

PROMETRIUM 100 AND 200 MG, SOFT CAPSULE
DRAFT PRODUCT INFORMATION

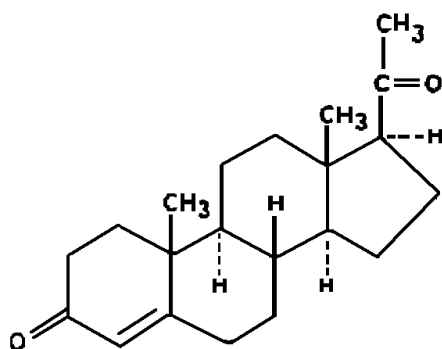
PRODUCT INFORMATION

PROMETRIUM 100 and 200 mg (For Oral Use)

NAME OF THE MEDICINE

Progesterone (micronised) 100 and 200 mg, soft capsule

Progesterone



Chemical name: Pregn-4-ene-3,20-dione

Molecular formula: $C_{21}H_{30}O_2$.

MW: 314.5

CAS: 57-83-0.

DESCRIPTION

Progesterone: is a white or almost white crystalline powder or colourless crystals. Is practically insoluble in water, freely soluble in ethanol and sparingly soluble in acetone and in fatty oils.

The capsules contain the following active ingredient: Progesterone (micronised) 100 mg or 200 mg. They also contain sunflower oil, soya lecithin, gelatin, glycerol and titanium dioxide.

PHARMACOLOGY

Pharmacodynamics

Progesterone is a naturally occurring steroid hormone that is secreted by the ovary, placenta and adrenal gland. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone is necessary to increase endometrial receptivity for implantation of an embryo, and once an embryo is implanted, progesterone acts to maintain the pregnancy. As well as gestagenic actions, progesterone also has anti-estrogenic, slightly anti-androgenic and anti-aldosterone effects.

Pharmacokinetics

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Absorption

After oral administration of progesterone as a micronised soft-gelatin capsule formulation, maximum serum concentrations were attained within 3 hours. The absolute bioavailability of micronised progesterone is not known. A bioavailability of 8.6% for the oral capsule of progesterone relative to the intramuscular dosage is suggested. Table 1 summarizes the mean pharmacokinetic parameters in postmenopausal women after five oral daily doses of PROMETRIUM Capsules 100 mg as a micronised soft-gelatin capsule formulation.

TABLE 1. Pharmacokinetic Parameters of PROMETRIUM

Parameter	PROMETRIUM Capsules Daily Dose		
	100 mg	200 mg	300 mg
C _{max} (ng/mL)	17.3 ± 21.9 ^a	38.1 ± 37.8	60.6 ± 72.5
T _{max} (hr)	1.5 ± 0.8	2.3 ± 1.4	1.7 ± 0.6
AUC (0-10) (ng × hr/mL)	43.3 ± 30.8	101.2 ± 66.0	175.7 ± 170.3

^a Mean ± S.D.

Serum progesterone concentrations appeared linear and dose proportional following multiple dose administration of PROMETRIUM Capsules 100 mg over the dose range 100 mg per day to 300 mg per day in postmenopausal women. Although doses greater than 300 mg per day were not studied in females, serum concentrations from a study in male volunteers appeared linear and dose proportional between 100 mg per day and 400 mg per day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

Pharmacokinetic studies conducted in healthy volunteers have shown that after oral administration of two 100 mg capsules (200 mg), plasma progesterone levels increased to reach the C_{max} of 13.8 ng/ml +/- 2.9 ng/ml in 2.2 +/- 1.4 hours.

Although there were inter-individual variations, the individual pharmacokinetic characteristics were maintained over several months, indicating predictable responses to the drug.

Distribution

Progesterone is approximately 96-99% bound to serum proteins, primarily to serum albumin (50-54%) and transcortin [corticosteroid binding globulin] (43-48%).

Metabolism

Progesterone is metabolised primarily by the liver. Following oral administration, the main plasma metabolites are 20 α hydroxy- Δ 4 α -prenolone and 5 α -dihydroprogesterone. Some progesterone metabolites are excreted in the bile and these may be deconjugated and further metabolised in the gut via reduction, dehydroxylation and epimerisation.

The main plasma and urinary metabolites are similar to those found during the physiological secretion of the corpus luteum.

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Following vaginal administration, only low plasma levels of pregnanolone and 5 α -dihydroprogesterone are detected, due to the lack of first-pass metabolism.

