CLINICAL MONOGRAPH · HORMONE OPTIMIZATION

Progesterone

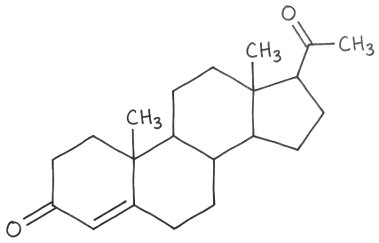
Bioidentical progesterone for HRT and gynecologic care

Progesterone is the body's main natural progestogen, the hormone the ovary's corpus luteum makes in the second half of the menstrual cycle, and the hormone the placenta makes in large amounts during pregnancy [fonseca2007shortcervix]. Bioidentical micronized progesterone is the same molecule, prepared in a form the body can absorb.

Doctors prescribe progesterone primarily for two reasons: to protect the lining of the uterus in women who are taking estrogen for menopause symptoms, and to support pregnancy in assisted reproductive technology (IVF) or to prevent preterm birth in women with a short cervix [stuenkel2015endo; nams2022ht; pepi1996endometrium]. There are FDA-approved products for each of these uses, Prometrium (oral capsule), Crinone (vaginal gel), and Endometrin (vaginal insert).

RonanRx can also compound bioidentical progesterone, a custom-strength oral capsule, a vaginal suppository at a strength the manufactured market does not offer, a troche for patients who cannot tolerate the peanut-oil excipient in Prometrium, or a cream for a specific patient-prescribed use. We are explicit about one limitation: progesterone creams do not reliably reach blood levels high enough to protect the uterine lining from estrogen, so compounded creams should not be used as the progestogen arm of a combined estrogen-plus-progestogen regimen unless a different route is also in place [nasem2020bht].

Progesterone is not a controlled substance, but it is a prescription medication that requires evaluation by a clinician, with dosing and route chosen for the specific clinical reason [epppic2021ipd].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED

REVIEWED **2026-05-11**

State-licensed 503A	Pharmacist reviewed	Doctor led	Cold-chain ready	Patient choice preserved

Contents

Click any section to jump there. Page numbers update on render.

FOR CLINICIANS

Bioidentical micronized progesterone has two well-established FDA-approved roles: endometrial protection in estrogen-containing menopausal hormone therapy (oral Prometrium 100, 200 mg, cyclic or continuous; PEPI established endometrial-protection equivalence with medroxyprogesterone acetate) [pepi1996endometrium], and luteal support in assisted reproduction (Crinone vaginal gel, Endometrin vaginal insert) with broad Cochrane-supported evidence for clinical pregnancy outcomes [vanderlinden2011luteal]. A third evidence-based role, vaginal progesterone for prevention of preterm birth in women with a short cervix, emerged from Da Fonseca 2003, Fonseca 2007, and Hassan 2011 and was consolidated by the EPPPIC 2021 individual-patient-data meta-analysis [dafonseca2003preterm] [fonseca2007shortcervix] [hassan2011shortcervix] [epppic2021ipd].

The bioidentical-progesterone vs synthetic-progestin distinction is meaningful but constrained. PEPI [pepi1996endometrium] and WHI [rossouw2002whi] used medroxyprogesterone acetate (MPA), not micronized progesterone. The E3N observational cohort [fournier2008e3n] reported that estrogen-plus-progesterone HRT carried a smaller breast-cancer signal than estrogen-plus-synthetic-progestin HRT, supportive but not equivalent to a head-to-head randomized trial. NAMS 2022 [nams2022ht] and the Endocrine Society 2015 [stuenkel2015endo] frame micronized progesterone as a reasonable choice for endometrial protection in combined HRT, while the NASEM 2020 report on compounded bioidentical hormone therapy [nasem2020bht] is the consensus document on the scope and limits of compounding in this space.

Transdermal/topical progesterone cream is a specific point of caution: published serum levels and endometrial biopsy data do not support its use as the progestogen arm of combined estrogen HRT, because serum progesterone with creams typically does not reach the threshold associated with reliable secretory transformation of estrogen-primed endometrium. This is consistent across the NAMS, Endocrine Society, and NASEM positions [nasem2020bht] [stuenkel2015endo].

