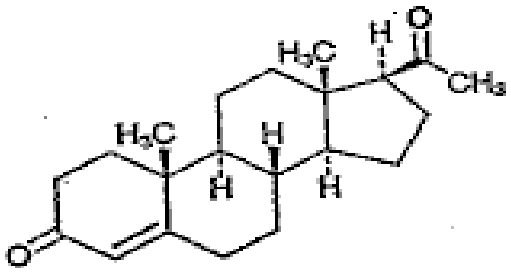
PRODUCT INFORMATION

PROMETRIUM®
(progesterone, USP)
Capsules 100 mg

DESCRIPTION

Each PROMETRIUM (progesterone, USP) Capsule contains 100 mg micronized progesterone for oral administration. Progesterone has a molecular weight of 314.47 and an empirical 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. Each peach-colored, opaque, soft-gelatin capsule contains 100 mg micronized progesterone as the active ingredient. The inactive ingredients are peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C Yellow No. 10 and FD&C Red No. 40.

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

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 as a micronized soft-gelatin capsule formulation.

Table 1

Parameter	PROMETRIUM Capsules Dose QD		
	100 mg	200 mg	300 mg
Cmax (ng/ml)	17.3±21.9[a]	38.1±37.8	60.6±72.5
Tmax (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 over the dose range 100 mg/day to 300 mg/day in postmenopausal women. Although doses greater than 300 mg/day were not studied in females, serum concentrations from a

study in male volunteers appeared linear and dose proportional between 100 mg/day and 400 mg/day. The pharmacokinetic parameters in male volunteers were generally consistent with those seen in postmenopausal women.

Distribution

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

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 gut via reduction, dehydroxylation, and epimerization.

Excretion

The glucuronide and sulfate conjugates of pregnanediol and pregnanolone are excreted in the bile and urine. Progesterone metabolites which are excreted in the bile may undergo enterohepatic recycling or may be excreted in the feces.

Special Populations

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

Race:

There is insufficient information available from trials conducted with PROMETRIUM Capsules to compare progesterone pharmacokinetics in different racial groups.

Hepatic Insufficiency:

No formal studies have evaluated the effect of hepatic disease on the disposition of

progesterone. However, since progesterone is metabolized by the liver, use in patients with severe liver dysfunction or disease is contraindicated **(See CONTRAINDICATIONS).** If treatment with progesterone is indicated in patients with mild to moderate hepatic dysfunction, these patients should be monitored carefully.

Renal Insufficiency:

No formal studies have evaluated the effect of renal disease on the disposition of progesterone. Since progesterone metabolites are eliminated mainly by the kidneys, PROMETRIUM Capsules should be used with caution and only with careful monitoring in patients with renal dysfunction. **(See PRECAUTIONS)**

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.

Drug-Drug Interaction:

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 (Cmax 3.68 ng/ml to 4.93 ng/ml) and total equilin concentrations (Cmax 2.27 ng/ml to 3.22 ng/ml) and a decrease in circulating 17β estradiol concentrations (Cmax 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 Co-administration of Conjugated Estrogens 0.625 mg and PROMETRIUM Capsules 200mg for 12 Days to Postmenopausal Women						
	Conjugated Estrogens			Conjugated Estrogens plus PROMETRIUM Capsules		
Drug	Cmax (ng/mL)	Tmax (hr)	AUC(0-24h) (ng•h/mL)	Cmax (ng/mL)	Tmax (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						
Total[a]	3.68 ±1.55	10.6 ±6.8	61.3 ±26.36	4.93 ±2.07	7.5 ±3.8	85.9 ±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

Endometrial Protection

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/day for 12 days per 28 day cycle in combination with conjugated estrogens 0.625 mg/day (n=120); conjugated estrogens 0.625 mg/day only (n=119); or placebo (n=119). The subjects in all three treatment groups were primarily Caucasian women (87% 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% combination product vs. 64% estrogen alone) in the PROMETRIUM Capsules plus conjugated estrogens treatment group, throughout 36 months of treatment.

