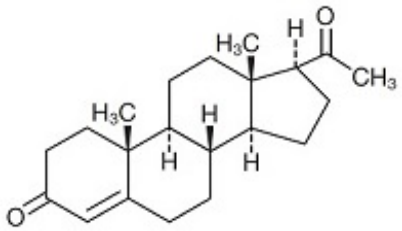
PROGESTERONE- progesterone capsule
Xiromed, LLC

Progesterone Capsules

Rx only

DESCRIPTION

Progesterone 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 chemically identical to progesterone of human ovarian origin. Progesterone capsules are available in multiple strengths to afford dosage flexibility for optimum management. Each progesterone capsule for oral administration contains 100 mg or 200 mg of micronized progesterone and the following inactive ingredients: peanut oil, gelatin, glycerin, soya lecithin, titanium dioxide, and triglycerides medium chain.

CLINICAL PHARMACOLOGY

Progesterone 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 progesterone capsules 100 mg as a micronized soft-gelatin capsule formulation.

TABLE 1. Pharmacokinetic Parameters of Progesterone Capsules

Parameter	Progesterone 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 progesterone 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 progesterone capsules have not been assessed in low body weight or obese patients.

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

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

F. Food-Drug Interaction

Concomitant food ingestion increased the bioavailability of progesterone 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 progesterone 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 progesterone 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 Progesterone Capsules 200 mg for 12 Days to Postmenopausal Women

	Conjugated Estrogens			**Conjugated Estrogens plus Progesterone 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 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

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: Progesterone 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 progesterone 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 progesterone 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 + Progesterone 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 progesterone capsules group (6 percent).

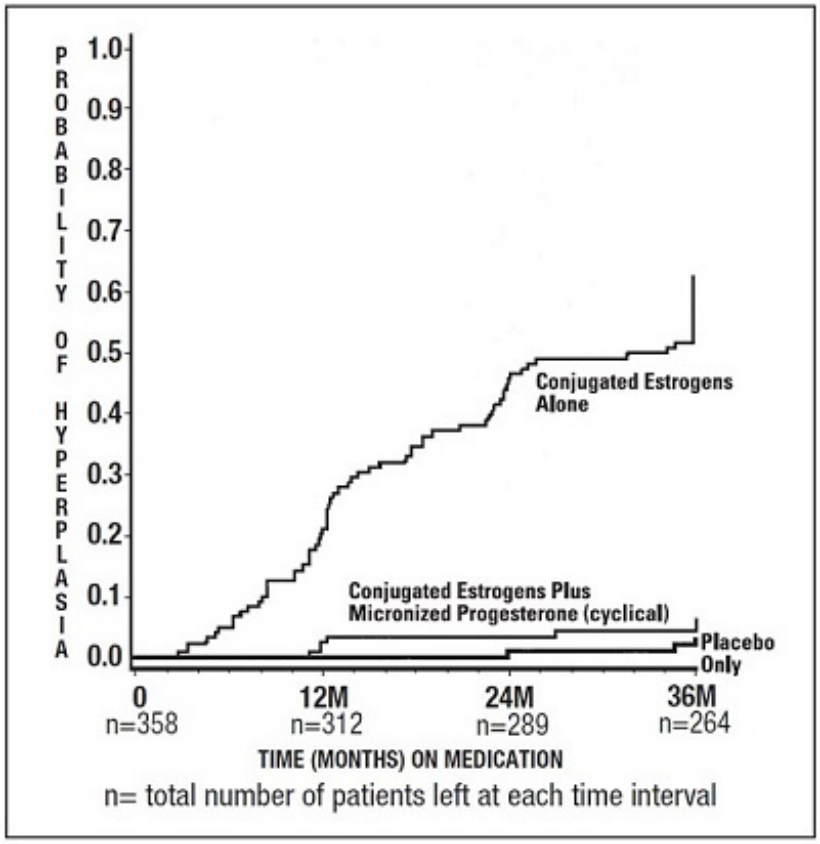


Figure 1. Time to Hyperplasia in Women Receiving up to 36 Months of Treatment

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 progesterone 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 + Progesterone 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 progesterone capsules therapy resulted in 80 percent of women experiencing withdrawal bleeding within 7 days of the last dose of progesterone 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 progesterone 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. Progesterone 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 progesterone 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 Estrogen Plus Progestin Trial

The WHI estrogen plus progestin trial enrolled predominantly healthy postmenopausal women to assess the risks and benefits of daily oral CE (0.625 mg) in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal 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, PE, endometrial cancer colorectal cancer, hip fracture, or death due to other causes. This trial did not evaluate the effects of CE plus MPA on menopausal symptoms.

