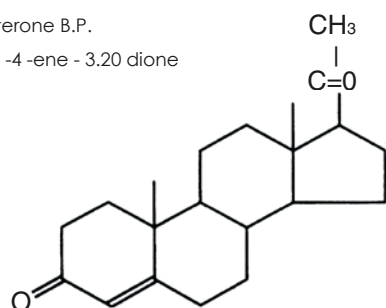


## PRODUCT INFORMATION

**COMPOSITION:** Progesterone B.P.

**CHEMICAL NAME:** Prog -4 -ene - 3.20 dione



Progesterone  
C<sub>21</sub>H<sub>30</sub>O<sub>2</sub>

**DESCRIPTION:** PRO-FEME™ is a transdermal drug delivery system consisting of a white vanishing cream intended for topical administration of progesterone and

contains dl-α-tocopherol acetate (vitamin E), almond oil and macadamia oil formulated to optimise systemic absorption of the active ingredient. Also contains cetomacrogol 1000, cetostearyl alcohol, butylated hydroxytoluene, propyl hydroxybenzoate, citric acid, methyl hydroxybenzoate, triethanolamine, carbomer 940, phenonip and water.

**PHARMACOLOGY:** Progesterone is secreted primarily from the corpus luteum of the ovary during the latter half of the menstrual cycle. Progesterone is formed from steroid precursors in the ovary, testes, adrenal cortex and placenta. Lutenizing hormone (LH) stimulates the synthesis and secretion of progesterone from the corpus luteum. Progesterone is multifactorial in its actions. Maintenance of a secretory endometrium, precursor to steroid synthesis and a host of intrinsic biological properties make progesterone a hormone vital in providing a balance to oestradiol, the oestrogenic hormone secreted by the ovary. Progesterone has minimal oestrogenic and androgenic activity. Orally administered progesterone is rapidly metabolised by the liver and the first pass effect is extremely high. The hormone is reduced to inactive metabolites pregnenedione, pregnenadone and pregnenediol in the liver, conjugated with glucuronic acid, then excreted in the bile and urine. Transdermal absorption of progesterone avoids the first-pass metabolism. Progesterone has a short plasma half-life of several minutes. Progesterone is extremely lipophilic and binds to plasma protein carriers, cortisol binding globulin (CBG), sex hormone binding globulin (SHBG), red blood cellular membranes (1, 2) and fatty tissue. 2-10% progesterone circulates unbound through plasma. Progesterone administration achieves improvement in lipid and lipoprotein profiles and when combined with oestrogen therapies indicates no increased risk of endometrial hyperplasia (3, 4) and may prevent breast epithelial hyperplasia (5).

**INDICATIONS:** PRO-FEME™ is indicated in progesterone deficient conditions. Progesterone deficiency is associated with natural or surgical menopause, pre-menstrual syndrome (PMS), breast cancer, ovarian cysts, uterine fibroids, endometrial hyperplasia and associated oestrogen dependent malignancies, fibrocystic breasts, post-natal depression and endometriosis.

**PRO-FEME™ is not a substitute for oestrogen replacement therapy.**

**CONTRA-INDICATIONS:** Progesterone should not be used by women with any of the following conditions:

- Severe liver disease ie. cholestatic jaundice, Rotor syndrome or Dubin-Johnson syndrome
- Any unexplained abnormal vaginal bleeding
- History of herpes gestationis, jaundice of pregnancy
- Known sensitivity to PRO-FEME™ cream or any of its individual components

**ADVERSE REACTIONS:** Because PRO-FEME™ contains the hormone identical to that produced by the human ovary side effects are usually minimal. If experienced these may include breast tenderness and swelling, fluid retention or slight vaginal bleeding. Dizziness, nausea, fatigue, headache and light headedness have been reported occasionally and usually disappear with adjustment of dose.

**USE IN PREGNANCY:** Progesterone is the hormone essential for promotion and maintenance of pregnancy. Ovarian output of progesterone in the non-pregnant state is 25-30mg daily during the luteal phase. The placental output during the third Trimester of pregnancy is 350-400 mg per day. Where as progestagens are contraindicated in pregnancy progesterone exhibits no adverse effects on the fetus.

**DRUG INTERACTION: Thyroid stimulating agents** Potential interaction exists in patients using thyroid supplementation. Progesterone may cause a potentiation of thyroxine's effects leading to hyperthyroidism. Normal T3 and T4 levels with elevated TSH suggests impaired thyroid hormone activity rather than insufficiency. Periodical TSH testing should be adopted on initiation of progesterone treatment in these patients.