Off-label progesterone uses with published evidence: catamenial epilepsy in women with cycle-locked seizure exacerbation [herzog2012epilepsy] [herzog2012epilepsy] [herzog2014allopreg]; perimenopausal vasomotor symptoms [hitchcock2012vms] [hitchcock2012vms]; sleep quality [caufriez2011sleep] [caufriez2011sleep]; premenstrual syndrome and PMDD (negative, Wyatt 2001 systematic review and Ford 2012 Cochrane do not support efficacy) [wyatt2001pms] [ford2012pms]; first-trimester bleeding (PRISM 2019, no overall effect, possible benefit in women with prior miscarriages) [coomarasamy2019prism]; recurrent preterm birth (17-OHPC, Meis 2003 positive [meis2003ohpc], PROLONG 2020 failed confirmatory trial [blackwell2020prolong], Makena withdrawn 2023). Traumatic brain injury, ProTECT III [wright2014protect3] was negative [wright2014protect3]. Postpartum depression mechanism, IV allopregnanolone (brexanolone, FDA 2019) is the validated proof of the GABAergic-neurosteroid mechanism that distinguishes bioidentical progesterone from synthetic progestins [meltzerbrody2018brexanolone].

Compounded progesterone occupies a real but circumscribed 503A niche: custom oral strengths (e.g., 50 mg, 75 mg, 150 mg between Prometrium's 100 and 200 mg), vaginal suppositories at strengths not provided by Crinone/Endometrin, troches for patients who cannot tolerate the peanut-oil excipient in Prometrium, and patient-specific combination preparations. Compounded creams are not appropriate for endometrial protection.

Why Personalized Progesterone

Prometrium was approved at 100 mg and 200 mg oral capsules. Crinone was approved at 4% and 8% vaginal gel. Those strengths and routes were chosen because they cleared the endpoints the FDA wanted to see, endometrial protection in combined HRT and luteal support in IVF. The trials did not pick a dose for your baseline progesterone level, your sleep response, your sensitivity to peanut-oil excipient, your tolerance for the next-morning grogginess that oral micronized progesterone produces in some women, or where you actually sit in the perimenopausal transition. They picked one dose for a population.

Compounding is what closes that gap. The molecule is the same bioidentical progesterone the FDA reviewed in Prometrium. RonanRx can prepare it at a custom oral strength between the standard 100 mg and 200 mg when a prescriber is titrating sleep or mood response, as a peanut-oil-free troche or capsule for patients with peanut allergy or excipient sensitivity, or as a vaginal suppository at a strength Crinone and Endometrin do not offer. For continuous combined HRT regimens that pair a specific estradiol dose with a non-standard progesterone strength, the compounded preparation is the only way to land both numbers on the same prescription. We are explicit about one limit, transdermal cream does not reach serum levels high enough to protect the uterine lining from estrogen, so cream is not the progestogen arm of a combined HRT regimen.

This is what pharmacy looked like before mass manufacturing arrived. A prescriber wrote the order for a named patient, and a pharmacist prepared it to match. Compounded progesterone is that older arrangement, kept honest by modern oversight.

Quick Facts About Progesterone

Category: Endogenous progestogen (C21 steroid hormone); the principal natural progestogen in humans

Active ingredient: Progesterone (bioidentical, micronized), chemically identical to the endogenous hormone (pregn-4-ene-3,20-dione)

FDA-approved branded products: Prometrium (oral micronized capsule, 1998), Crinone (vaginal gel, 1997), Endometrin (vaginal insert, 2007). 17-α-hydroxyprogesterone caproate (Makena) was withdrawn from the US market in 2023 after the PROLONG confirmatory trial failed to replicate the original Meis 2003 benefit.

Routes studied in humans: Oral micronized (Prometrium), vaginal gel (Crinone), vaginal insert (Endometrin), intramuscular (progesterone in oil), and compounded routes: vaginal suppository, troche, rectal suppository, topical/transdermal cream

Evidence posture: Multiple FDA-approved manufactured products; foundational randomized evidence from PEPI (endometrial protection), WHI (combined estrogen-progestin arm with MPA), and large vaginal-progesterone preterm-birth program (Fonseca, Hassan, Norman OPPTIMUM, EPPPIC IPD meta-analysis). E3N observational cohort distinguishes bioidentical progesterone from synthetic progestins on breast safety.

FDA-approval status: Prometrium, Crinone, and Endometrin are FDA-approved manufactured products. Compounded preparations are not FDA-approved but address established patient-specific needs (custom strengths between 100 / 200 mg, alternative routes, excipient sensitivities, troches).

Compounded under: 503A, patient-specific prescription only. Not a controlled substance.

Compounded role: Custom strengths the manufactured market does not offer (between standard 100 mg / 200 mg oral; vaginal compounded suppositories at specified strengths; female-physiologic compounded creams for adjunct use), troches for patients who cannot tolerate the peanut-oil excipient in Prometrium, and combination preparations on a documented patient-specific prescription. Routine substitution of compounded oral progesterone for Prometrium without a documented clinical reason is not within the FDA's 503A framing.