Excretion

Urinary elimination is observed for 95% in the form of glycuconjugated metabolites, mainly 3 α , 5 β -pregnanediol (pregnandiol).

CLINICAL TRIALS

Adjunctive use with an oestrogen in postmenopausal women with an intact uterus (for hormone replacement therapy [HRT])

Three company-sponsored studies have been conducted to investigate efficacy of Prometrium during hormone replacement therapy.

1. Study Lorrain 1994 was an open-label, single-centre, randomised, parallel-group, prospective trial that evaluated and compared the efficacy, safety and tolerance of Prometrium and medroxyprogesterone acetate (MPA) in menopausal women receiving transdermal oestradiol for a period of at least 13 cycles.

This clinical study was an open-label, single-centre, randomised, parallel-group, prospective trial. Postmenopausal women were randomised to treatment with Prometrium 200 mg/day (two 100 mg oral tablets taken at bedtime) or MPA (Provera) 10 mg/day (one 10 mg tablet taken at bedtime). Prometrium or MPA were taken from Day 14 to Day 25. All women received 17- β -estradiol 0.05 mg/day patches that were applied twice weekly from Day 1 to Day 25.

The efficacy outcome measures assessed were bleeding patterns. A total of 40 women were randomised to receive Prometrium (n=20) or MPA (n=20). The incidence of amenorrhic cycles was greater in women treated with Prometrium (42/215 cycles, 19.5%) versus MPA (6/178, 3.4%). The incidence of breakthrough bleeding was similar in women treated with Prometrium (7/222, 3.2%) versus MPA (8/181, 4.4%).

Menstruation occurred earlier, was less abundant, and of shorter duration in women treated with Prometrium versus MPA (Table 2)

Table 2: Mean \pm SD onset, intensity, and duration of menses

Pattern	Prometrium	MPA	P-value
Cycle day of onset (mean \pm SD)	23.1 \pm 2.4	24.9 \pm 2.4	0.0001
Bleeding intensity (total score*)	9.6 \pm 5.9	11.3 \pm 5.5	0.0087
Bleeding duration (days)	4.8 \pm 2.5	6.0 \pm 2.4	0.0001

* from 0 to 4, 0 = none, 1 = spotting, 2 = light, 3 = moderate, 4 = important.
Abbreviations: MPA, medroxyprogesterone acetate; SD, standard deviation.

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In conclusion, the use of Prometrium (progesterone) for postmenopausal HRT produced more desirable bleeding patterns than MPA.

2. Study Moyer 1987 was a 5-year, open-label, non-controlled, single-centre, observational study that evaluated the endometrial situation of patients who regularly used combinations of Oestrogen (E₂) and Prometrium (P) for at least 5 years. The primary outcome for this study was endometrial histology in response to treatment with HRT.

This was a 5-year, open-label, non-controlled, single-centre, observational study. Women were administered combinations of percutaneous oestrogen (Oestrogen) at either 1.5 mg/day or 3 mg/day on Days 1 to 21 of their cycle and oral Prometrium capsules at either 200 mg/day or 300 mg/day on Days 8 to 21 of their cycle for at least 5 years. Initially, women were administered Oestrogen 1.5 mg/day plus Prometrium 200 mg/day. The dose of Oestrogen was increased to 3.0 mg/day if optimal improvement in clinical menopause symptoms was not obtained within the first 6 months of treatment. The dose of Prometrium was increased to 300 mg/day if cyclic withdrawal bleeding was not occurring during the first 6 months of treatment and women preferred cyclic withdrawal bleeding.

In conclusion, Oestrogen and Prometrium resulted in favourable bleeding patterns with higher doses of Oestrogen and Prometrium resulting in a higher incidence of cyclic bleeding.

3. Study Christiansen 1985 was a single-centre, double-blind (1st year) then single-blind (2nd year), randomised, parallel-group study that compared and evaluated the efficacy and safety of percutaneous oestradiol versus placebo and calcium as prophylaxis of symptoms in early postmenopausal women.

For the oestradiol cream (Oestrogen 60 mg oestradiol per 100 g gel), 5 grams was applied topically from Days 1 to 24 of the woman's cycle. The oestradiol gel, Ca²⁺ tablet, and matching placebos were supplied double blind.

In the 2nd year of the study, progesterone (Prometrium 100 mg oral capsules) was added to the treatment regimen for Groups I and II. Women were instructed to take two Prometrium 100 mg capsules at bedtime from Days 13 to 24 of their cycle. Progesterone was dispensed open label.

Enrolled women were healthy women 45 to 54 years of age who had experienced a spontaneous menopause in the previous 6 months to 3 years.