**DOSAGE AND ADMINISTRATION General considerations A) Distribution:**

Maximum absorption is achieved by using PRO-FEME™ over a large skin area. Skin site of choice are the inner arms, neck and upper chest, abdomen and inner thighs on a rotating basis. PRO-FEME™ can be applied to the breasts. Progesterone is first absorbed into the subcutaneous fat layer then passively diffuses throughout the body via the circulation. The rate which this is achieved is dependant on the amount of body fat. In general most significant physiological results are not experienced by patients until the fourth

to sixth week of usage. In women using oestrogen supplements the initial effect of progesterone is to sensitise oestrogen receptors. A reduction in oestrogen dosage may be required should breast swelling and tenderness, fluid retention or scant bleeding result.

**WARNING: To date, PRO-FEME™ cream has not been shown to be protective against oestrogen-induced endometrial hyperplasia. Caution should be exercised and patients monitored if combination therapy is to be initiated.**

In peri-menopausal women with irregular menstrual flows the addition of PRO-FEME™ may result in a return of menses. This may lead to the conclusion that progesterone caused the menses when in fact oestrogen created the endometrial proliferation and the cessation of progesterone allowed for shedding of this proliferation. This effect is normal and there is no reason to cease using PRO-FEME™.

**B) Cycling** In a normal menstrual cycle progesterone is produced as the dominant hormone for approximately fourteen days per cycle. Receptor stimulation is not continuous. Aim of treatment is to mimic natural ovarian production as much as possible, thus monthly cycling is recommended. In post menopausal women progesterone should be used for 21 - 25 days per calendar month followed by a 5 - 7 day progesterone free state. In peri-menopausal women administration should be synchronised with normal corpus luteal progesterone production ie. day 12 to day 26 of the menstrual cycle. If, after initiating treatment, menstruation occurs after 5-10 days it is recommended to cease application of PRO-FEME™ and re-commence 12 days later.

**C) Eligibility** All women, regardless of whether the uterus is intact or not, exhibiting signs of oestrogen imbalance have a requirement for progesterone. Hysterectomized women are not exempt from using PRO-FEME™. PRO-FEME™ cream is available in two strengths 3.2% and 10% w/w. Dosage should be tailored to individual requirements and the patient reviewed on a regular basis. Dosage adjustments may be made by altering the volume of cream applied or alteration of the percentage strength prescribed. When applying PRO-FEME™ use the supplied measured applicator to achieve correct dosage. Squeeze the necessary amount of cream from the tube onto the applicator, then place the applicator with the cream side down onto the site of application. Massage the cream over desired area until absorbed.

#### USUAL THERAPEUTIC DOSES

**Menopausal Women:** Apply 2 units of PRO-FEME™ 3.2% cream (32mg progesterone) daily or in divided doses for 25 days per calendar month.

**Peri-menopausal:** Apply 2 units of PRO-FEME™ 3.2% cream (32mg progesterone) daily or in divided doses from day 12-26 days of menstrual cycle.

**Pre-menstrual Syndrome:** Apply 2 units of PRO-FEME™ 3.2% cream (32mg progesterone) daily or in divided doses from day 12-26 of cycle. Significant alterations to this dose may be made to achieve a crescendo effect 4-5 days prior to menses.

**Endometriosis or Post Natal Depression:** Apply 3 units of PRO-FEME™ 10% w/w cream (150mg progesterone) daily or in individual doses for 21 days per calendar month.

NOTE: Amount and duration of application must be tailored to individual requirements.

**OVERDOSAGE:** Toxicity of progesterone is extremely low. No specific antidote is available.

#### PRESENTATION:

PRO-FEME™ 3.2% cream containing 32mg/g progesterone BP 50gm boxed tube. PRO-FEME™ 10% cream containing 100mg/g progesterone BP 50gm boxed tube.

**STORAGE:** Store below 25°C DO NOT FREEZE

**POISONS SCHEDULE:** S4

**SPONSOR** Lawley Pharmaceuticals Address 61 Walcott St Mt Lawley 6050 Postal Address PO Box 448 Mt Lawley Perth 6929 Australia  
Phone 08 9228 9033 Fax 08 9228 9455  
Website: [www.lawleypharm.com.au](http://www.lawleypharm.com.au)  
Email: [info@lawleypharm.com.au](mailto:info@lawleypharm.com.au)

#### REFERENCES

- (1) M. Holzbauer: The Association of Steroids with blood cells in vivo. J. Steroid Biochem. 3:579-92. 1972.
- (2) E. Ohtsuka and S.S. Koide: Incorporation of Steroids into human, dog and duck erythrocytes. Gen Camp Endo 12: 598-603, 1969.
- (3) J. Hargrove: Menopausal Hormone Replacement Therapy with Continuous Daily Oral Micronized Estradiol and Progesterone Obstet Gynecol 73:4: 606-12. 1989.
- (4) The Writing Group for the PEPI Trial: Effects of Hormone Replacement Therapy on Endometrial Histology In Postmenopausal Women JAMA 275:5:371-5, 1996.
- (5) K-J Chang: Influence of percutaneous administration of oestradiol and progesterone on human breast epithelial cell cycle in vivo Fertil Steril 63: 4:785-91, 1995.