Notable caution: Transdermal progesterone cream produces serum levels that are inadequate to reliably oppose estrogen-induced endometrial proliferation; it should not be used as the endometrial-protection arm of a combined hormone-therapy regimen. The NASEM 2020 report addresses this directly.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Progesterone described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.

- **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
- **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
- **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
- **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
- **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Progesterone?

Progesterone (pregn-4-ene-3,20-dione) is the principal endogenous progestogen in humans, a C21 steroid synthesized from pregnenolone, which is itself derived from cholesterol [campagnoli2005breast]. In a non-pregnant cycling woman, the dominant source is the corpus luteum during the luteal (second) half of the menstrual cycle, producing approximately 20, 25 mg per day at peak. In pregnancy the placenta becomes the dominant source after roughly the 7th, 9th week of gestation and produces several hundred milligrams per day by the third trimester. Small amounts derive from the adrenal cortex year-round.

Bioidentical progesterone, the same chemical entity as the endogenous hormone, has been used pharmaceutically since the 1930s and 1940s [campagnoli2005breast]. Oral bioavailability of unmodified progesterone is very low because of extensive first-pass hepatic metabolism. The modern oral formulation became practical when micronization (reduction to small particle size, suspended in an oil vehicle) substantially improved absorption [hargrove1989oral]. Prometrium (oral micronized progesterone in peanut oil) received FDA approval in 1998; Crinone (vaginal gel) in 1997; Endometrin (vaginal insert) in 2007.

Progesterone is structurally and functionally distinct from synthetic progestins (medroxyprogesterone acetate, norethindrone, levonorgestrel, drospirenone, and others) used in oral contraceptives and the original WHI combined-HRT regimen. Synthetic progestins are designed for selectivity, potency, oral activity, or progesterone-receptor binding profile, they are not equivalent to the endogenous hormone in receptor selectivity, metabolite spectrum, or adverse-event profile [schindler2003classification] [stanczyk2013progestogens] [campagnoli2005breast; sitrukware2006progestagens].

How Progesterone Works

Progesterone acts at the nuclear progesterone receptor (PR), a ligand-activated transcription factor expressed in two principal isoforms, PR-A and PR-B, encoded by a single gene with two promoters. The two isoforms have distinct, sometimes opposing, transcriptional programs: PR-B is the principal transcriptional activator in mammary gland and several reproductive tissues, while PR-A is dominant in uterus and is required for normal reproductive function. Isoform-selective knockout mice established the in vivo separation of function [mulac2000prb] [conneely2001isoforms].

Beyond classical genomic PR signaling, progesterone has rapid nongenomic effects through membrane-associated progesterone receptors (mPRα, mPRβ, PGRMC1) and is the precursor for the neurosteroid 5α-pregnan-3α-ol-20-one (allopregnanolone), a potent positive allosteric modulator of the GABA-A receptor

[schumacher2014progesterone] [guennoun2015allopreg]. The GABA-A modulation by allopregnanolone is mechanistically distinct from synthetic progestins (which do not reliably generate allopregnanolone) and underlies progesterone's sedating, anxiolytic, and anticonvulsant properties. The FDA approval of intravenous allopregnanolone (brexanolone, Zulresso, 2019) for severe postpartum depression is the clinical proof of this mechanism [meltzerbrody2018brexanolone].

Endometrial action is the best-characterized clinical effect of progesterone: in estrogen-primed endometrium, progesterone induces secretory transformation, opposes estrogen-driven mitogenic activity, and prevents the development of endometrial hyperplasia and carcinoma. The PEPI trial [pepi1996endometrium] established that micronized progesterone (200 mg cyclic 12 days/month) protects estrogen-primed endometrium at a rate equivalent to medroxyprogesterone acetate, with markedly less hyperplasia than estrogen alone. The vaginal route exploits a first uterine pass effect: vaginally administered progesterone concentrates in the uterus at concentrations several-fold higher than serum [deziegler1997firstpass] [cicinelli1998uterine].

Biological Role of Progesterone

Progesterone has three principal physiologic roles in adult women [schumacher2014progesterone]. First, it is the luteal-phase hormone of the menstrual cycle: after ovulation, the corpus luteum secretes 20, 25 mg/day at peak, transforming estrogen-primed endometrium into a receptive secretory phase that supports implantation if it occurs. Withdrawal of progesterone (corpus luteum involution if no pregnancy) triggers menstrual sloughing. Second, it is the pregnancy hormone: placental progesterone production rises from milligrams per day in early pregnancy to several hundred milligrams per day at term, maintaining uterine quiescence, immunologic tolerance of the fetus, and decidual integrity. Third, it is a continuous low-level neurosteroid precursor and adrenal-derived contributor in both sexes.

