP

Usual adult and adolescent dose

Amenorrhea, secondary or
Dysfunctional uterine bleeding¾
Oral, 2.5 to 10 mg a day on Day 5 through Day 25 of the menstrual cycle or for five to ten days during the last half of menstrual cycle. 82, 83

Note: Withdrawal bleeding occurs within three to seven days after progestin treatment ends. 82

Endometriosis¾
Initial: Oral, 5 mg a day for two weeks, increasing by 2.5 mg a day at two-week intervals to reach a total dose of 15 mg a day. 82

Maintenance: Oral, 15 mg a day for six to nine months, unless temporarily discontinued because of breakthrough menstrual bleeding. 82, 83, 102

Strength(s) usually available

U.S.¾5 mg (Rx)[Aygestin (scored 82)]

Canada¾5 mg (Rx)[Norlutate 65]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container. 82

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patients unless reproduction is impossible. 82, 83

NORGESTREL

Summary of Differences

Category¾
Contraceptive agent.

Indication¾
Pregnancy prophylaxis.

Pharmacology/pharmacokinetics¾
19-nor derivative of testosterone; has progestogenic, estrogenic, androgenic, and anti-estrogenic effects.

Oral Dosage Forms

NORGESTREL TABLETS USP

Usual adult and adolescent dose

Pregnancy, prevention of¾
Oral, 75 mcg (0.075 mg) a day, starting on Day 1 of menstrual cycle and continuing uninterrupted at the same time every day of the year whether or not menstrual bleeding occurs. 86, 90

Strength(s) usually available

U.S.¾75 mcg (0.075 mg) (Rx)[Ovrette 86]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patients unless reproduction is impossible.

PROGESTERONE

Summary of Differences

Category¾
Progestational agent.

Indications¾
Indicated for secondary amenorrhea and dysfunctional uterine bleeding but is also used for corpus luteum insufficiency.

Pharmacology/pharmacokinetics¾
Natural hormone with progestational, androgenic, and anti-estrogenic effects.

Precautions¾
Pregnancy¾Although not proven effective, progesterone has been used during first few months of pregnancy to prevent habitual or threatened abortion due to hormonal imbalance but may also delay expulsion of a defective ovum.

Additional Dosing Information

See also General Dosing Information.

Twenty to 25 mg progesterone (intramuscular) produces an equivalent progestogenic effect compared to 100 mg progesterone (vaginal suppository).

Oral Dosage Forms

PROGESTERONE CAPSULES (Micronized)

Usual adult dose

Amenorrhea, secondary *¾
Oral, 400 mg once a day in the evening for ten days 253.

[Hyperplasia, endometrial, estrogen-induced, postmenopausal, prophylaxis]¾
Oral, 200 mg once a day at bedtime for fourteen days beginning Day 8 through Day 21 of a twenty-eight-day cycle or beginning Day 12 to Day 25 of a thirty-day cycle. A dose of 300 mg progesterone divided as 100 mg in the morning two hours after breakfast and 200 mg at bedtime may be required for patients taking doses of estrogen 1.25 mg or greater. The progestin dose should be adjusted until desired uterine response is achieved (regular withdrawal uterine bleeding or amenorrhea). In many treatment regimens, the last five to seven days of each month are often left free of hormone use. 245

Strength(s) usually available

U.S.¾100 mg (Rx)[Prometrium (glycerin) (lecithin) (peanut oil) (titanium dioxide) 253]

Canada¾100 mg (Rx)[Prometrium (glycerin) (lecithin) (peanut oil) (titanium dioxide) 245]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 245

Auxiliary labeling:

May cause dizziness or drowsiness 245.

Note: Include patient package insert (PPI) when dispensing progestins to premenopausal patients, unless reproduction is impossible 245.

Parenteral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use or indications that are not included in U.S. product labeling.