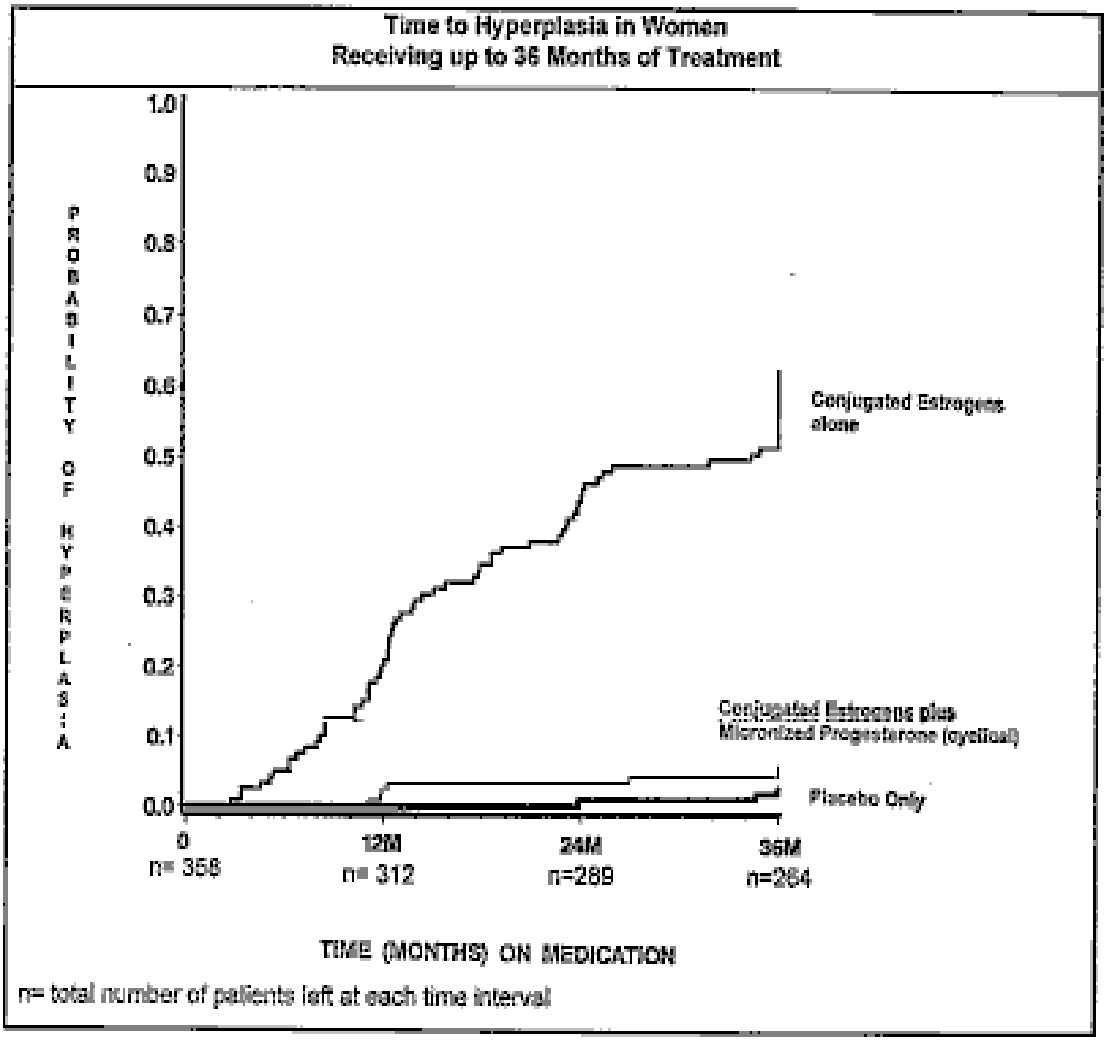
Table 3

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 (only)		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%) compared to the conjugated estrogens plus PROMETRIUM Capsules group (6%).