In men and in non-cycling women (prepubertal, postmenopausal, or amenorrheic), basal progesterone concentrations are low, adrenal-derived at approximately 0.1, 0.3 ng/mL, and the principal physiologic role is as substrate for neurosteroid synthesis (allopregnanolone), corticosteroid biosynthesis (progesterone is the immediate precursor of 11-deoxycorticosterone in the mineralocorticoid pathway), and the broader steroidogenic cascade [schumacher2014progesterone].

Endogenous progesterone declines abruptly at menopause (in the year or two surrounding ovarian senescence) alongside the more gradually declining estradiol. Perimenopausal progesterone deficiency is one of the proposed mechanisms underlying perimenopausal sleep disruption, mood lability, and vasomotor symptoms, and is the conceptual basis for off-label perimenopausal progesterone use [caufriez2011sleep] [hitchcock2012vms] [schumacher2014progesterone].

Detailed Mechanism of Progesterone

Progesterone receptor isoform biology. The PR gene is transcribed from two estrogen-induced promoters yielding PR-B (the full-length isoform, ~114 kDa) and the N-terminally truncated PR-A (~94 kDa). Both isoforms bind progesterone and the same DNA progesterone-response elements, but their N-terminal domains recruit different coregulators and produce different transcriptional outputs. PR-A can function as a transdominant repressor of PR-B in some tissue contexts. Isoform-selective knockout mice [mulac2000prb] [conneely2001isoforms] demonstrated that PR-A is required for the antiproliferative endometrial effect of progesterone and for normal ovulation and decidualization, while PR-B is required for normal mammary gland alveologenesis during pregnancy and lactation. This isoform separation underlies why the tissue-specific effects of progesterone in uterus, breast, and brain are not interchangeable.

Neurosteroid pathway. Approximately 5, 15% of administered progesterone is metabolized by 5α-reductase to 5α-dihydroprogesterone and then by 3α-hydroxysteroid dehydrogenase to 5α-pregnan-3α-ol-20-one (allopregnanolone). Allopregnanolone is one of the most potent endogenous positive allosteric modulators of the GABA-A receptor, comparable in efficacy to benzodiazepines at synaptic GABA-A subtypes and uniquely active at tonic-inhibition extrasynaptic δ-subunit-containing GABA-A receptors [schumacher2014progesterone] [guennoun2015allopreg]. This pathway explains progesterone's CNS effects (sedation, anxiolysis, anticonvulsant action) and is the basis for the dose-dependent somnolence experienced with bedtime oral progesterone. The pathway is also why bedtime dosing of Prometrium is recommended and why bioidentical progesterone has CNS effects that synthetic progestins do not reproduce.

First uterine pass effect. Vaginally administered progesterone produces serum levels lower than oral or IM administration at comparable doses but concentrates in the uterus at concentrations several-fold higher than serum [deziegler1997firstpass]. Cicinelli demonstrated higher progesterone concentrations in uterine artery than in radial artery after vaginal administration, providing direct evidence of preferential uterine delivery [cicinelli1998uterine]. This pharmacokinetic feature is the basis for the efficacy of vaginal progesterone in luteal support and in preventing preterm birth in women with a short cervix, where local rather than systemic concentration is the relevant target [hassan2011shortcervix] [romero2018ipd].

Endometrial physiology. In estrogen-primed endometrium, progesterone via PR-A induces secretory transformation: glandular convolution, glycogen accumulation, stromal pre-decidualization, and ultimately decidualization if implantation occurs or menstrual sloughing if not. Pharmacologically, this antiproliferative effect on estrogen-driven mitosis is the mechanism by which adequate progestogen exposure prevents endometrial hyperplasia and adenocarcinoma in women receiving estrogen replacement. PEPI [pepi1996endometrium] established the quantitative threshold: estrogen-only therapy produced complex/atypical hyperplasia in ~10, 34% of cycles per arm, while estrogen plus micronized progesterone

200 mg cyclic 12 days/month produced rates indistinguishable from placebo. PEPI is the principal randomized evidence for oral micronized progesterone as endometrial-protective.

Pregnancy maintenance. Progesterone maintains uterine quiescence by reducing myometrial contractility (membrane progesterone receptor signaling), suppresses maternal cell-mediated immunity at the maternal-fetal interface, and supports decidual stability. In assisted reproduction, exogenous progesterone substitutes for the corpus luteum (which is suppressed in stimulated cycles) until the placenta becomes the dominant source. Vaginal and IM progesterone are the principal routes used in ART [vanderlinden2011luteal].

