PROMETRIUM®
(progesterone, USP)
Capsules 100 mg
Capsules 200 mg

WARNING: CARDIOVASCULAR DISORDERS, BREAST CANCER AND PROBABLE DEMENTIA FOR ESTROGEN PLUS PROGESTIN THERAPY

Cardiovascular Disorders and Probable Dementia

Estrogens plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Probable dementia**.)

The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders**.)

The WHI Memory Study (WHIMS) estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women. (See **CLINICAL STUDIES** and **WARNINGS, Probable dementia** and **PRECAUTIONS, Geriatric Use**.)

Breast Cancer

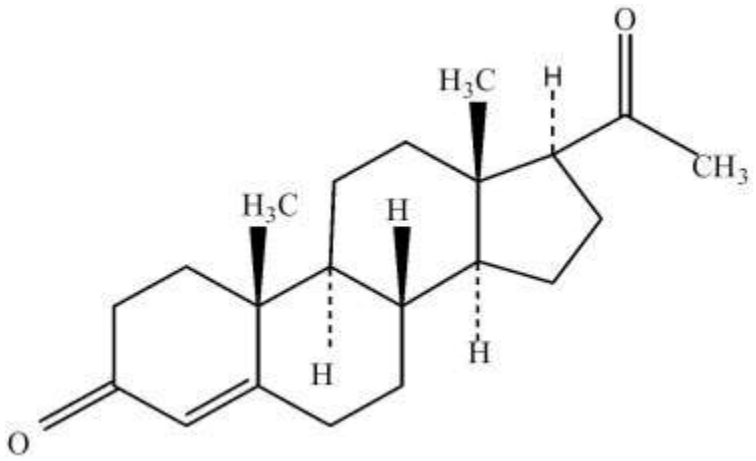
The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer. (See **CLINICAL STUDIES** and **WARNINGS, Malignant neoplasms, *Breast Cancer***.)

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Progestins with estrogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

PROMETRIUM (progesterone, USP) Capsules contain micronized progesterone for oral administration. Progesterone has a molecular weight of 314.47 and a molecular formula of $C_{21}H_{30}O_2$. Progesterone (pregn-4-ene-3, 20-dione) is a white or creamy white, odorless, crystalline powder practically insoluble in water, soluble in alcohol, acetone and dioxane and sparingly soluble in vegetable oils, stable in air, melting between 126° and 131°C. The structural formula is:



Progesterone is synthesized from a starting material from a plant source and is chemically identical to progesterone of human ovarian origin. PROMETRIUM Capsules are available in multiple strengths to afford dosage flexibility for optimum management. PROMETRIUM Capsules contain 100 mg or 200 mg micronized progesterone.

The inactive ingredients for PROMETRIUM Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, FD&C Red No. 40, and D&C Yellow No. 10.

The inactive ingredients for PROMETRIUM Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Yellow No. 6.

CLINICAL PHARMACOLOGY

PROMETRIUM Capsules are an oral dosage form of micronized progesterone which is chemically identical to progesterone of ovarian origin. The oral bioavailability of progesterone is increased through micronization.

Pharmacokinetics

A. Absorption

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

TABLE 1. Pharmacokinetic Parameters of PROMETRIUM Capsules

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.

B. Distribution

Progesterone is approximately 96 percent to 99 percent bound to serum proteins, primarily to serum albumin (50 to 54 percent) and transcortin (43 to 48 percent).

C. Metabolism

Progesterone is metabolized primarily by the liver largely to pregnanediols and pregnanolones. Pregnanediols and pregnanolones are conjugated in the liver to glucuronide and sulfate metabolites. Progesterone metabolites which are excreted in the bile may be deconjugated and may be further metabolized in the intestine via reduction, dehydroxylation, and epimerization.

D. Excretion

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites are eliminated mainly by the kidneys. Progesterone

metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

E. Special Populations

The pharmacokinetics of PROMETRIUM Capsules have not been assessed in low body weight or obese patients.

Hepatic Insufficiency: The effect of hepatic impairment on the pharmacokinetics of PROMETRIUM Capsules has not been studied.