Figure 1



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 (only)		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

In the same three year clinical trial, postmenopausal women were treated with PROMETRIUM Capsules in combination with conjugated estrogens, conjugated estrogens only, or placebo. There was no statistically significant difference between the PROMETRIUM Capsules plus conjugated estrogens group and the conjugated estrogens only group in increases of HDL-C and triglycerides, or in decreases of LDL-C. The changes observed in lipid profiles are shown in Table 5.

Table 5

Mean Changes from Baseline in Lipid Profiles After 36 Months of Treatment						
Parameter	Treatment Group Mean (Mean % Change)					
	Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)[a] N= 176 to 177[b]		Conjugated Estrogens 0.625 mg (only) N=171 to 173[b]		Placebo N=171	
	mean	Mean % change	mean	mean % change	mean	mean % change
LIPID PROFILE						
HDL-C(mmol/L)	0.07	5.1	0.10	7.2	-0.05	-2
LDL-C(mmol/L)	-0.43	-11.8	-0.36	-9.5	-0.14	-2.9
Cholesterol (mmol/L)	-0.26	-4.0	-0.22	-3.6	-0.15	-1.8
Triglyceride (mmol/L)[c]	0.20	17.8	0.15	13.7	0.01	0.6

a: There are no significant changes ($p<0.05$) from conjugated estrogens values
b: Number of subjects (N) varies by parameter
c: Computed from log transformed data

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% of women experiencing withdrawal bleeding within 7 days of the last dose of PROMETRIUM Capsules, 300 mg/day (n=20), compared to 10% of women experiencing withdrawal bleeding in the placebo group (n=21).

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/day (n=22) induced complete secretory changes in the endometrium in 45% of women compared to 0% in the placebo group (n=23).

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

1. **Known sensitivity to PROMETRIUM Capsules or its ingredients. PROMETRIUM Capsules contain peanut oil and should never be used by patients allergic to peanuts.**
2. Known or suspected pregnancy.
3. Thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or patients with a past history of these conditions.
4. Severe liver dysfunction or disease.
5. Known or suspected malignancy of breast or genital organs.
6. Undiagnosed vaginal bleeding.
7. Missed abortion.
8. As a diagnostic test for pregnancy.

WARNINGS

1. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drug should be discontinued immediately.
2. Discontinue medication 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, medication should be withdrawn.

3. The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of mothers receiving progestins. The effect of this on the nursing infant has not been determined.
4. Retrospective studies of morbidity and mortality in Great Britain and studies of morbidity in the United States have shown a statistically significant association between thrombophlebitis, pulmonary embolism, cerebral thrombosis and embolism, and the use of oral contraceptives. The estimate of the relative risk of thromboembolism in the study by Vessey and Doll was about seven fold, while Sartwell and associates in the United States found a relative risk of 4.4, meaning that the users are several times as likely to undergo thromboembolic disease without evident cause as nonusers. The American study also indicated that the risk did not persist after discontinuation of administration, and that it was not enhanced by long-continued administration. The American study was not designed to evaluate a difference between products.

PRECAUTIONS

General

1. The pretreatment physical examination should include special reference to breast and pelvic organs, as well as Papanicolaou smear.
2. Because progesterone may cause some degree of fluid retention, conditions which might be influenced by this factor, such as epilepsy, migraine, asthma, cardiac or renal dysfunction, require careful observation.
3. In cases of breakthrough bleeding, as in any cases of irregular bleeding per vaginum, nonfunctional causes should be borne in mind. In cases of undiagnosed vaginal bleeding, adequate diagnostic measures are indicated.
4. Patients who have a history of psychic depression should be carefully observed and the drug discontinued if the depression recurs to a serious degree.