Breast tissue. Progesterone effects on normal and neoplastic breast tissue are complex and clinically consequential. The E3N cohort [fournier2008e3n] reported that combined HRT with synthetic progestins (most commonly MPA in the European prescribing context) carried a higher breast-cancer risk than estrogen alone or estrogen plus bioidentical progesterone. The mechanistic interpretation, that progesterone's PR-A/PR-B isoform balance and lack of off-target androgen-receptor activity distinguish it from synthetic progestins on breast tissue, is supported by Campagnoli's reviews [campagnoli2005breast] and the Stanczyk progestogens framework [stanczyk2013progestogens]. The randomized evidence for breast safety of bioidentical progesterone vs synthetic progestins in combined HRT remains observational; WHI [rossouw2002whi] used MPA, not micronized progesterone.

CNS effects beyond GABA-A. Progesterone has progesterone-receptor and neurosteroid-mediated effects on sleep architecture (REM modulation), thermoregulation (the hypothalamic warming effect responsible for the luteal-phase basal temperature rise; also relevant to vasomotor symptoms in perimenopause), and seizure threshold (allopregnanolone's anticonvulsant effect underlies the catamenial-epilepsy biology characterized by Herzog [herzog2012epilepsy] [herzog2014allopreg]).

Progesterone Research History

Progesterone was isolated in 1934 by four research groups in rapid succession (Butenandt, Slotta, Hartmann, and others), with characterization of the molecule and total synthesis from cholesterol following over the next several years. Early clinical use was limited by the very poor oral bioavailability of unmodified progesterone, which drove the development of synthetic progestins in the 1940s and 1950s, pharmacologically active orally and patentable, but not structurally identical to the endogenous hormone.

The modern era of bioidentical oral progesterone began with Hargrove and Maxson's 1989 demonstration that micronization (reducing particle size and suspending in oil) substantially improved oral absorption [hargrove1989oral]. Subsequent pharmacokinetic and pharmacodynamic work by de Lignières and colleagues [delignieres2000pd] characterized the oral micronized progesterone profile and its applicability to combined hormone therapy. Prometrium received FDA approval in 1998.

The vaginal route emerged in parallel. De Ziegler and Bulletti demonstrated the 'first uterine pass effect', preferential uterine concentration after vaginal administration [deziegler1997firstpass], and Cicinelli

confirmed the uterine-artery vs systemic gradient [cicinelli1998uterine]. Crinone vaginal gel (FDA 1997) and Endometrin vaginal insert (FDA 2007) followed, principally for luteal support in assisted reproduction.

The PEPI trial [pepi1996endometrium] established that oral micronized progesterone 200 mg cyclic protects estrogen-primed endometrium as effectively as MPA, the foundational endometrial-safety evidence for bioidentical progesterone in combined menopausal hormone therapy. PEPI's endometrial-histology analysis remains a touchstone in NAMS and Endocrine Society guidance [stuenkel2015endo] [nams2022ht].

The WHI combined-HRT arm [rossouw2002whi] was stopped early in 2002 for an excess of cardiovascular events, breast cancer, and venous thromboembolism in the estrogen-plus-MPA arm. The estrogen-alone arm in hysterectomized women [stefanick2006wbi] showed a different signal, no breast cancer excess, in fact a non-significant reduction. Long-term follow-up [manson2017whi] consolidated the picture. The WHI is universally cited but is not a randomized test of bioidentical progesterone vs synthetic progestin; it used MPA throughout.

Observational evidence on the bioidentical-vs-synthetic distinction is dominated by the E3N French cohort. Fournier 2008 [fournier2008e3n] reported that, compared with never-users, estrogen-plus-progesterone HRT was not associated with an increased breast-cancer risk over 8 years of follow-up, while estrogen plus synthetic progestins (including MPA and norethisterone) was. This observational signal is supportive but not equivalent to randomized evidence; it is cited by NAMS [nams2022ht] and by the Endocrine Society [stuenkel2015endo] as informing the rationale for considering micronized progesterone over synthetic progestins in combined HRT.