The primary outcome measures assessed were the evaluation of menopausal symptoms using the Kupperman index.

The Kupperman index was based on 11 symptoms of menopause: hot flushes, paraesthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgias/myalgias, headaches, palpitations and formication. In the calculation of this index, some of the symptoms are weighted: hot flushes (x4), paraesthesias (x2), insomnia (x2), and nervousness (x2). The maximum score was 51 and the severity of symptoms was scored on a scale of 0 (none) to 3 (severe).

Overall, the median percent decrease in Kupperman score from baseline was greatest for Groups I and II (Table 3). After 3 months of treatment, there were statistically significant differences among groups in the median percent decrease from baseline. Both Groups I and II had significantly greater improvements in their scores compared with Groups III and IV ($P=0.0033$). Significantly greater improvements were also recorded at 18 months for Groups I and II compared with Groups III and IV ($P=0.0377$). However, there were no statistically significant differences among groups at 6, 9,

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12, 15, 21 or 24 months. The addition of progesterone to the treatment regimen in Groups I and II at 12 months did not appear to have any significant effect on the menopausal symptoms.

Table 3: Median percent decreases from baseline by treatment and visit in women receiving Oestrogel, with and without calcium, or placebo

Months	Placebo	Calcium Only	Oestrogel Only	Oestrogel + Calcium
3*	10.0	0.0	62.5	71.4
6	33.3	52.6	66.7	75.0
9	0.0	26.3	43.8	66.7
12	0.0	28.6	40.0	66.7
15	40.0	37.5	66.7	85.7
18*	20.0	15.8	66.7	87.5
21	16.3	10.5	62.5	78.6
24	33.3	15.8	50.0	87.5

* Statistical significance between treatments ($P < 0.05$).

In conclusion, percutaneous Oestrogel is effective and safe in the prophylaxis of menopausal symptoms. The addition of calcium or progesterone does not have any appreciable effect on these symptoms.

Findings from the efficacy analysis provided strong evidence for the use of oral progesterone in combination with oestrogen for HRT in postmenopausal women with an intact uterus. These findings were based primarily on the pivotal company-sponsored studies showing favourable bleeding patterns with Prometrium and a Cochrane review and meta-analysis of data from placebo-controlled RCTs^[MacLennan et al, 2004], which was considered to be of high quality. Findings from the meta-analysis of 6 placebo-controlled RCTs showed a significant reduction in the frequency and severity of hot flushes in peri or postmenopausal women receiving oral oestrogen in combination with progestogens compared with placebo for at least 3 months. The most recent guidelines from the British Menopause Society^[Panay et al, 2013] recommend that transdermal preparations should be used in high-risk women who require HRT and that micronised progesterone or dydrogesterone are suitable options when a progestogen is required. Overall, the aim is to replace hormones to as close to physiological levels as possible.

The body of evidence from national guidelines from Australia^[RANZCOG, 2011], Canada^[Reid et al, 2009], and the US^[NAMS, 2012], and international guidelines^[de Villiers et al, Mauritius 2013, de Villiers et al, 2013] suggest that HRT is the most effective treatment for controlling menstrual cycles and for reducing vasomotor symptoms, including hot flushes and night sweats, in postmenopausal women with an intact uterus.

Menstrual irregularities due to ovulation disorders or anovulation

Study Simon 1988^[52, 53] was a single-centre, double-blind, placebo-controlled phase III study that assessed the efficacy and safety of Prometrium 200 and 300 mg with placebo in the initiation of withdrawal bleedings in nonmenopausal patients with 2° amenorrhoea.

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The aim of this clinical study was to compare the efficacy of Prometrium with placebo for the initiation of withdrawal bleeding in women with secondary amenorrhoea.

The primary outcome was the initiation of withdrawal bleeding. Withdrawal bleeding was defined as any bleeding or blood stained discharge from the vagina during the withdrawal interval. The withdrawal interval was defined as the time from the beginning of treatment up to, and including, 1 week after the final dose. The number of days until bleeding occurred was determined by computing the number of days between the first dose of medication and the initiation of withdrawal bleeding. The maximum number of days allowed to be considered as a positive response was 16 days.

The percentage of women experiencing withdrawal bleeding in the 3 groups was 53% (10/19) in the Prometrium 200 mg group, 90% (18/20) in the Prometrium 300 mg group and 24% (5/21) in the placebo group (Table 4). The differences between the Prometrium 300 mg group and Prometrium 200 mg group, and the Prometrium 300 mg group and placebo, were both statistically significant. The difference between the Prometrium 200 mg group and placebo was not statistically significant. However, when the analysis was expanded to include all women who had bleeding within 30 days of starting treatment, there was a significant difference between the Prometrium 200 mg group and placebo.