5. Any possible influence of prolonged progestin therapy on pituitary, ovarian, adrenal, hepatic or uterine functions awaits further study.
6. Although concomitant use of conjugated estrogens and PROMETRIUM Capsules did not result in a decrease in glucose tolerance, diabetic patients should be carefully observed while receiving estrogen-progestin therapy.
7. The pathologist should be advised of progestin therapy when relevant specimens are submitted.
8. Because of the occurrence of thrombotic disorders (thrombophlebitis, pulmonary embolism, retinal thrombosis, and cerebrovascular disorders) in patients taking estrogen-progestin combinations, the physician should be alert to the earliest manifestation of these disorders.
9. Transient dizziness may occur in some patients. Use caution when driving a motor vehicle or operating machinery. A small percentage of women may experience extreme dizziness and/or drowsiness during initial therapy. For these women, bedtime dosing is advised.

Information for the Patient

See accompanying Patient Insert.

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

Drug Lab Test Interactions

The following laboratory results may be altered by the use of estrogen-progestin combination drugs:

Increased sulfobromophthalein retention and other hepatic function tests.

Coagulation tests: increase in prothrombin factors VII, VIII, IX and X.

Metyrapone test.

Pregnanediol determination.

Thyroid function: increase in PBI, and butanol extractable protein bound iodine

and decrease in T3 uptake values.

Fasting and 2-hour plasma insulin and glucose levels following an oral glucose tolerance test (OGTT) and fibrinogen levels were measured in patients receiving PROMETRIUM Capsules at a dose of 200 mg/day for 12 days per 28 day cycle in combination with conjugated estrogens 0.625 mg/day (n=120). Table 6 summarizes this data. Plasma insulin levels 2 hours post-OGTT were decreased from baseline. The fasting plasma glucose and fasting plasma insulin levels were also decreased from baseline. Glucose levels 2 hours post-OGTT were increased slightly. There was no effect on fibrinogen levels.

For information on changes in lipid profile, see the Clinical Studies subsection, Table 5.

Table 6

Mean Changes from Baseline in Insulin and Glucose Levels After 36 Months of Treatment

Parameter	Treatment Group Mean (Mean % Change)					
	Conjugated Estrogens 0.625 mg + PROMETRIUM Capsules 200 mg (cyclical)[a] N= 173 to 176[b]		Conjugated Estrogens 0.625 mg (only) N=170 to 172[b]		Placebo N=171	
	mean	mean % change	mean	mean % change	mean	mean % change
OGTT						
Insulin(pmol/L) fasting	-2.2	-6.2	-1.1	-3.2	5.1	14.2
2 hour	-45.2	-14.5	-23.9	-7.9	-29.7	-9.1
Glucose(mg/dL) fasting	-3.0	-2.9	-2.7	-2.7	-1.0	-0.9
2 hour	3.6	5.2	5.0	7.8	2.1	3.9

a: There are no significant changes ($p<0.05$) from conjugated estrogens values
b: Number of subjects (N) varies by parameter

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 (1). In dogs, long term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors (2). 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 (3).

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 (4). 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.

Pregnancy Category B

Reproductive studies have been performed in mice, rats, rabbits, guinea pigs and rhesus monkeys at doses up to 2 times the human dose, based on body surface area, and have revealed little or no evidence of impaired fertility or harm to the fetus due to progesterone.

Several studies in women exposed to progesterone have not demonstrated any significant increase in fetal malformations. A single case of cleft palate was observed in the child of a woman using PROMETRIUM in early pregnancy, although definitive causality has not been established. Rare instances of fetal death have been reported in pregnant women prescribed PROMETRIUM Capsules for

unapproved indications. Because the studies in humans cannot rule out the possibility of harm, PROMETRIUM should be used during pregnancy only if indicated (see CONTRAINDICATIONS).

Nursing Mothers

The administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. Detectable amounts of progestin have been identified in the milk of nursing mothers receiving progestins. The effect of this on the nursing infant has not been determined.

Pediatric Use

The safety and effectiveness of PROMETRIUM Capsules in pediatric patients have not been established.

ADVERSE REACTIONS

Endometrial Protection

Table 7 lists adverse experiences which were reported in ≥2% of patients (regardless of relationship to treatment) who received cyclic PROMETRIUM Capsules, 200 mg daily (12 days per calendar month cycle) with daily 0.625 mg conjugated estrogen, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in 875 postmenopausal women.