The preterm-birth program developed across two decades. Da Fonseca 2003 [dafonseca2003preterm] reported reduction in spontaneous preterm birth with vaginal progesterone suppositories in women at increased risk. Meis 2003 [meis2003ohpc] reported large benefit with 17-α-hydroxyprogesterone caproate (17-OHPC) IM in women with prior preterm birth, leading to FDA accelerated approval of Makena. Fonseca 2007 [fonseca2007shortcervix] and Hassan 2011 [hassan2011shortcervix] established benefit of vaginal progesterone specifically in women with a sonographic short cervix. Norman OPPTIMUM 2016 [norman2016opptimum] failed to replicate broad benefit in a heterogeneous-risk UK trial. The Romero 2018 IPD meta-analysis [romero2018ipd] and the EPPPIC 2021 IPD meta-analysis [epppic2021ipd] consolidated the field: vaginal progesterone reduces preterm birth in women with a short cervix; 17-OHPC failed confirmatory replication in PROLONG [blackwell2020prolong] and Makena was withdrawn from the US market in 2023.

Allopregnanolone biology was developed across the 1990s and 2000s by Majewska, Belelli, Lambert, and others, with foundational reviews by Schumacher [schumacher2014progesterone] and Guennoun [guennoun2015allopreg]. The FDA approvals of brexanolone (IV allopregnanolone, 2019) for postpartum depression on the basis of Meltzer-Brody's phase 3 program [meltzerbrody2018brexanolone] and the oral allopregnanolone analog zuranolone (2023) clinically validated the GABA-A neurosteroid mechanism. The

ProTECT III trial of progesterone for traumatic brain injury [wright2014protect3] was negative, ending an active translational hypothesis.

Compounded bioidentical hormone therapy, including compounded progesterone, was the subject of the 2020 NASEM report [nasem2020bht], which acknowledged legitimate compounding for documented patient-specific need while explicitly criticizing routine substitution of compounded for FDA-approved products without clinical rationale, and explicitly criticizing transdermal progesterone creams marketed for endometrial protection. NAMS 2022 [nams2022ht] and Endocrine Society 2015 [stuenkel2015endo] echo this scope.

Progesterone Timeline

1934 • Progesterone isolated and characterized by Butenandt, Slotta, Hartmann, and others in rapid succession; total synthesis from cholesterol follows

1989 • Hargrove and Maxson demonstrate that micronization plus oil vehicle substantially improves oral progesterone absorption, the pharmaceutical basis for modern oral bioidentical progesterone [hargrove1989oral]

1996 • PEPI (Postmenopausal Estrogen/Progestin Interventions) endometrial-histology paper published, oral micronized progesterone 200 mg cyclic 12 days/month protects estrogen-primed endometrium at a rate equivalent to MPA [pepi1996endometrium]

1997 • Crinone (vaginal progesterone gel) FDA-approved for luteal support and secondary amenorrhea; De Ziegler and Bulletti publish 'The first uterine pass effect' establishing preferential uterine delivery after vaginal administration [deziegler1997firstpass]

1998 • Prometrium (oral micronized progesterone in peanut oil) FDA-approved for endometrial protection in combined HRT and for secondary amenorrhea; Cicinelli publishes uterine-artery vs radial-artery progesterone gradient confirming uterine-targeted delivery via vaginal route [cicinelli1998uterine]

2000 • Mulac-Jericevic publishes Science paper on PR-B isoform-selective knockout mouse, demonstrates separate-of-function reproductive phenotypes of PR-A and PR-B [mulac2000prb]

2001 • Conneely reviews the lessons of progesterone receptor knockout mice, A vs B isoform-selective biology, in Steroids; Wyatt publishes systematic review concluding progesterone/progestogens are not efficacious for PMS [conneely2001isoforms; wyatt2001pms]

2002 • Women's Health Initiative combined estrogen-plus-MPA arm (Rossouw, JAMA) stopped early for excess CV events, breast cancer, and VTE [rossouw2002whi]

2003 • Schindler publishes classification and pharmacology of progestins; Meis publishes 17-OHPC trial in NEJM showing reduction in recurrent preterm birth (basis for FDA approval of Makena, later withdrawn); Da Fonseca publishes vaginal progesterone suppository trial showing reduction in preterm birth in women at increased risk [schindler2003classification; meis2003ohpc; dafonseca2003preterm]

2006 • WHI estrogen-only (CEE) arm in hysterectomized women published (Stefanick et al, JAMA), no breast cancer excess and a non-significant reduction; supports the interpretation that the progestogen component of combined HRT was responsible for much of the breast signal in the combined arm [stefanick2006wbi]

2007 • Endometrin (vaginal insert) FDA-approved for luteal support in ART; Fonseca publishes 'Progesterone and the risk of preterm birth among women with a short cervix' in NEJM, vaginal progesterone reduces preterm birth in women with sonographic short cervix [fonseca2007shortcervix]