Renal Insufficiency: The effect of renal impairment on the pharmacokinetics of PROMETRIUM Capsules has not been studied.

F. Food–Drug Interaction

Concomitant food ingestion increased the bioavailability of PROMETRIUM Capsules relative to a fasting state when administered to postmenopausal women at a dose of 200 mg.

G. Drug Interactions

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC_{50} < 0.1 μM). Ketoconazole is a known inhibitor of cytochrome P450 3A4, hence these data suggest that ketoconazole or other known inhibitors of this enzyme may increase the bioavailability of progesterone. The clinical relevance of the *in vitro* findings is unknown.

Coadministration of conjugated estrogens and PROMETRIUM Capsules to 29 postmenopausal women over a 12-day period resulted in an increase in total estrone concentrations (C_{max} 3.68 ng/mL to 4.93 ng/mL) and total equilin concentrations (C_{max} 2.27 ng/mL to 3.22 ng/mL) and a decrease in circulating 17β estradiol concentrations (C_{max} 0.037 ng/mL to 0.030 ng/mL). The half-life of the conjugated estrogens was similar with coadministration of PROMETRIUM Capsules. Table 2 summarizes the pharmacokinetic parameters.

TABLE 2. Mean (± S.D.) Pharmacokinetic Parameters for Estradiol, Estrone, and Equilin Following Coadministration of Conjugated Estrogens 0.625 mg and PROMETRIUM Capsules 200 mg for 12 Days to Postmenopausal Women

	Conjugated Estrogens			Conjugated Estrogens plus PROMETRIUM Capsules		
Drug	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$AUC_{(0-24h)}$ (ng × h/mL)**	**C_{max} (ng/mL)**	**T_{max} (hr)**	**$AUC_{(0-24h)}$ (ng × h/mL)**
Estradiol	0.037 ± 0.048	12.7 ± 9.1	0.676 ± 0.737	0.030 ± 0.032	17.32 ± 1.21	0.561 ± 0.572
Estrone	3.68	10.6	61.3	4.93	7.5	85.9

Total [a]	± 1.55	± 6.8	± 26.36	± 2.07	± 3.8	± 41.2
Equilin Total [a]	2.27 ± 0.95	6.0 ± 4.0	28.8 ± 13.0	3.22 ± 1.13	5.3 ± 2.6	38.1 ± 20.2
[a] Total estrogens is the sum of conjugated and unconjugated estrogen.						

CLINICAL STUDIES

Effects on the endometrium

In a randomized, double-blind clinical trial, 358 postmenopausal women, each with an intact uterus, received treatment for up to 36 months. The treatment groups were: PROMETRIUM Capsules at the dose of 200 mg per day for 12 days per 28-day cycle in combination with conjugated estrogens 0.625 mg per day (n=120); conjugated estrogens 0.625 mg per day only (n=119); or placebo (n=119). The subjects in all three treatment groups were primarily Caucasian women (87 percent or more of each group). The results for the incidence of endometrial hyperplasia in women receiving up to 3 years of treatment are shown in Table 3. A comparison of the PROMETRIUM Capsules plus conjugated estrogens treatment group to the conjugated estrogens only group showed a significantly lower rate of hyperplasia (6 percent combination product versus 64 percent estrogen alone) in the PROMETRIUM Capsules plus conjugated estrogens treatment group throughout 36 months of treatment.

TABLE 3. Incidence of Endometrial Hyperplasia in Women Receiving 3 Years of Treatment

Endometrial Diagnosis	**Treatment Group**					
	Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)		**Conjugated Estrogens 0.625 mg (alone)**		**Placebo**	
	Number of patients	**% of patients**	**Number of patients**	**% of patients**	**Number of patients**	**% of patients**
	n=117		**n=115**		**n=116**	
HYPERPLASIA [a]	7	6	74	64	3	3
Adenocarcinoma	0	0	0	0	1	1
Atypical hyperplasia	1	1	14	12	0	0
Complex hyperplasia	0	0	27	23	1	1
Simple hyperplasia	6	5	33	29	1	1
[a] Most advanced result to least advanced result: Adenocarcinoma > atypical hyperplasia > complex hyperplasia > simple hyperplasia						

The times to diagnosis of endometrial hyperplasia over 36 months of treatment are shown in Figure 1. This figure illustrates graphically that the proportion of patients with hyperplasia was significantly greater for the conjugated estrogens group (64 percent) compared to the conjugated estrogens plus PROMETRIUM Capsules group (6 percent).