The WHI estrogen plus progestin trial was stopped early. After an average follow-up of 5.6 years of treatment, the increased risk of invasive breast cancer crossed the predefined stopping threshold. The global index was supportive of a finding of overall harm. The absolute excess risk of events included in the global index was 19 per 10,000 women-years. Results of the trial, which enrolled 16,608 women (average 63 years of age, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% 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 WHI Estrogen Plus Progestin Trial at an Average of 5.6 Years[a,b]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE/MPA vs placebo/10,000 WYs)
CHD events	1.18 (0.95-1.45)	6 (41 vs 35)
Non-fatal MI	*1.24 (0.98-1.56)*	*6 (35 vs 29)*
CHD death	*1.05 (0.76-1.45)*	*1 (16 vs 15)*
All Strokes	1.37 (1.07-1.76)	9 (33 vs 24)
Deep vein thrombosis [d]	1.87 (1.37-2.54)	12 (25 vs 14)
Pulmonary embolism	1.98 (1.36-2.87)	9 (18 vs 9)
Invasive breast cancer [e]	1.24 (1.01-1.53)	9 (43 vs 35)
Colorectal cancer	0.62 (0.43-0.89)	-6 (10 vs 17)
Endometrial cancer [d]	0.83 (0.49-1.40)	-1 (6 vs 7)
Hip fracture	0.67 (0.47-0.95)	-6 (11 vs 17)
Vertebral fractures [d]	0.68 (0.48-0.96)	-6 (12 vs 17)
Total fractures [d]	0.76 (0.69-0.83)	-51 (161 vs 212)
Overall mortality [f]	0.97 (0.81-1.16)	-1 (52 vs 53)
Global Index [g]	1.12 (1.02-1.24)	20 (189 vs 168)

[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 results of the WHI estrogen plus progestin trial in women 50 to 59 years of age (N=2,837 for CE/MPA; N=2,683 for placebo) are shown in **Table 6**.

Table 6. Relative Risk and Risk Difference Observed Among Women 50-59

Years of Age in the WHI Estrogen Plus Progestin Trial at an Average of 5.6[a,b]

Event	Relative Ratio (95% CI)[c]	Risk Difference (CE/MPA vs placebo/10,000 WYs)
CHD events	1.34 (0.82-2.19)	5 (23 vs 17)
Non-fatal	*1.32 (0.77-2.25)*	*4 (19 vs 15)*
MI CHD death	*0.77 (0.33-1.79)*	*-2 (6 vs 8)*
All Strokes	1.51 (0.81-2.82)	5 (15 vs 10)
Deep vein thrombosis [d]	3.01 (1.36-6.66)	10 (15 vs 5)
Pulmonary embolism	2.05 (0.89-4.71)	6 (11 vs 5)
Invasive breast cancer [e]	1.21 (0.81-1.80)	6 (33 vs 27)
Colorectal cancer	0.79 (0.29-2.18)	-1 (4 vs 5)
Endometrial cancer [d]	1.07 (0.33-3.53)	0 (4 vs 3)
Hip fracture	0.17 (0.22-1.45)	-3 (1 vs 3)
Vertebral fractures [d]	0.38 (0.15-0.97)	-6 (4 vs 10)
Total fractures [d]	0.82 (0.68-1.00)	-25 (120 vs 145)
Overall mortality [f]	0.67 (0.43-1.04)	-10 (21 vs 31)
Global Index [g]	1.12 (0.89-1.40)	12 (103 vs 91)

[a] Adapted from 2013 WHI trial (CE/MPA n=2,837; placebo=2,683). WHI publications can be viewed at www.nhlbi.nih.gov/whi.

[b] Results are based on centrally adjudicated data.

[c] In the WHI studies, hazard ratios were estimated using Cox proportional hazards models comparing treatment to placebo; however, they are described here as relative risks. 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 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, PE, colorectal cancer, hip fracture, or death due to other causes.

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 **PRECAUTIONS, Geriatric Use**.)

INDICATIONS AND USAGE

Progesterone 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

Progesterone capsules is contraindicated in women with any of the following conditions:

1. **Hypersensitivity to its ingredients. Progesterone capsules contain peanut oil and is contraindicated in patients allergic to peanuts.**
2. Abnormal genital bleeding of unknown etiology.
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.

WARNINGS

1. Cardiovascular disorders

Progesterone capsules are contraindicated in females with active DVT, PE, arterial thromboembolic disease (e.g., stroke, MI) disease, or a history of these conditions (See **CONTRAINDICATIONS**). Immediately discontinue progesterone capsules if a PE, DVT, stroke, or MI occurs or is suspected.