Table 7

Adverse Experiences (≥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 (N=178)	**Conjugated Estrogens 0.625 mg (only) (N= 175)**	**Placebo (N=174)**
Headache	31	30	27
Breast Tenderness	27	16	6
Joint Pain	20	22	29
Depression	19	18	12
Dizziness	15	5	9
Abdominal Bloating	12	10	5
Hot Flashes	11	14	35
Urinary Problems	11	10	9
Abdominal Pain	10	13	10
Vaginal Discharge	10	10	3
Nausea / Vomiting	8	6	7
Worry	8	5	4
Chest Pain	7	4	5
Diarrhea	7	7	4
Night Sweats	7	5	17
Breast Pain	6	6	2
Swelling of Hands and Feet	6	9	9
Vaginal Dryness	6	8	10
Constipation	3	3	2
Breast Carcinoma	2	<1	<1
Breast Excisional Biopsy	2	1	<1
Cholecystectomy	2	<1	<1

Secondary Amenorrhea

Table 8 lists adverse experiences which were reported in ≥5% of patients receiving PROMETRIUM Capsules, 400 mg/day, in a multicenter, randomized, double-blind, placebo-controlled clinical trial in estrogen-primed (6 weeks) postmenopausal women receiving conjugated estrogens 0.625 mg/day and cyclic (10 days per calendar month cycle) PROMETRIUM Capsules at a dose of 400 mg/day, for three cycles.

Table 8

Adverse Experiences (≥5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women		
Adverse Experience	PROMETRIUM Capsules 400 mg N=25	Placebo 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

The most common adverse experiences reported in ≥5% of patients in all PROMETRIUM Capsules dosage groups studied in this trial (100 mg/day to 400 mg/day) were: dizziness (16%), breast pain (11%), headache (10%), abdominal pain (10%), fatigue (9%), viral infection (7%), abdominal distention (6%), musculoskeletal pain (6%), emotional lability (6%), irritability (5%), and upper

respiratory tract infection (5%).

Other adverse events reported in <5% of patients taking PROMETRIUM Capsules include:

Autonomic Nervous System Disorders: dry mouth

Body As A Whole: accidental injury, chest pain, fever

Cardiovascular System Disorders: hypertension

Central and Peripheral Nervous System Disorders: confusion, somnolence, speech disorder

Gastrointestinal System Disorders: constipation, dyspepsia, gastroenteritis, hemorrhagic rectum, hiatus hernia, vomiting

Hearing and Vestibular Disorders: earache

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: edema, edema peripheral

Musculoskeletal System Disorders: arthritis, leg cramps, hypertonia, muscle disorder, myalgia

Myo/Endo/Pericardial and Valve Disorders: angina pectoris

Psychiatric Disorders: anxiety, impaired concentration, insomnia, personality disorder

Reproductive System Disorders: leukorrhea, uterine fibroid, vaginal dryness, fungal vaginitis, vaginitis

Resistance Mechanism Disorders: abscess, herpes simplex

Respiratory System Disorders: bronchitis, nasal congestion, pharyngitis, pneumonitis, sinusitis

Skin and Appendages Disorders: acne, verruca, wound debridement

Urinary System Disorders: urinary tract infection

Vision Disorders: abnormal vision

White Cell and Resistance Disorders: lymphadenopathy

The following adverse experiences have been reported with PROMETRIUM Capsules in other U.S. clinical trials: increased sweating, asthenia, tooth disorder, anorexia, increased appetite, nervousness, and breast enlargement.

The following spontaneous adverse events have been reported during the foreign marketing of PROMETRIUM Capsules: reversible cases of hepatitis and elevated transaminases. These events occurred mainly in patients receiving high doses of up to 1200 mg.

The following additional adverse experiences have been observed in women taking progestins in general: breakthrough bleeding, spotting, change in menstrual flow, amenorrhea, changes in weight (increase or decrease), changes in the cervical squamo-columnar junction and cervical secretions, cholestatic jaundice, anaphylactoid reactions and anaphylaxis, rash (allergic) with and without pruritus, melasma or chloasma, pyrexia, and insomnia.

