Patient Information Leaflet

ONEVE 100 mg capsules

progesterone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet

1. What ONEVE is and what it is used for

ONEVE contain the female hormone called progesterone.

ONEVE used for:

Treatment of Menstrual Irregularities
ONEVE is 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, ONEVE may be prescribed to provide the progesterone you need.

Protection of the Endometrium (Lining of the Uterus)
ONEVE is 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).

2. What you need to know before you take ONEVE

The most important information I should know about ONEVE:

- 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 ONEVE.

Do not start taking ONEVE 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 ONEVE.
- Had a stroke or heart attack
- Currently have or have had blood clots
- Currently have or have had liver problems
- Are allergic to ONEVE or any of its ingredients
  See the list of ingredients in ONEVE at the end of this leaflet.
- Think you may be pregnant

Tell your healthcare provider:

- If you are breastfeeding. The hormone in ONEVE 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 ONEVE work. ONEVE may also affect how your other medicines work.

3. How to take ONEVE

1. Prevention of Endometrial Hyperplasia: A postmenopausal woman with a uterus who is taking estrogens should take a single daily dose of 200 mg ONEVE at bedtime for 12 continuous days per 28-day cycle.
2. Secondary Amenorrhea: ONEVE may be given as a single daily dose of 400 mg at bedtime for 10 days.
3. ONEVE are to be taken at bedtime as some women become very drowsy and/or dizzy after taking ONEVE. 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 ONEVE, it is recommended that you take your daily dose at bedtime with a glass of water while in the standing position.

4. Possible side effects

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 ONEVE. For more information, ask your healthcare provider or pharmacist for advice about side effects.

5. How to store ONEVE

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from excessive moisture.

6. Further information

What ONEVE contains

- The active substance is progesterone, USP.
- The other ingredients are soy lecithin USP/NF, arachis oil refined Ph. Eur./peanut oil NF, gelatin NF (pharmaceutical gelatin B150), glycerin USP, D & C yellow No.10 aluminum lake, FD&C yellow #6 aluminum lake, titanium dioxide USP and purified water USP.

What ONEVE looks like and contents of the pack

ONEVE are rounds, light orange soft gelatin, capsules printed with "A87".

ONEVE is available as 100's and 500's counts in bottle pack.

Marketing Authorisation Holder
Amneal Pharmaceuticals of New York, LLC

Manufacturer
Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road, Brookhaven, NY 11719

This leaflet was last revised in 08/2023.

To report any side effect(s):

- **Saudi Arabia:**

- The National Pharmacovigilance Centre (NPC):
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/

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Space for Edge code

Package Leaflet

ONEVE

Progesterone Capsules 100 mg

amneal®

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1. NAME OF THE MEDICINAL PRODUCT

ONEVE (Progesterone Capsules 100 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Each capsule contains:
Progesterone, USP ……..100 mg
Excipients……..q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

Rounds, Light Orange Soft Gelatin, Capsules Printed with "A87".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONEVE is 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.

4.2 Posology and method of 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.

4.3 Contraindications

Progesterone capsules should not be used in women with any of the following conditions:

1. Progesterone capsules should not be used in patients with known hypersensitivity to its ingredients. Progesterone 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.

4.4 Special warnings and precautions for use

WARNINGS

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. 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.

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. 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.

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 to 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.

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 to 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.

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 to 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.

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

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

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.

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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

See sections 4.4 and 5.2.

4.6 Fertility, pregnancy and lactation

Pregnancy

Progesterone capsules should not be used during pregnancy (see section 4.3).

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.

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.

4.7 Effects on ability to drive and use machines

This medicine may cause drowsiness or dizziness; therefore care should be taken when driving or using machines.

4.8 Undesirable effects

4.8.1 Adverse reactions

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 1 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 1. 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 2 lists adverse reactions greater than or equal to 5 percent of women who received progesterone capsules or placebo.

Table 2. 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 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.

4.8.2 Clinical Studies Experience (upon request from any regulatory Authority in GCC)

4.8.3 Post-marketing Experience (upon request from any regulatory Authority in GCC)

To reports any side effect(s):

Saudi Arabia:

- The National Pharmacovigilance Centre (NPC):
  - SFDA Call Center: 19999
  - E-mail: npc.drug@sfda.gov.sa
  - Website: https://ade.sfda.gov.sa/

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system; Progestogens; Pregnen-(4) derivatives

ATC code: G03DA04

Mechanism of Action

Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. It acts on the endometrium by converting the proliferating phase to the secretory phase. Progesterone capsules have all the properties of endogenous progesterone, in particular gestagenic, antiestrogenic, slightly anti-androgenic and antialdosterone effects.

5.2 Pharmacokinetic properties

Absorption

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

Table 3. 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
$AUC_{(0\text{-}10)}$ (ng × hr/mL)	43.3 ± 30.8	101.2 ± 66	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.

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).

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.

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.

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.

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.

Drug Interactions

The metabolism of progesterone by human liver microsomes was inhibited by ketoconazole (IC50 <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.

Co-administration 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 co-administration of progesterone capsules. Table 4 summarizes the pharmacokinetic parameters.

Table 4. Mean (± S.D.) Pharmacokinetic Parameters for Estradiol, Estrone and Equilin Following Co-administration 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)	$AUC_{(0\text{-}24h)}$ (ng × h/mL)	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0\text{-}24h)}$ (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 ± 4	28.8 ± 13	3.22 ± 1.13	5.3 ± 2.6	38.1 ± 20.2
[a] Total estrogens is the sum of conjugated and unconjugated estrogen.						

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, and 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Soy Lecithin USP/NF
Arachis Oil Refined Ph. Eur./Peanut Oil NF
Gelatin NF (Pharmaceutical Gelatin B150)
Glycerin USP
D & C Yellow No.10 Aluminum Lake
FD&C Yellow #6 Aluminum Lake
Titanium Dioxide USP
Purified Water USP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Store at 20° to 25°C (68° to 77°F); excursions permitted between 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.

Keep out of the sight and reach of children.

6.5 Nature and contents of container

Progesterone Capsules 100 mg are available as 100's and 500's counts in bottle pack.

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amneal Pharmaceuticals of New York, LLC
50 Horseblock Road, Brookhaven, NY 11719

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9. DATE OF REVISION OF THE TEXT

Iss. 08-2023-00

10. DOSIMETRY

Not Applicable

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not Applicable