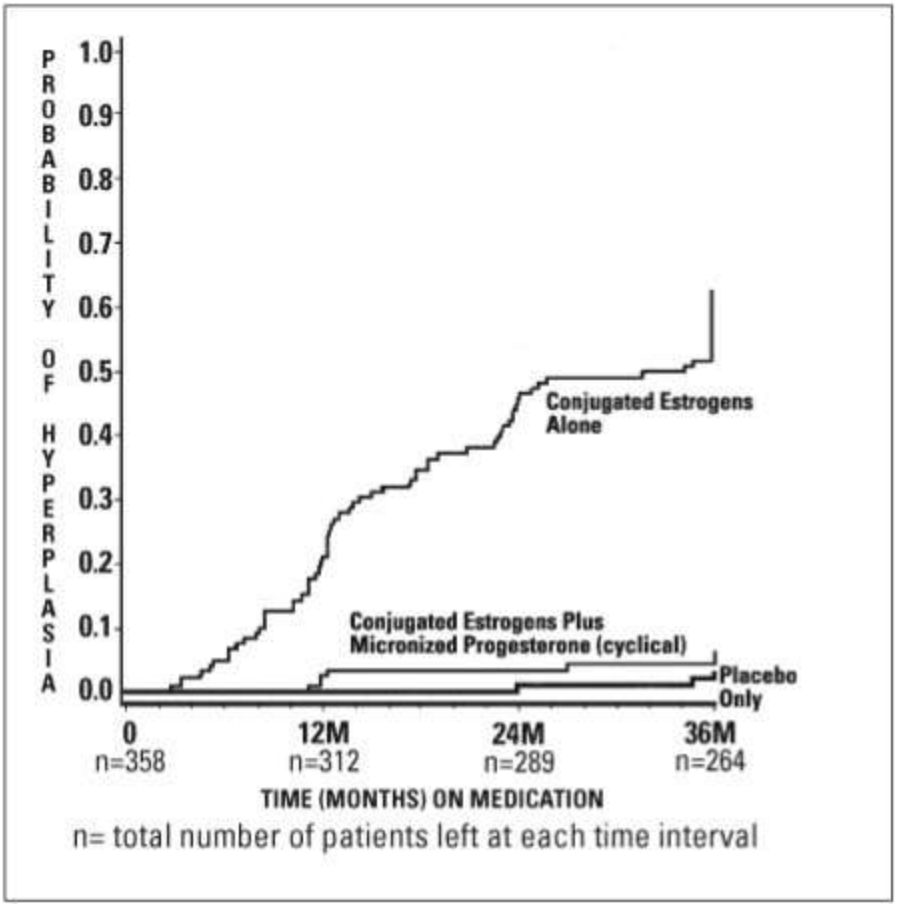


Figure 1. Time to Hyperplasia in Women Receiving up to 36 Months of Treatment

The discontinuation rates due to hyperplasia over the 36 months of treatment are as shown in Table 4. For any degree of hyperplasia, the discontinuation rate for patients who received conjugated estrogens plus PROMETRIUM Capsules was similar to that of the placebo only group, while the discontinuation rate for patients who received conjugated estrogens alone was significantly higher. Women who permanently discontinued treatment due to hyperplasia were similar in demographics to the overall study population.