2008 • Fournier publishes the E3N cohort analysis showing estrogen-plus-progesterone HRT carries a smaller breast-cancer signal than estrogen-plus-synthetic-progestin HRT, the principal observational evidence for the bioidentical-vs-synthetic distinction in HRT [fournier2008e3n]

2011 • Hassan publishes the PREGNANT trial, vaginal progesterone reduces preterm birth in women with a sonographic short cervix in a multicenter randomized double-blind placebo-controlled trial; Caufriez publishes randomized trial of oral progesterone in postmenopausal women showing improvement in sleep architecture and modulation of GH/TSH/melatonin; van der Linden publishes Cochrane review of luteal phase support in ART [hassan2011shortcervix; caufriez2011sleep; vanderlinden2011luteal]

2012 • Herzog publishes randomized trial of progesterone in women with epilepsy, overall negative, with a pre-specified subgroup of perimenstrually-exacerbated catamenial epilepsy showing benefit; Hitchcock and Prior publish placebo-controlled randomized trial of oral micronized progesterone for vasomotor symptoms; Ford publishes Cochrane review concluding progesterone is not effective for PMS [herzog2012epilepsy; hitchcock2012vms; ford2012pms]

2013 • Stanczyk publishes 'Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects', the standard reference for the pharmacology of progestogen heterogeneity; Dodd publishes Cochrane review of antenatal progesterone for preterm birth prevention [stanczyk2013progestogens; dodd2013cochrane]

2014 • Schumacher publishes 'Revisiting the roles of progesterone and allopregnanolone in the nervous system' (Prog Neurobiol); Herzog publishes follow-up showing allopregnanolone levels track seizure frequency in progesterone-treated women with epilepsy; Wright publishes ProTECT III in NEJM, IV progesterone for severe traumatic brain injury, negative [schumacher2014progesterone; herzog2014allopreg; wright2014protect3]

2015 • Endocrine Society Clinical Practice Guideline on Treatment of Symptoms of the Menopause (Stuenkel et al, JCEM), frames micronized progesterone as a reasonable option for endometrial protection in combined HRT; Guennoun publishes review on progesterone and allopregnanolone CNS effects in J Steroid Biochem Mol Biol [stuenkel2015endo; guennoun2015allopreg]

2016 • Norman publishes the OPPTIMUM trial (Lancet), vaginal progesterone for preterm birth prophylaxis in heterogeneous-risk women, primary endpoint negative; Hodis publishes ELITE (NEJM), early postmenopausal oral estradiol plus vaginal progesterone reduced subclinical atherosclerosis vs placebo, while late initiation did not [norman2016opptimum; hodis2016elite]

2017 • Manson publishes long-term WHI mortality follow-up (JAMA), no increase in all-cause or cause-specific mortality through 18 years of cumulative follow-up; Hembree publishes updated Endocrine Society guideline on endocrine treatment of gender-dysphoric/gender-incongruent persons (JCEM) [manson2017whi; hembree2017transgender]

2018 • Romero publishes the individual-patient-data meta-analysis of vaginal progesterone for preterm birth prevention in women with a sonographic short cervix, confirms efficacy in the short-cervix subgroup; Meltzer-Brody publishes brexanolone (IV allopregnanolone) phase 3 program in Lancet, clinical proof of GABAergic-neurosteroid mechanism [romero2018ipd; meltzerbrody2018brexanolone]

2019 • Coomarasamy publishes PRISM (NEJM), vaginal progesterone for women with bleeding in early pregnancy, no overall effect on live birth, possible benefit in subgroup with prior miscarriages; FDA approves brexanolone (Zulresso) for postpartum depression [coomarasamy2019prism; meltzerbrody2018brexanolone]

2020 • Blackwell publishes PROLONG (Am J Perinatol), confirmatory phase 4 trial of 17-OHPC for recurrent preterm birth in singletons, negative, failed to replicate Meis 2003; NASEM publishes report on compounded bioidentical hormone therapy [blackwell2020prolong; nasem2020bht]

2021 • EPPPIC group publishes individual-patient-data meta-analysis (Lancet) of vaginal progesterone, 17-OHPC, and oral progesterone across the preterm-birth prevention literature, vaginal progesterone confirmed effective in women with short cervix or prior preterm birth; oral progesterone and 17-OHPC not supported [epppic2021ipd]

2022 • NAMS publishes the 2022 hormone therapy position statement; Coleman publishes WPATH Standards of Care Version 8, both reference micronized progesterone within their respective frameworks [nams2022ht; coleman2022wpath]

2023 • FDA initiates withdrawal of Makena (17-OHPC) from the US market after PROLONG confirmatory trial failure; vaginal progesterone retains evidence and labeling for short-cervix indication via Crinone and via individual prescription; Prior publishes a phase 3 Canada-wide randomized placebo-controlled 4-month trial of oral micronized progesterone for perimenopausal night sweats and hot flushes [blackwell2020prolong; prior2023vms]

Clinical Contexts for Progesterone

Endometrial protection in estrogen-containing menopausal hormone therapy

FDA APPROVED

FDA-approved indication for oral micronized progesterone (Prometrium); foundational evidence from PEPI.