PROGESTERONE INJECTION USP

Usual adult and adolescent dose

Amenorrhea, secondary¾
Intramuscular, 5 to 10 mg a day for six to ten consecutive days or 100 to 150 mg injected intramuscularly as a single dose. 58, 80, 81, 202

Note: If there has been sufficient ovarian activity to produce a proliferative endometrium or two weeks of prior estrogen therapy 58, 81 , withdrawal bleeding will occur forty-eight to seventy-two hours after the last injection. The patient should discontinue therapy if menstrual cycle occurs. 59, 80 This may be followed by spontaneous normal cycles. 59, 80, 81 Progesterone should be discontinued if menses occurs during the series of injections. 81

Dysfunctional uterine bleeding¾
Intramuscular, 5 to 10 mg a day for six consecutive days. 58, 80, 81

Note: Bleeding should cease within six days. 58, 80 When estrogen is being given, the administration of progesterone should begin after two weeks of estrogen therapy. 58, 59, 80 Progesterone should be discontinued if menses occurs during the series of injections. 58, 59, 80

[Corpus luteum insufficiency] *¾
Intramuscular, 12.5 mg or more a day initiated within several days of ovulation. Treatment duration is usually two weeks, but it may be continued, if necessary, up to eleventh week of gestation. 7, 35

[Estrogen production, endogenous, diagnosis] *¾
Intramuscular, 100 mg as a single dose. 202

Strength(s) usually available

U.S.¾50 mg per mL (Rx)[Gesterol 50 (in sesame seed oil) (benzyl alcohol 10%) 80] [Generic] (in sesame seed or peanut oil) 58, 59

Canada¾50 mg per mL (Rx)[PMS-Progesterone (in sesame seed oil) (benzyl alcohol 10%) 81]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing. 58, 59

Auxiliary labeling:

May cause dizziness or drowsiness.

Note: Include mandatory patient package insert (PPI) when dispensing progestins to premenopausal patients unless reproduction is impossible. 80

Vaginal Dosage Forms

PROGESTERONE GEL (Micronized)

Note: Bracketed uses in the Dosage Forms section refer to categories of use or indications that are not included in U.S. product labeling.

Usual adult and adolescent dose

Amenorrhea, secondary¾
Vaginal, 45 mg (one applicatorful of 4% vaginal gel) once every other day for up to six doses. Dose may be increased to 90 mg (one applicatorful of 8% vaginal gel) once every other day for up to six doses. 244

Note: Increasing the dose to 90 mg by doubling the amount of the 4% vaginal gel used does not increase the amount of medication absorbed, and the 8% vaginal gel should be used instead 244.

Assisted reproductive technologies, in females or
[Corpus luteum insufficiency] *¾
For patients needing luteal phase support: Vaginal, 90 mg (one applicatorful of 8% vaginal gel) once a day for progesterone supplementation. For patients undergoing in vitro fertilization (IVF), treatment may begin within 24 hours of embryo transfer and continue through Day 30 post-transfer. If pregnancy occurs, treatment can be extended until placental autonomy is achieved, up to ten to twelve weeks. 244

For patients with partial or complete ovarian failure: Vaginal, 90 mg (one applicatorful of 8% vaginal gel) two times a day to receive full progesterone replacement doses while undergoing donor oocyte transfer procedure. If pregnancy occurs, treatment can be extended until placental autonomy is achieved, up to ten to twelve weeks. 244

Strength(s) usually available
U.S.¾4% (Rx)[Crinone 244]

8% (Rx)[Crinone 244]

Note: Available as single-use prefilled applicators. One applicatorful of 4% or 8% vaginal gel delivers 1.125 grams of gel. 244

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 25 °C (59 and 77 °F), unless otherwise specified by manufacturer. 244

Auxiliary labeling:

For vaginal use only.
May cause dizziness or drowsiness.

PROGESTERONE SUPPOSITORIES

Note: Because progesterone suppositories are not commercially available in the U.S. or Canada, the bracketed uses and the use of the superscript 1 in this Dosage Forms section reflect the lack of labeled (approved) indications for this product in these countries.

Usual adult and adolescent dose

[Assisted reproductive technologies, in females] * or
[Corpus luteum insufficiency] *¾
Vaginal, 25 to 100 mg one to two times a day initiated within several days of ovulation. Treatment duration is usually continued if the patient is pregnant up to about the eleventh week of gestation. 7, 35, 201, 203

Strength(s) usually available

U.S.¾Not commercially available. Compounding required for prescription.
Canada¾Not commercially available. Compounding required for prescription.

Packaging and storage:

Store between 2 and 8 °C (36 and 46 °F), in a tight container.

Preparation of dosage form:

A formulation that has been used for the extemporaneous compounding of progesterone suppositories is as follows: 179, 180, 181

- 710 mg (0.71 grams) progesterone powder
- 33.7 grams polyethylene glycol 400
- 22.3 grams polyethylene glycol 6000

Makes 28 suppositories, 25 mg progesterone per suppository.

Auxiliary labeling:

- For vaginal use only.
- Refrigerate. Do not freeze.