TABLE 4. Discontinuation Rate Due to Hyperplasia Over 36 Months of Treatment

Most Advanced Biopsy Result Through 36 Months of Treatment	Treatment Group					
	Conjugated Estrogens + PROMETRIUM Capsules (cyclical)		Conjugated Estrogens (alone)		Placebo	
	n=120		n=119		n=119	
	Number of patients	% of patients	Number of patients	% of patients	Number of patients	% of patients
Adenocarcinoma	0	0	0	0	1	1

Atypical hyperplasia	1	1	10	8	0	0
Complex hyperplasia	0	0	21	18	1	1
Simple hyperplasia	1	1	13	11	0	0

Effects on secondary amenorrhea

In a single-center, randomized, double-blind clinical study that included premenopausal women with secondary amenorrhea for at least 90 days, administration of 10 days of PROMETRIUM Capsules therapy resulted in 80 percent of women experiencing withdrawal bleeding within 7 days of the last dose of PROMETRIUM Capsules, 300 mg per day (n=20), compared to 10 percent of women experiencing withdrawal bleeding in the placebo group (n=21).

In a multicenter, parallel-group, open label, postmarketing dosing study that included premenopausal women with secondary amenorrhea for at least 90 days, administration of 10 days of PROMETRIUM Capsules during two 28-day treatment cycles, 300 mg per day (n=107) or 400 mg per day (n=99), resulted in 73.8 percent and 76.8 percent of women, respectively, experiencing withdrawal bleeding.

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

A second multicenter, parallel-group, open label postmarketing dosing study in premenopausal women with secondary amenorrhea for at least 90 days also evaluated the rate of secretory transformation. All subjects received daily oral conjugated estrogens over 3 consecutive 28-day treatment cycles and PROMETRIUM Capsules, 300 mg per day (n=107) or 400 mg per day (n=99) for 10 days of each treatment cycle. The rate of complete secretory transformation was 21.5 percent and 28.3 percent, respectively.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral conjugated estrogens (CE) [0.625 mg]-alone or in combination with medroxyprogesterone acetate (MPA) [2.5 mg] compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease [(CHD) defined as nonfatal myocardial infarction (MI), silent MI and CHD death], with invasive breast cancer as the primary adverse outcome. A “global index” included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the CE plus MPA

substudy), colorectal cancer, hip fracture, or death due to other cause. These sub studies did not evaluate the effects of CE–alone or CE plus MPA on menopausal symptoms.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the estrogen plus progestin substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 5. Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a, b]

Event	Relative Risk CE/MPA versus Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
Non-fatal MI	*1.28 (1.00-1.63)*	*31*	*25*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All stroke	1.31 (1.03-1.88)	33	25
Ischemic Stroke	*1.44 (1.09-1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer[d]	0.81 (0.48-1.36)	6	7
Cervical cancer[d]	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures[d]	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59-0.85)	44	62
Total fractures[d]	0.76 (0.69-0.83)	152	199
Overall mortality[f]	1.00 (0.83-1.19)	52	52

Global Index [g]	1.13 (1.02-1.25)	184	165
[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.			
[b] Results are based on centrally adjudicated data.			
[c] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.			
[d] Not included in Global Index.			
[e] Includes metastatic and non-metastatic breast cancer with the exception of *in situ* breast cancer.			
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.			
[g] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.			

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified for age showed in women 50 to 59 years of age a non-significant trend toward reducing risk of overall mortality [hazard ratio (HR) 0.69 (95 percent CI, 0.44-1.07)].

Women's Health Initiative Memory Study

The estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years of age; and 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21 – 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See **WARNINGS, Probable dementia** and **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

PROMETRIUM Capsules are indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets. They are also indicated for use in secondary amenorrhea.

CONTRAINDICATIONS

PROMETRIUM Capsules should not be used in women with any of the following conditions:

1. **PROMETRIUM Capsules should not be used in patients with known hypersensitivity to its ingredients. PROMETRIUM Capsules contain peanut oil and should never be used by patients allergic to peanuts.**
2. Undiagnosed abnormal genital bleeding.
3. Known, suspected, or history of breast cancer.
4. Active deep vein thrombosis, pulmonary embolism or history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions.
6. Known liver dysfunction or disease.
7. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNING**.