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 in the evening, 200 mg orally for 12 days sequentially per 28 day cycle, to postmenopausal women with a uterus who are receiving daily conjugated estrogens tablets.

Secondary Amenorrhea - PROMETRIUM Capsules may be given as a single daily dose of 400 mg in the evening for 10 days.

HOW SUPPLIED

PROMETRIUM® (progesterone, USP) Capsules 100 mg are round, peach-colored capsules branded with black imprint “SV”, available in bottles of 100 capsules (NDC0032-1708-01).

Store at controlled room temperature at 25°C (77°F).

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

Rx only

Manufactured by: R. P. Scherer North America, St. Petersburg, FL 33716

Marketed by: Solvay Pharmaceuticals, Inc., Marietta, GA 30062.

References:

1. International Agency for Research on Cancer (IARC) V.6, 1974; IRAC V.21, 1979.

2. K.S. Larrson and D. Machin, Safety requirements for contraceptive steroids. F. Michal (ed.) Cambridge University Press, Cambridge. Pp. 30-269, 1989.

3. Sixth Annual Report on Carcinogens V.2, pp 693-696, 1991.

4. Med. Sci. Res. 1987; 15:703-704

PATIENT INSERT

PROMETRIUM®

(progesterone, USP)

Capsules 100 mg

Please read this information carefully before you start to use PROMETRIUM Capsules, and each time your prescription is renewed, in case anything has changed. This patient information leaflet does not take the place of discussions with your doctor. If you have any questions, ask your doctor or health-care provider.

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

ABOUT PROMETRIUM CAPSULES

PROMETRIUM Capsules contain the female hormone called progesterone and are used for postmenopausal hormone replacement therapy and the treatment of secondary amenorrhea (absence of menstrual periods in women who have previously had a menstrual period). It is chemically identical to progesterone of ovarian origin. PROMETRIUM Capsules have several important uses which are described below.

USES OF PROMETRIUM CAPSULES

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 progesterone deficiency. Progesterone is one of the hormones

essential for regular menstrual periods. If your doctor has determined your body does not produce enough progesterone on its own, PROMETRIUM Capsules may be prescribed to provide the progesterone you need. When you do not produce enough progesterone, menstrual irregularities can occur. PROMETRIUM Capsules can provide you with the progesterone needed during a normal menstrual cycle.

PROTECTION OF THE ENDOMETRIUM (Lining of the Uterus)

PROMETRIUM Capsules are used in combination with estrogen-containing medications in postmenopausal women. Taking estrogens alone increases the risk of developing a condition called endometrial hyperplasia, that may lead to cancer of the lining of the uterus. Taking PROMETRIUM Capsules with estrogens lowers the risk of developing this condition.

YOU SHOULD NOT USE PROMETRIUM CAPSULES

- If you are allergic to progesterone, progesterone-like drugs, or any of the inactive ingredients in the capsules. **Note: PROMETRIUM Capsules contain peanut oil and should not be used if you are allergic to peanuts.**
- **If you are pregnant or suspect that you are pregnant.**
- If you have or have had blood clots in the legs, lungs, eyes, brain, or elsewhere.
- If you have liver disease.
- If you have known or suspected cancer of the breast or reproductive organs.
- If you have unusual bleeding from the vagina which has not been evaluated by your doctor.
- If you have a miscarriage and your physician suspects some tissue is still in the uterus.
- If you are nursing.

RISKS OF PROMETRIUM CAPSULES

- *Risk to the Fetus.* A case of cleft palate has been reported in the child of a woman who was using PROMETRIUM Capsules during early pregnancy. Although it is not clear this event was drug related, you should check with your doctor about the risks to your unborn child of any medication taken during pregnancy.