If feasible, discontinue progesterone capsules at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

The safety and efficacy of estrogen plus progestogen for the prevention of cardiovascular disorders has not been established. (See **CLINICAL STUDIES**)

The Women’s Health Initiative (WHI) estrogen plus progestin trial reported increased risks of PE, DVT, stroke, and MI in postmenopausal women (50 to 79 years of age,

average age 63.4 years) 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. Analyses were also conducted in women aged 50-59 years, a group of women more likely to present with new onset of moderate to severe VMS compared to women in other age groups in the trial. (See **CLINICAL STUDIES.**)

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin trial of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products.

a. Venous Thromboembolism

In women aged 50 to 59 years, the WHI estrogen plus progestin trial reported a relative risk for PE of 2.05 (95% confidence interval [CI], 0.89, 4.71) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 women- years (WYs; 11 versus 5). The relative risk for DVT was 3.01 (95% CI, 1.36, 6.66) in those receiving CE/MPA compared to placebo, with a risk difference of 10 per 10,000 WYs (15 versus 5). (See **CLINICAL STUDIES**).

In the overall study population of women aged 50 to 79 years (average 63.4 years), the trial reported a relative risk for PE of 1.98 (95% CI, 1.36, 2.87) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (18 versus 9). The relative risk for DVT was 1.87 (95% CI, 1.37, 2.54) for CE/MPA compared to placebo, with a risk difference of 12 per 10,000 WYs (25 versus 14). (See **CLINICAL STUDIES**).

b. Stroke

In women aged 50 to 59 years, the WHI estrogen plus progestin trial reported a relative risk for stroke of 1.51 (95% CI, 0.81, 2.82) for CE/MPA compared to placebo, with a risk difference of 5 per 10,000 WYs (15 versus 10). (See **CLINICAL STUDIES**).

In the overall study population of women aged 50 to 79 years (average 63.4 years), the WHI estrogen plus progestin trial reported relative risk for stroke of 1.37 (95% CI, 1.07, 1.76) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (33 versus 24). (See **CLINICAL STUDIES**).

c. ***Coronary Heart Disease***

In women 50 to 59 years of age, the WHI estrogen plus progestin trial reported a relative risk for coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) of 1.34 (95% CI, 0.82, 2.19) for CE/MPA compared placebo, with a risk difference of 5 per 10,000 WYs (23 versus 17).

In the overall study population of women aged 50 to 79 years (average 63.4 years), the trial reported a relative risk of CHD of 1.18 (95% CI, 0.95, 1.45) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 WYs (41 versus 35). (See **CLINICAL STUDIES**).

In the Heart and Estrogen/Progestin Replacement Study (HERS) and open label extension (HERS II), postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) received daily CE (0.625 mg) plus MPA or placebo. In

Year 1, there were more CHD events in the CE plus MPA-treated group than placebo; however, rates of CHD events were comparable among both groups for the remainder of the duration of the studies (average total follow-up of 6.8 years).

2. Malignant neoplasms

a. Breast Cancer

Progesterone capsules are contraindicated in women with breast cancer, a history of breast cancer, or estrogen-dependent neoplasia. (See **CONTRAINDICATIONS**).

Discontinue progesterone capsules if a hormone-sensitive malignancy is diagnosed. The use of estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

Only daily oral CE 0.625 mg and MPA 2.5 mg were studied in the estrogen-alone trial of the WHI. Therefore, the relevance of the WHI findings regarding breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products.

In women 50-59 years of age, the WHI estrogen plus progestin trial reported a relative risk for invasive breast cancer of 1.21 (95% CI, 0.81, 1.80) for CE/MPA compared to placebo, with a risk difference of 6 per 10,000 WYs (33 versus 27).

In this age group, among those who reported no prior use of hormone therapy, the relative risk was 1.06 (95% CI, 0.67, 1.67) for CE/MPA compared to placebo, with a risk difference of 2 per 10,000 WYs (33 versus 31).

In the overall study population of women aged 50-79 years (average 63.4 years), the WHI estrogen plus progestin trial reported a relative risk for invasive breast cancer of 1.24 (95% CI, 1.01, 1.53) for CE/MPA compared to placebo, with a risk difference of 9 per 10,000 WYs (43 versus 35). In the overall study population, among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.85, (95% CI 1.18, 2.90) for CE/MPA compared to placebo, with a risk difference of 21 per 10,000 WYs (46 versus 25). Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, (95% CI 0.86, 1.39), with a risk difference of 4 per 10,000 WYs (40 versus 36). Invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE/MPA 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**.) Extension of the WHI trial also demonstrated increased breast cancer risk associated with estrogen plus progestin therapy.