1. Cardiovascular disorders

An increased risk of pulmonary embolism, deep vein thrombosis (DVT), stroke, and myocardial infarction has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (for example, personal history or family history of venous thromboembolism [VTE], obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the Women's Health Initiative (WHI) estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years). The increase in risk was demonstrated after the first year and persisted. (See **CLINICAL STUDIES**.) Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction [MI], silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1 and a trend toward decreasing relative risk was reported in years 2 through 5. (See **CLINICAL STUDIES**.)

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years), in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

c. Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and pulmonary embolism [PE]) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted. (See **CLINICAL STUDIES**.) Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens with progestins should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant neoplasms

a. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the Women's Health Initiative (WHI) substudy of daily CE

(0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24 (95 percent nCI, 1.01-1.54), and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo.

Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for estrogen plus progestin compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups. (See **CLINICAL STUDIES**.)

Consistent with the WHI clinical trials, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on

duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent nCI, 0.77 – 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies and some report no association.

3. Probable dementia

In the estrogen plus progestin Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

In the WHIMS estrogen plus progestin ancillary study, after an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for estrogen plus progestin versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years. It is unknown whether these findings apply to younger postmenopausal women. (See **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**.)

4. Vision abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogen. Discontinue estrogen plus progestin therapy pending examination if there is sudden partial or complete loss of vision, or if there is a sudden onset of proptosis, diplopia or migraine. If examination reveals papilledema or retinal vascular lesions, estrogen plus progestin therapy should be permanently discontinued.

PRECAUTIONS

A. General

1. Addition of a progestin when a woman has not had a hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include an increased risk of breast cancer.

2. Fluid Retention

Progesterone may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation.

3. Dizziness and Drowsiness

PROMETRIUM Capsules may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery. PROMETRIUM Capsules should be taken as a single daily dose at bedtime.

B. Patient Information

General: This product contains peanut oil and should not be used if you are allergic to peanuts.

Physicians are advised to discuss the contents of the Patient Information leaflet with patients for whom they prescribe PROMETRIUM Capsules.

C. Drug-Laboratory Test Interactions

The following laboratory results may be altered by the use of estrogen plus progestin therapy:

- Increased sulfobromophthalein retention and other hepatic function tests.
- Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.
- Pregnanediol determination.
- Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values.

D. Carcinogenesis, Mutagenesis, Impairment of Fertility

Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. 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.

Progesterone did not show evidence of genotoxicity in *in vitro* studies for point mutations or for chromosomal damage. *In vivo* studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. 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.

E. Pregnancy

PROMETRIUM Capsules should not be used during pregnancy. (See **CONTRAINDICATIONS**).
Pregnancy Category B: Reproductive studies have been performed in mice at doses up to 9 times the human oral dose, in rats at doses up to 44 times the human oral dose, in rabbits at a dose of 10 mcg/day delivered locally within the uterus by an implanted device, in guinea pigs at doses of approximately one-half the human oral dose and in rhesus monkeys at doses approximately the human dose, all based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

F. Nursing Women

Detectable amounts of progestin have been identified in the milk of nursing women receiving progestins. Caution should be exercised when PROMETRIUM Capsules are administered to a nursing woman.

G. Pediatric Use

PROMETRIUM Capsules are not indicated in children. Clinical studies have not been conducted in the pediatric population.

H. Geriatric Use

There have not been sufficient numbers of geriatric women involved in clinical studies utilizing PROMETRIUM Capsules to determine whether those over 65 years of age differ from younger subjects in their response to PROMETRIUM Capsules.

The Women's Health Initiative Study

In the Women's Health Initiative (WHI) estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age. (See **CLINICAL STUDIES** and **WARNINGS, Cardiovascular disorders** and **Malignant neoplasms**.)

The Women's Health Initiative Memory Study

In the Women's Health Initiative Memory Study (WHIMS) of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in the estrogen plus progestin ancillary study when compared to placebo. (See **CLINICAL STUDIES** and **WARNINGS, Probable dementia**.)

