

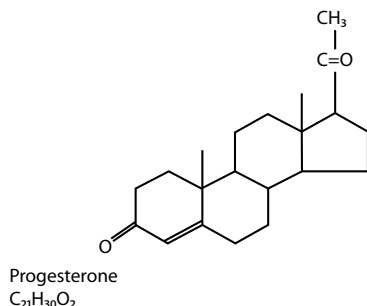
PRODUCT INFORMATION

Composition Active: Progesterone B.P.

Chemical Name: Prog -4 -ene - 3.20 dione

Molecular Weight: 314.47

CAS: 57-83-0



Description

PROFEME® is a transdermal drug delivery system consisting of a white oil-in-water 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, B&J Phenonip® and purified water. PROFEME® contains the naturally occurring hormone progesterone.

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 estradiol, the estrogenic hormone secreted by the ovary. Progesterone has minimal estrogenic 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 pregnanediol, pregnenadone and pregnanediol 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 estrogen therapies indicates no increased risk of endometrial hyperplasia^{3,4} and may prevent breast epithelial hyperplasia⁵.

Indications

PROFEME® is indicated in progesterone-deficient conditions. Progesterone deficiency is associated with natural or surgical menopause, premenstrual syndrome (PMS), breast cancer, ovarian cysts, uterine fibroids, endometrial hyperplasia and associated estrogen-dependent malignancies, fibrocystic breasts, post-partum depression, repeat first-term miscarriages and endometriosis. PROFEME® is not a substitute for estrogen replacement therapy.

Contraindications

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 PROFEME® cream or any of its individual components

Adverse Reactions

Because PROFEME® 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. Whereas 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 PROFEME® over a large skin area. The optimal skin sites to apply PROFEME® progesterone cream are to the inner aspects of the arms and the upper thigh. Other areas suitable for use include the abdomen and upper chest/neck.

Progesterone is first absorbed into the subcutaneous fat layer then passively diffuses throughout the body via the circulation. The rate at 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 estrogen supplements the initial effect of progesterone is to sensitise estrogen receptors. A reduction in estrogen dosage may be required should breast swelling and tenderness, fluid retention or scant bleeding result.

WARNING: To date, PROFEME® cream has not been shown to be protective against estrogen-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 PROFEME® may result in a return of menses. This may lead to the conclusion that progesterone caused the menses when in fact estrogen created the endometrial proliferation. This effect is not abnormal when starting PROFEME® and there is no reason to cease use of PROFEME®.

PRODUCT INFORMATION (cont'd)

B) Cycling: In a normal menstrual cycle progesterone is produced as the dominant hormone for approximately fourteen days per cycle (luteal phase). Progesterone 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 perimenopausal 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 PROFEME® and re-commence 12 days later.

C) Eligibility: All women, regardless of whether the uterus is intact or not, exhibiting signs of estrogen imbalance (estrogen dominance) have a requirement for progesterone. Hysterectomized women are not exempt from using PROFEME®. PROFEME® 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 PROFEME® use the supplied graduated applicator to achieve correct dosage. Massage the cream until completely absorbed.

Usual Therapeutic Doses

Menopausal women.

Apply 1ml of PROFEME® 3.2% cream via measured applicator (32mg progesterone) daily or in divided doses for either 25 days per calendar month or for 3 weeks on and 1 week off. Symptoms abate in 2nd or 3rd month of use.

Perimenopausal women.

Apply 1ml of PROFEME® 3.2% cream via measured applicator (32mg progesterone) daily or in divided doses from day 12-26 of each menstrual cycle. If a menstrual period starts prior to day 26 cease using PROFEME® and consider the first day of bleeding as Day 1 of the new cycle. This is a common occurrence when initiating treatment in perimenopausal women and should be considered a sign that the treatment is having a positive effect. Symptoms abate in 2nd or 3rd month of use.

Premenstrual syndrome (PMS).

Apply 1ml of PROFEME® 3.2% cream via measured applicator (32mg progesterone) daily or in divided doses from day 12-26 of each menstrual cycle. Significant alterations to this dosage may be made to achieve a crescendo effect 4-5 days prior to menses. Symptoms abate in 2nd or 3rd month of use.

Premenstrual dysphoric disorder (PMDD).

(Use PROFEME® 10%)

Apply 0.5 - 1ml of PROFEME® 10% cream via measured applicator (50-100mg progesterone) daily or in divided doses from day 12-26 of each menstrual cycle. Significant alterations to this dosage may be made to achieve a crescendo effect 4-5 days prior to menses. Symptoms abate in 2nd or 3rd month of use.

Endometriosis, Menorrhagia and Post partum depression.

(Use PROFEME® 10%)

Apply 1.0 - 2.0ml of PROFEME® 10% cream via measured applicator (100-200mg progesterone) daily or in divided doses depending upon the severity of the condition. In reproductive cyclical women initiate treatment on a day 12-26 basis, but can increase frequency to 3 week in 4 if symptoms/pain emerge upon withdrawal.

Infertility/Repeated First-term Miscarriage.

(Use PROFEME® 10%)

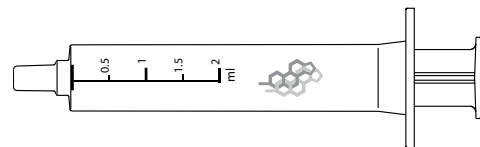
Luteal phase and first trimester corpus luteal support. Apply 1ml of PROFEME® 10% cream (100mg progesterone) daily or in divided doses via measured applicator from day 12-26 of each cycle until pregnancy is confirmed and then 1-2ml daily on a continuous basis until at least week 13 or until full term.

Note: Amount and duration of application for all conditions must be tailored to individual requirements.

Presentation

PROFEME® is available in two strengths, 3.2% and 10%.

PROFEME® 3.2% cream contains 32mg/mL progesterone BP in a 50ml boxed tube. PROFEME® 3.2% is supplied with a dose measuring applicator calibrated in 0.5ml graduations. The patient should measure the appropriate dose using the applicator and apply directly to the skin massaging until absorbed. Directions for use of the applicator are contained within the box.



Overdosage

Toxicity of progesterone is extremely low.

Storage

Store below 25°C. DO NOT FREEZE.

Shelf-life under these conditions is 2 years.

Sponsor

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PROFEME® 3.2% cream AUST L 66355

PROFEME® 10% cream AUST L 95335

Date of Preparation: May 2011

PROFEME® is registered trademark.

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 estradiol and progesterone on human breast epithelial cell cycle in vivo Fertil Steril 63; 4:785-91, 1995.