Consistent with the WHI trial, observational studies have also reported an increased risk of breast cancer with estrogen plus progestin therapy. A large meta-analysis including 24 prospective studies of postmenopausal women comparing current use of estrogen

plus progestin products with use duration of 5 to 14 years (average of 9 years) versus never use reported a relative risk for breast cancer of 2.08 (95% CI, 2.02 to 2.15). 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.

Regarding breast cancer mortality, the WHI estrogen plus progestin trial did not show a statistically significant difference between CE/MPA and placebo. The trial reported a relative risk of 1.35 (95% CI, 0.94 to 1.95) for CE/MPA compared to placebo, with a risk difference of 1 per 10,000 WYs (5 versus 4) after a median of 19 years of cumulative follow-up.

b. Ovarian Cancer

In the overall WHI study population of women aged 50 to 79 years (average 63.4 years), the estrogen plus progestin trial reported a relative risk for ovarian cancer of 1.41 (95% CI, 0.75 to 2.66) for CE/MPA versus placebo after an average follow-up of 5.6 years. The risk difference was 1 per 10,000 WYs (5 versus 4). Comparing CE/MPA to placebo, women 50 to 59 years of age had a relative risk for ovarian cancer of 0.30 (95% CI 0.06, 1.47) and the risk difference was -3 per 10,000 WYs (1 versus 4).

A large meta-analysis including 17 prospective studies of postmenopausal women compared current use of estrogen plus progestin products versus never use and reported a relative risk for ovarian cancer of 1.37 (95% CI, 1.26 to 1.48). The duration of hormone therapy use that was associated with an increased risk of ovarian cancer is unknown.

3. 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. 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.

2. Dizziness and Drowsiness

Progesterone capsules may cause transient dizziness and drowsiness and should be used with caution when driving a motor vehicle or operating machinery. Progesterone 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 progesterone 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

Progesterone capsules should not be used during pregnancy.

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 progesterone capsules are administered to a nursing woman.

G. Pediatric Use

Progesterone 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 progesterone capsules to determine whether those over 65 years of age differ from younger subjects in their response to progesterone 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**.)

ADVERSE REACTIONS

See **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 progesterone capsules on the endometrium was studied in a total of 875 postmenopausal women. **Table 7** lists adverse reactions greater than or equal to 2 percent of women who received cyclic progesterone capsules 200 mg daily (12 days per calendar month cycle) with 0.625 mg conjugated estrogens or placebo.

TABLE 7. Adverse Reactions (≥ 2%) Reported in an 875 Patient Placebo-Controlled Trial in Postmenopausal Women Over a 3-Year Period [Percentage (%) of Patients Reporting]

	Progesterone 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 progesterone capsules on secondary amenorrhea was studied in 49 estrogen-primed postmenopausal women. **Table 8** lists adverse reactions greater than or equal to 5 percent of women who received progesterone capsules or placebo.

TABLE 8. Adverse Reactions (≥ 5%) Reported in Patients Using 400 mg/day in a Placebo-Controlled Trial in Estrogen-Primed Postmenopausal Women

Adverse Experience	Progesterone 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 progesterone capsules, 300 mg per day (n=113) or progesterone 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 progesterone 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, progesterone capsules should be discontinued and the patient should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Prevention of Endometrial Hyperplasia

Progesterone 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

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

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

HOW SUPPLIED

Progesterone capsules, 100 mg are off-white, ovoid, capsules with "*PR1*" marked.

NDC 70700-162-01, Bottle of 100 capsules

Progesterone capsules, 200 mg are off-white, ovoid, capsules with "*PR2*" marked.

NDC 70700-163-01, Bottle of 100 capsules

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from excessive moisture.

Dispense in tight, light-resistant container as defined in USP.

Keep out of reach of children.

Manufactured for:
Xiromed LLC, Florham Park, NJ 07932

Manufactured by:

Laboratorios León Farma, S.A. Villaquilambre, León Spain 24193

Rev. February 2026

PATIENT INFORMATION

Progesterone Capsules (proe-JES-ter-own)

Read this PATIENT INFORMATION before you start taking progesterone capsules and read what you get each time you refill your progesterone 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.

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

What is progesterone capsules?

Progesterone capsules contain the female hormone called progesterone.

What is progesterone capsules used for?

Treatment of Menstrual Irregularities

Progesterone 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, progesterone capsules may be prescribed to provide the progesterone you need.