ADVERSE REACTIONS

See **BOXED WARNING**, **WARNINGS** and **PRECAUTIONS**.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a multicenter, randomized, double-blind, placebo-controlled clinical trial, the effects of PROMETRIUM Capsules on the endometrium was studied in a total of 875 postmenopausal women. Table 6 lists adverse reactions greater than or equal to 2 percent of women who received

cyclic PROMETRIUM Capsules 200 mg daily (12 days per calendar month cycle) with 0.625 mg conjugated estrogens or placebo.

TABLE 6. Adverse Reactions (≥ 2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women Over a 3-Year Period [Percentage (%) of Patients Reporting]

	PROMETRIUM Capsules 200 mg with Conjugated Estrogens 0.625 mg	Placebo
	(n=178)	(n=174)
Headache	31	27
Breast Tenderness	27	6
Joint Pain	20	29
Depression	19	12
Dizziness	15	9
Abdominal Bloating	12	5
Hot Flashes	11	35
Urinary Problems	11	9
Abdominal Pain	10	10
Vaginal Discharge	10	3
Nausea / Vomiting	8	7
Worry	8	4
Chest Pain	7	5
Diarrhea	7	4
Night Sweats	7	17
Breast Pain	6	2
Swelling of Hands and Feet	6	9
Vaginal Dryness	6	10
Constipation	3	2
Breast Carcinoma	2	<1
Breast Excisional Biopsy	2	<1
Cholecystectomy	2	<1

Effects on Secondary Amenorrhea

In a multicenter, randomized, double-blind, placebo-controlled clinical trial, the effects of PROMETRIUM Capsules on secondary amenorrhea was studied in 49 estrogen-primed postmenopausal women. Table 7 lists adverse reactions greater than or equal to 5 percent of women who received PROMETRIUM Capsules or placebo.

TABLE 7. Adverse Reactions (≥ 5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women

Adverse Experience	PROMETRIUM Capsules 400 mg	Placebo
	n=25	n=24
	Percentage (%) of Patients	
Fatigue	8	4
Headache	16	8

Dizziness	24	4
Abdominal Distention (Bloating)	8	8
Abdominal Pain (Cramping)	20	13
Diarrhea	8	4
Nausea	8	0
Back Pain	8	8
Musculoskeletal Pain	12	4
Irritability	8	4
Breast Pain	16	8
Infection Viral	12	0
Coughing	8	0

In a multicenter, parallel-group, open label postmarketing dosing study consisting of three consecutive 28-day treatment cycles, 220 premenopausal women with secondary amenorrhea were randomized to receive daily conjugated estrogens therapy (0.625 mg conjugated estrogens) and PROMETRIUM Capsules, 300 mg per day (n=113) or PROMETRIUM Capsules, 400 mg per /day (n=107) for 10 days of each treatment cycle. Overall, the most frequently reported treatment-emergent adverse reactions, reported in greater than or equal to 5 percent of subjects, were nausea, fatigue, vaginal mycosis, nasopharyngitis, upper respiratory tract infection, headache, dizziness, breast tenderness, abdominal distension, acne, dysmenorrhea, mood swing, and urinary tract infection.

Postmarketing Experience:

The following additional adverse reactions have been reported with PROMETRIUM Capsules. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Genitourinary System: endometrial carcinoma, hypospadia, intra-uterine death, menorrhagia, menstrual disorder, metrorrhagia, ovarian cyst, spontaneous abortion.

Cardiovascular: circulatory collapse, congenital heart disease (including ventricular septal defect and patent ductus arteriosus), hypertension, hypotension, tachycardia.

Gastrointestinal: acute pancreatitis, cholestasis, cholestatic hepatitis, dysphagia, hepatic failure, hepatic necrosis, hepatitis, increased liver function tests (including alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased), jaundice, swollen tongue.

Skin: alopecia, pruritus, urticaria.

Eyes: blurred vision, diplopia, visual disturbance.

Central Nervous System: aggression, convulsion, depersonalization, depressed consciousness, disorientation, dysarthria, loss of consciousness, paresthesia, sedation, stupor, syncope (with and without hypotension), transient ischemic attack, suicidal ideation.

During initial therapy, a few women have experienced a constellation of many or all of the following symptoms: extreme dizziness and/or drowsiness, blurred vision, slurred speech, difficulty walking, loss of consciousness, vertigo, confusion, disorientation, feeling drunk, and shortness of breath.