Table 4: Bleeding response in women receiving Prometrium 300 mg, Prometrium 200 mg, or placebo

Variable	Prometrium 300 mg	Prometrium 200 mg	Placebo
Bleeders	18	10	5
Spotters	0	1	1
Delayed bleeders*	0	2	3
Nonbleeders	2	6	12
Total	20	19	21

* Delayed bleeders had onset of bleeding >16 days after initiating treatment.

In conclusion, both Prometrium 200 mg and 300 mg were effective in the initiation of withdrawal bleeding in women with secondary amenorrhoea.

One literature study (a Cochrane systematic review) was retrieved from the systematic search. Findings from this systematic review of the literature, published in 2012^[88], indicated that no high quality evidence currently exists for this indication and that further research is needed to establish the role of progesterone in the management of menstrual irregularities. No RCTs are available to provide strong evidence of a beneficial effect of progesterone in the treatment of menstrual irregularities, primarily due to ovulation disorders and anovulation. However, anecdotal information and limited clinical data do suggest that progesterone does have a beneficial effect when used to treat menstrual irregularities. Progestogens, including Prometrium, are widely used, alone or in combination with oestrogens, and are authorised in many countries for this indication. The regimen, dose and type of progestogen used vary widely, with little consensus about the optimum treatment approach. The weakness in the data does not preclude treatment where, in the judgment of the physician, progesterone, alone or in combination with oestrogen, could help with symptomatic control.

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INDICATIONS

Prometrium 100 and 200 mg, soft capsules are indicated for:

Treatment of menstrual irregularities

- In women with menstrual abnormalities or secondary amenorrhoea due to normogonadotrophic amenorrhoea (see dosage and administration)

Hormone replacement therapy

- Hormone replacement therapy – adjunctive use with an oestrogen in postmenopausal women with an intact uterus

CONTRAINDICATIONS

Prometrium should not be used in individuals with any of the following conditions:

- Known allergy or hypersensitivity to progesterone or to any of the excipients.
- Severe hepatic dysfunction.
- Undiagnosed vaginal bleeding.
- Known missed abortion or ectopic pregnancy
- Mammary or genital tract carcinoma.
- Thromboembolic disorders.
- Thrombophlebitis
- Cerebral haemorrhage.
- Porphyria.

PRECAUTIONS

The use of oral Prometrium is not a treatment for premature labour.

During pregnancy, progesterone should only be used during the first three months and only by the vaginal route. Prescription of progesterone beyond the first trimester of pregnancy may reveal gravidic cholestasis.

Prometrium is not suitable for use as a contraceptive.

If unexplained, sudden or gradual, partial or complete loss of vision, proptosis or diplopia, papilloedema, retinal vascular lesions or migraine occur during therapy, the drug should be discontinued and appropriate diagnostic and therapeutic measures instituted.

Prometrium is intended to be co-prescribed with an oestrogen product as HRT. Epidemiological evidence suggests that the use of HRT is associated with an increased risk of developing deep vein thrombosis (DVT) or pulmonary embolism. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of venous thromboembolism.

There is suggestive evidence of a small increased risk of breast cancer with oestrogen replacement therapy. It is not known whether concurrent progesterone influences the risk of cancer in post-

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menopausal women taking hormone replacement therapy. The prescribing information for the co-prescribed oestrogen product should be referred to for information about the risks of breast cancer.

Prior to taking hormone replacement therapy (and at regular intervals thereafter) each woman should be assessed. A personal and family medical history should be taken and physical examination should be guided by this and by the contraindications and warnings for this product. Prometrium should not be taken with food and should be taken at bedtime. Concomitant food ingestion increases the bioavailability of Prometrium.

Prometrium should be used cautiously in patients with conditions that might be aggravated by fluid retention (e.g. hypertension, cardiac disease, renal disease, epilepsy, migraine, asthma); in patients with a history of depression, diabetes, mild to moderate hepatic dysfunction, migraine or photosensitivity and in breast-feeding mothers.

Clinical examination of the breasts and pelvic examination should be performed where clinically indicated rather than as a routine procedure. Women should be encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical cancer screening programme (cervical cytology) as appropriate for their age. Breast awareness should also be encouraged and women advised to report any changes in their breasts to their doctor or nurse.