- *Abnormal Blood Clotting*. Use of progestational drugs has been associated with changes in the blood-clotting system. These changes allow the blood to clot more easily, possibly allowing clots to form in the bloodstream. If blood clots do form in your bloodstream, they can cut off the blood supply to vital organs, causing serious problems. These problems may include a stroke (by cutting off blood to part of the brain), a heart attack (by cutting off blood to part of the heart), a pulmonary embolus (by cutting off blood to part of the lungs), visual loss or blindness (by cutting off blood vessels in the eye), or other problems. Any of these conditions may cause death or serious long-term disability. Call your doctor immediately if you suspect you have any of these conditions. He or she may advise you to stop using this drug.

- *Eye Abnormalities*. Discontinue medication and call your physician immediately if you experience sudden partial or complete loss of vision, blurred vision, or sudden onset of bulging eyes, double vision, or migraine.

POSSIBLE SIDE EFFECTS OF PROMETRIUM CAPSULES

Consult your doctor if you experience any of the side effects mentioned below or other side effects.

SIDE EFFECTS REPORTED IN GREATER THAN OR EQUAL TO 5% OF PATIENTS AT DOSES OF 100 MG/DAY to 400 MG/DAY:

- Dizziness*
- Headache
- Muscle or Bone Pain / Back Pain / Joint Pain
- Fatigue
- Diarrhea
- Chest Pain
- Coughing
- Upper Respiratory Tract Infection / Viral Infection
- Hot Flashes
- Urinary Problems
- Vaginal Discharge / Vaginal Dryness
- Night Sweats
- Abdominal Pain (Cramping)
- Breast Pain / Breast Tenderness
- Bloating
- Nausea / Vomiting
- Irritability / Mood Swings / Depression/ Worry

SIDE EFFECTS REPORTED IN LESS THAN 5% OF PATIENTS:

Dry mouth, chest pain, fever, high blood pressure, confusion, drowsiness*, constipation, heartburn, indigestion, stomach pain, intestinal pain, vomiting, pounding or racing of the heart, fluid retention, swelling in legs or arms, arthritis, leg cramps, muscle cramps, anxiety, decreased concentration, sleep disorder, personality disorder, vaginal discharge, uterine fibroid, vaginal dryness, fungal vaginal infection, inflammation of vagina, infections, bronchitis, nasal congestion, sore throat, swelling of lungs, swelling or fluid in sinus cavities, acne, urinary tract infection, blurred vision, swelling of the lymph nodes.

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

PRECAUTIONS

Be alert for unusual signs and symptoms. If any of these warning signals (or any other unusual symptoms) happen while you are using PROMETRIUM Capsules, call

your doctor immediately:

- Breast lumps (ask your doctor or healthcare provider to show you how to examine your breasts monthly).
- Pain, swelling, or tenderness in the abdomen.
- Tremors or seizures, migraine headaches, shortness of breath or asthma, heart problems, or kidney problems.
- Abnormal bleeding from the vagina.
- Feelings of depression.
- Pains in the calves or chest; a sudden shortness of breath; or coughing blood, indicating possible clots in the legs, heart or lungs.
- Severe headache, vomiting, dizziness, faintness, or changes in vision or speech; weakness or numbness in an arm or leg, indicating possible clots in the brain or eye.

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

Inform your doctor if you are diabetic.

You should inform your doctors that you are taking a hormone before lab tests or biopsies are performed.

OTHER INFORMATION

- Your doctor has prescribed this drug for you and you alone. Do not give this drug to anyone else.
- This medication was prescribed for your particular medical condition. Do not use it for another condition.
- Keep this and all drugs out of the reach of children.
- PROMETRIUM Capsules should be taken as a single daily dose in the evening. A small percentage of women may experience extreme dizziness and/or drowsiness during initial therapy. For these women, a single bedtime dose is

advised.

HOW SUPPLIED

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

PROMETRIUM Capsules should be stored at controlled room temperature at 25°C (77 °F).

Manufactured By:
R. P. Scherer North America, St. Petersburg, FL 33716

Marketed By:
Solvay Pharmaceuticals, Inc., Marietta, GA 30062.