Miscellaneous: abnormal gait, anaphylactic reaction, arthralgia, blood glucose increased, choking, cleft lip, cleft palate, difficulty walking, dyspnea, face edema, feeling abnormal, feeling drunk, hypersensitivity, asthma, muscle cramp, throat tightness, tinnitus, vertigo, weight decreased, weight increased.

OVERDOSAGE

No studies on overdosage have been conducted in humans. In the case of overdosage, PROMETRIUM Capsules should be discontinued and the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Prevention of Endometrial Hyperplasia

PROMETRIUM Capsules should be given as a single daily dose at bedtime, 200 mg orally for 12 days sequentially per 28-day cycle, to a postmenopausal woman with a uterus who is receiving daily conjugated estrogens tablets.

Treatment of Secondary Amenorrhea

PROMETRIUM Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.

Some women may experience difficulty swallowing PROMETRIUM Capsules. For these women, PROMETRIUM Capsules should be taken with a glass of water while in the standing position.

HOW SUPPLIED

PROMETRIUM (progesterone, USP) Capsules 100 mg are round, peach-colored capsules branded with black imprint "SV."
NDC 0032-1708-01 (Bottle of 100)

PROMETRIUM (progesterone, USP) Capsules 200 mg are oval, pale yellow-colored capsules branded with black imprint "SV2."
NDC 0032-1711-01 (Bottle of 100)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Protect from excessive moisture.

Dispense in tight, light-resistant container as defined in USP/NF, accompanied by a Patient Insert.

Keep out of reach of children.

Manufactured by:
Catalent Pharma Solutions
St. Petersburg, FL 33716

Marketed by:
AbbVie Inc.
North Chicago, IL 60064, USA

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PATIENT INFORMATION

PROMETRIUM® (progesterone, USP)
Capsules 100 mg
Capsules 200 mg

Read this PATIENT INFORMATION before you start taking PROMETRIUM Capsules and read what you get each time you refill your PROMETRIUM Capsules prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT PROMETRIUM

CAPSULES (A Progesterone Hormone)?
• Progestins with estrogens should not be used to prevent heart disease, heart attacks, strokes, or dementia. • Using progestins with estrogens may increase your chance of getting heart attacks, strokes, breast cancer, and blood clots. • Using progestins with estrogens may increase your chance of getting dementia, based on a study of women age 65 and older. • You and your healthcare provider should talk regularly about whether you still need treatment with PROMETRIUM Capsules.

THIS PRODUCT CONTAINS PEANUT OIL AND SHOULD NOT BE USED IF YOU ARE ALLERGIC TO PEANUTS.

What is PROMETRIUM Capsules?

PROMETRIUM Capsules contain the female hormone called progesterone.

What is PROMETRIUM Capsules used for?

Treatment of Menstrual Irregularities

PROMETRIUM Capsules are used for the treatment of secondary amenorrhea (absence of menstrual periods in women who have previously had a menstrual period) due to a decrease in progesterone. When you do not produce enough progesterone, menstrual irregularities can occur. If your healthcare provider has determined your body does not produce enough progesterone on its own, PROMETRIUM Capsules may be prescribed to provide the progesterone you need.

Protection of the Endometrium (Lining of the Uterus)

PROMETRIUM Capsules are used in combination with estrogen-containing medications in a postmenopausal woman with a uterus (womb). Taking estrogen-alone increases the chance of developing a condition called endometrial hyperplasia that may lead to cancer of the lining of the uterus (womb). The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus (womb).

Who should not take PROMETRIUM Capsules?

Do not start taking PROMETRIUM Capsules if you:

- **Are allergic to peanuts**
- **Have unusual vaginal bleeding**

- **Currently have or have had certain cancers**
  Estrogen plus progestin treatment may increase the chance of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should take PROMETRIUM Capsules.
- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Are allergic to PROMETRIUM Capsules or any of its ingredients**

  See the list of ingredients in PROMETRIUM Capsules at the end of this leaflet.