Protection of the Endometrium (Lining of the Uterus)

Progesterone 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 progesterone capsules?

Do not start taking progesterone 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 progesterone capsules.
- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Are allergic to progesterone capsules or any of its ingredients**
  See the list of ingredients in progesterone capsules at the end of this leaflet.

Tell your healthcare provider:

- **If you are breastfeeding.** The hormone in progesterone 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 progesterone capsules work. Progesterone capsules may also affect how your other medicines work.

How should I take progesterone capsules?

1. Prevention of Endometrial Hyperplasia: A post-menopausal woman with a uterus who is taking estrogens should take a single daily dose of 200 mg progesterone capsules at bedtime for 12 continuous days per 28-day cycle.
2. Secondary Amenorrhea: Progesterone capsules may be given as a single daily dose of 400 mg at bedtime for 10 days.
3. **Progesterone capsules are to be taken at bedtime as some women become very drowsy and/or dizzy after taking progesterone 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 progesterone 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 progesterone 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 progesterone capsules. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to Xiromed, LLC at 1-844-XIROMED (1-844-947-6633) or to FDA at 1-800-FDA-1088.

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

- Talk with your healthcare provider regularly about whether you should continue taking progesterone capsules.
- See your healthcare provider right away if you get unusual vaginal bleeding while taking progesterone 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 progesterone capsules

- Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not take progesterone capsules for conditions for which it was not prescribed.
- Your healthcare provider has prescribed this drug for you and you alone. Do not give progesterone capsules to other people, even if they have the same symptoms you have. It may harm them.
- Progesterone 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 progesterone capsules out of the reach of children.

This leaflet provides a summary of the most important information about progesterone capsules. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about progesterone capsules that is written for health professionals. You can get more information by calling the toll free number 1-844-XIROMED (1-844-947-6633).

What are the ingredients in progesterone capsules?

Active ingredient: 100 mg or 200 mg micronized progesterone

Inactive ingredients: peanut oil, gelatin, glycerin, soya lecithin, titanium dioxide, and triglycerides medium chain.

HOW SUPPLIED

Progesterone capsules, 100 mg are off-white, ovoid, capsules with "*PR1*" marked.

NDC 70700-162-01, Bottle of 100 capsules.

Progesterone capsules, 200 mg are off-white, ovoid, capsules with "*PR2*" marked.

NDC 70700-163-01, Bottle of 100 capsules.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Protect from excessive moisture.

Manufactured for:
Xiromed LLC, Florham Park, NJ 07932

Manufactured by:

Laboratorios León Farma, S.A. Villaquilambre, León Spain 24193

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PI-162-04

PRINCIPAL DISPLAY PANEL - 100 mg Capsule Bottle Label

100 Capsules
NDC 70700-162-01

Progesterone Capsules

100 mg

Rx only

DO NOT USE IF ALLERGIC TO PEANUTS

Xiromed, LLC

PRINCIPAL DISPLAY PANEL - 200 mg Capsule Bottle Label

100 Capsules
NDC 70700-163-01

Progesterone Capsules

200 mg

Rx only

DO NOT USE IF ALLERGIC TO PEANUTS

Xiromed, LLC

PROGESTERONE

progesterone capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-162
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
PROGESTERONE (UNII: 4G7DS2Q64Y) (PROGESTERONE - UNII:4G7DS2Q64Y)	PROGESTERONE	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
PEANUT OIL (UNII: 5TL50QU0W4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	

Product Characteristics			
Color	WHITE (Off-White)	**Score**	no score
Shape	OVAL	**Size**	12mm
Flavor		**Imprint Code**	PR1
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70700-162-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	01/08/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205229	01/08/2021	

PROGESTERONE

progesterone capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70700-163
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
PROGESTERONE (UNII: 4G7DS2Q64Y) (PROGESTERONE - UNII:4G7DS2Q64Y)	PROGESTERONE	200 mg

Inactive Ingredients	
Ingredient Name	Strength
PEANUT OIL (UNII: 5TL50QU0W4)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	

Product Characteristics			
Color	WHITE (Off-White)	**Score**	no score
Shape	OVAL	**Size**	16mm
Flavor		**Imprint Code**	PR2
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70700-163-	100 in 1 BOTTLE; Type 0: Not a Combination	01/08/2021	

1	01	Product	01/08/2021	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205229	01/08/2021	

Labeler - Xiromed, LLC (080228637)

Establishment

Name	Address	ID/FEI	Business Operations
Laboratorios León Farma, SAU		467782459	manufacture(70700-162, 70700-163)

Revised: 2/2026 Xiromed, LLC