Prometrium contains soya lecithin which may cause hypersensitivity reactions (urticaria and anaphylactic shock).

Effects on fertility

Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Use in Pregnancy (Category A)

Prometrium should be ceased as soon as pregnancy is confirmed unless otherwise prescribed by the treating physician. Progesterone crosses the placenta. Data from clinical studies and post market adverse event reporting has not found an association between the use of progesterone in human pregnancy and fetal malformations. Male and female genital abnormalities (hypospadias and virilisation) have been observed in fetuses of animals treated with progesterone during gestation.

Use in Lactation

Detectable amounts of progesterone enter the breast milk. There are no indications for HRT during lactation.

Paediatric Use

There is no experience in children as there is no relevant indication for use of Prometrium in children

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Use in the Elderly

No clinical data have been collected in patients over age of 65.

Effects on ability to drive and use machines

Cases of drowsiness and dizzy sensations have been reported for the oral form.

Drivers and machine operators in particular are alerted to the risks of drowsiness and/or dizziness associated with oral use of this medicinal product. These problems can be avoided by taking the capsules at bedtime.

Genotoxicity

Progesterone did not induce chromosomal aberrations or sister chromatid exchanges in cultured human cells nor chromosomal aberrations or DNA strand breaks in rodent cells. Progesterone did not induce dominant lethal mutations in mice or chromosomal aberrations in the bone marrow of rats in vivo although in vivo studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg.

Weak clastogenic activity was found for progesterone in the rat hepatocyte micronucleus test after treatment with a high oral dose (100 mg/kg). Studies on transformation of rodent cells in vitro were inconclusive. Variable results were obtained in the mouse lymphoma tk assay. Progesterone was not mutagenic to bacteria.

Carcinogenicity

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. Progesterone has been shown to induce/promote the formation of ovarian, uterine, mammary, and genital tract tumours in animals. The clinical relevance of these findings is unknown. Literature data provides no indication of potential carcinogenicity in humans.

When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen.

Effect on laboratory tests

Prometrium may affect the results of laboratory tests of hepatic and/or endocrine functions.

INTERACTIONS WITH OTHER MEDICINES

Progesterone is metabolised primarily by the liver. Caution should be taken with drugs that are P450 enzyme inducers and inhibitors.

Metabolism of Prometrium is accelerated by rifamycin an antibacterial agent.

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC₅₀<0.1 µM), a known inhibitor of cytochrome P450 3A4. These data therefore suggest that ketoconazole may increase the bioavailability of progesterone. The clinical relevance of the in vitro findings is unknown.

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Combination with other medicinal products may decrease progesterone metabolism which may alter its effect.

This applies to:

- potent enzyme inducers such as barbiturates, antiepileptics (phenytoin), rifampicin, phenylbutazone, spironolactone and griseofulvin. These medicinal products increase hepatic metabolism.
- some antibiotics (ampicillins, tetracyclines): changes in the intestinal flora leading to a change in the steroid enterohepatic cycle.

Prometrium may interfere with the effects of bromocriptine and may raise the plasma concentration of ciclosporin.

As these interactions may vary between people, the clinical results are not necessarily predictable.

Progestogens, but not natural progesterone may impair glucose tolerance and, because of this, increase requirements for insulin or other antidiabetic agents in diabetic patients.

The bioavailability of progesterone may be reduced by smoking and increased by alcohol abuse.

ADVERSE EFFECTS

Somnolence or transient dizziness may occur 1 to 3 hours after intake of the drug. Bedtime dosing and reduction of the dose may reduce these effects.

Shortening of the cycle or breakthrough bleeding may occur. If this occurs, the dose of Prometrium can be reduced and taken at bedtime from day 1 to day 26 of each therapeutic cycle.

Acne, urticaria, rashes, fluid retention, weight changes, gastro-intestinal disturbances, changes in libido, breast discomfort, premenstrual symptoms, menstrual disturbances; also chloasma, depression, pyrexia, insomnia, alopecia, hirsutism; rarely jaundice.

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users.