- **Think you may be pregnant**

Tell your healthcare provider:

- **If you are breastfeeding.** The hormone in PROMETRIUM Capsules can pass into your breast milk.
- **About all of your medical problems.** Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, or kidneys, or have high calcium levels in your blood.
- **About all the medicines you take.** This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how PROMETRIUM Capsules work. PROMETRIUM Capsules may also affect how your other medicines work.

How should I take PROMETRIUM Capsules?

1. Prevention of Endometrial Hyperplasia: A postmenopausal woman with a uterus who is taking estrogens should take a single daily dose of 200 mg PROMETRIUM Capsules at bedtime for 12 continuous days per 28-day cycle.
2. Secondary Amenorrhea: PROMETRIUM Capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.
3. **PROMETRIUM Capsules are to be taken at bedtime as some women become very drowsy and/or dizzy after taking PROMETRIUM Capsules. In a few cases, symptoms may include blurred vision, difficulty speaking, difficulty with walking, and feeling**

abnormal. If you experience these symptoms, discuss them with your healthcare provider right away.

4. If you experience difficulty in swallowing PROMETRIUM Capsules, it is recommended that you take your daily dose at bedtime with a glass of water while in the standing position.

What are the possible side effects of PROMETRIUM Capsules?

Side effects are grouped by how serious they are and how often they happen when you are treated:

Serious, but less common side effects include:

- ***Risk to the Fetus:*** Cases of cleft palate, cleft lip, hypospadias, ventricular septal defect, patent ductus arteriosus, and other congenital heart defects.
- ***Abnormal Blood Clotting:*** Stroke, heart attack, pulmonary embolus, visual loss or blindness.

Some of the warning signs of serious side effects include:

- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Dizziness and faintness
- Vomiting

Call your healthcare provider right away if you get any of these warning signs, or any other unusual symptoms that concern you.

Less serious, but common side effects include:

- Headaches
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss

- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of PROMETRIUM Capsules. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to AbbVie Inc. at 1-800-633-9110 or to FDA at 1-800-FDA-1088.

What can I do to lower my chances of getting a serious side effect with PROMETRIUM Capsules?

- Talk with your healthcare provider regularly about whether you should continue taking PROMETRIUM Capsules.
- See your healthcare provider right away if you get unusual vaginal bleeding while taking PROMETRIUM Capsules.
- Have a pelvic exam, breast exam, and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of PROMETRIUM Capsules

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take PROMETRIUM Capsules for conditions for which it was not prescribed.
- Your healthcare provider has prescribed this drug for you and you alone. Do not give PROMETRIUM Capsules to other people, even if they have the same symptoms you have. It may harm them.
- PROMETRIUM Capsules should be taken as a single daily dose at bedtime. Some women may experience extreme dizziness and/or drowsiness during initial therapy. In a few cases, symptoms may include blurred vision, difficulty speaking, difficulty with walking, and feeling abnormal. If you experience these symptoms, discuss them with your healthcare provider right away.

- Use caution when driving a motor vehicle or operating machinery as dizziness or drowsiness may occur.

Keep PROMETRIUM Capsules out of the reach of children.

This leaflet provides a summary of the most important information about PROMETRIUM Capsules. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about PROMETRIUM Capsules that is written for health professionals. You can get more information by calling the toll free number 1-800-633-9110.

What are the ingredients in PROMETRIUM Capsules?

Active ingredient: 100 mg or 200 mg micronized progesterone

The inactive ingredients for PROMETRIUM Capsules 100 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, FD&C Red No. 40, and D&C Yellow No. 10.

The inactive ingredients for PROMETRIUM Capsules 200 mg include: peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10, and FD&C Yellow No. 6.

HOW SUPPLIED

PROMETRIUM Capsules 100 mg are round, peach-colored capsules branded with black imprint "SV."

PROMETRIUM Capsules 200 mg are oval, pale yellow-colored capsules branded with black imprint "SV2."

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Protect from excessive moisture.

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Catalent Pharma Solutions
St. Petersburg, FL 33716

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North Chicago, IL 60064, USA

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