The following effects have been reported for Prometrium administered **orally**:

System organ class	Common adverse effects $\geq 1/100$; $< 1/10$	Uncommon adverse effects $\geq 1/1000$; $< 1/100$	Rare adverse effects $(\geq 1/10,000$; $< 1/1000$)	Very rare adverse effects $\leq 1/10,000$
Reproductive system and breast disorders	Altered periods . Amenorrhoea . Intercurrent bleeding	. Mastodynia		
Nervous system disorders	. Headache	. Drowsiness . Fleeting dizzy		. Depression

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System organ class	Common adverse effects $\geq 1/100$; $< 1/10$	Uncommon adverse effects $\geq 1/1000$; $< 1/100$	Rare adverse effects ($\geq 1/10,000$; $< 1/1000$)	Very rare adverse effects $\leq 1/10,000$
		sensations		
Gastrointestinal disorders		. Vomiting . Diarrhoea . Constipation	. Nausea	
Hepatobiliary disorders		. Cholestatic jaundice		
Immune system disorders				. Urticaria
Skin and subcutaneous tissue disorders		. Pruritus . Acne		. Chloasma

Drowsiness and/or fleeting dizzy sensations are seen particularly with concomitant hypoestrogenism. These effects disappear immediately without compromising the benefit of treatment when doses are reduced or oestrogenization is increased.

If the treatment sequence is started too early in the month, particularly before the 15th day of the cycle, the cycle may be shortened or intercurrent bleeding may occur.

Changes in periods, amenorrhoea or intercurrent bleeding have been observed and associated with the use of progesterones in general.

DOSAGE AND ADMINISTRATION

In women receiving oestrogen replacement therapy with intact uterus, the adjunctive use of progesterone at a dose of 200 mg daily at bedtime should be administered for twelve days in the last half of each therapeutic cycle (beginning on day 15 of the cycle and ending on day 26). Withdrawal bleeding may occur in the following week. Alternatively 100 mg can be given at bedtime from day 1 to day 25 of each therapeutic cycle, withdrawal bleeding being less with this treatment schedule.

In women with secondary amenorrhoea, the treatment may be given as a single daily dose of 400 mg (2 capsules 200 mg) at bedtime for 10 days. Prior to use for this indication, other causes of secondary amenorrhoea such as outflow obstruction, pregnancy, prolactinoma, thyroid disorders, pituitary and hypothalamic disorders should be excluded.

The standard daily dosage regimen is 200 to 300 mg of progesterone taken in one or two doses (i.e. 200 mg in the evening before retiring and another 100 mg in the morning, if needed). In menstrual irregularities due to ovulation disorders or anovulation, the treatment is administered over 10 days per menstrual cycle, usually from **cycle days 17 to 26** inclusive.

Children: Not applicable.

Elderly: As for Adults

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Method of Administration: Oral. Prometrium should not be taken with food.

Overdose

Symptoms of overdose may include somnolence, dizziness, euphoria or dysmenorrhoea. Treatment is observation and, if necessary, symptomatic and supportive measures should be provided.

The usual dosage may be excessive in some people because of persistence or recurrence of unstable endogenous progesterone secretion, and some people with particular sensitivity to progesterone or excessively low concomitant blood oestradiol concentrations. In these situations:

- the dosage should be reduced or the progesterone should be administered IN THE EVENING AT BEDTIME, 10 days per cycle, if drowsiness or fleeting dizziness occurs.
- treatment should be started later in the cycle (such as on day 19 instead of day 17) if the cycle is shortened or spotting occurs.
- check that oestradiol concentration is sufficient in the perimenopausal period and in hormone replacement therapy in postmenopause.

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26) for advice.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Prometrium 100 mg, soft capsule is a round, slightly yellow, soft capsule containing a whitish oily suspension.

Prometrium 200 mg, soft capsule is an ovoid slightly yellow, soft capsule, containing a whitish oily suspension.

Prometrium 100 mg and 200 mg, soft capsule are supplied in a PVC/Aluminium blisters packaged in an outer carton.

Prometrium 100 mg is available in pack sizes of 14, 15, 28, 30, 56, 84 or 90 capsules*

Prometrium 200 mg is available in pack sizes of 7, 14, 15, 21, 28, 30, 42, 45, 56, 84 or 90 capsules*.

* not all pack sizes are currently marketed

Storage

Store below 30°C.

Do not refrigerate.

Store in the original container.

NAME AND ADDRESS OF THE SPONSOR

Besins Healthcare Australia Pty Ltd,

Attachment 1: Product information for AusPAR Prometrium / Utrogestan Besins Healthcare Australia Pty Ltd PM-2014-03908-1-5 Final 1 June 2017 This Product Information was approved at the time this AusPAR was published.

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Level 23 Governor Macquarie Tower
1 Farrer Place,
Sydney NSW 2000

Prometrium 100 mg, soft capsule – AUSTR: 232818

Prometrium 200 mg, soft capsule – AUSTR: 232823

POSITION SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

Xx xxxx xxxxx