Oral micronized progesterone is FDA-approved for the prevention of endometrial hyperplasia and adenocarcinoma in postmenopausal women with an intact uterus who are receiving estrogen therapy. The PEPI trial [pepi1996endometrium] established that micronized progesterone 200 mg cyclic for 12 days each month protects estrogen-primed endometrium at a rate equivalent to medroxyprogesterone acetate, with markedly lower hyperplasia rates than estrogen alone. Continuous-combined regimens use lower daily doses (typically 100 mg/day) with similar endometrial protection. NAMS [nams2022ht] and the Endocrine Society [stuenkel2015endo] support micronized progesterone as the bioidentical option in this indication, with the additional consideration from the E3N cohort [fournier2008e3n] that bioidentical progesterone may carry a smaller breast-cancer signal than synthetic progestins.

Branded product: Prometrium

Luteal support in assisted reproductive technology FDA APPROVED

FDA-approved indication for vaginal progesterone (Crinone, Endometrin); supported by Cochrane meta-analysis.

Vaginal progesterone, gel (Crinone 8%) or insert (Endometrin 100 mg), is FDA-approved for luteal-phase support in women undergoing assisted reproductive technology (IVF/ICSI). Vaginal administration exploits the first uterine pass effect [deziegler1997firstpass] [cicinelli1998uterine] to deliver progesterone preferentially to the uterus. The Cochrane review by van der Linden [vanderlinden2011luteal] confirms benefit on clinical pregnancy and ongoing pregnancy outcomes vs no support. IM progesterone in oil and oral micronized progesterone are alternative routes used in some protocols; vaginal is the most-used route in current US ART practice.

Branded product: Crinone, Endometrin

Secondary amenorrhea FDA APPROVED

FDA-approved for inducing withdrawal bleeding in non-pregnant women with secondary amenorrhea and estrogen-primed endometrium.

Oral micronized progesterone (Prometrium) 400 mg/day for 10 days induces a withdrawal bleed in non-pregnant women with secondary amenorrhea and adequate endogenous estrogen, the 'progesterone challenge test' in its diagnostic use, and a short course for inducing menstrual cyclicity in its therapeutic use [stuenkel2015endo].

Branded product: Prometrium

Prevention of preterm birth in women with a short cervix WELL STUDIED

Well-studied; vaginal progesterone has the strongest evidence in the short-cervix subgroup.

Vaginal progesterone (200 mg/day suppository, or 90 mg gel) reduces spontaneous preterm birth in women with a sonographic short cervix (typically defined as ≤25 mm in the mid-trimester) [dafonseca2003preterm]. The Fonseca 2007 [fonseca2007shortcervix] and Hassan 2011 [hassan2011shortcervix] RCTs are the foundational randomized evidence; the Romero 2018 individual-patient-data meta-analysis [romero2018ipd] and the EPPPIC 2021 IPD meta-analysis [epppic2021ipd] consolidated the short-cervix benefit across the trial program. Norman OPPTIMUM 2016 [norman2016opptimum] was negative in a heterogeneous-risk UK population (its primary endpoint was a composite; the short-cervix subgroup was small). 17-OHPC IM (Makena), positive in Meis 2003 [meis2003ohpc], failed confirmatory replication in PROLONG 2020 [blackwell2020prolong] and was withdrawn from the US market in 2023.

Endometrial hyperplasia treatment (off-label) and bioidentical-vs-synthetic considerations WELL STUDIED

Well-studied bioidentical-vs-synthetic distinction; endometrial protection is the foundational evidence base for the comparison.

PEPI [pepi1996endometrium] established that oral micronized progesterone protects estrogen-primed endometrium at a rate equivalent to MPA [campagnoli2005breast]. WHI [rossouw2002whi] [stefanick2006wbi] [manson2017whi] used MPA, not micronized progesterone, throughout; its breast and cardiovascular signals cannot be cleanly attributed to either the estrogen or the progestogen component. The E3N cohort [fournier2008e3n] is the principal observational evidence that estrogen-plus-bioidentical-progesterone may carry a smaller breast-cancer signal than estrogen-plus-synthetic-progestin combined HRT [stanczyk2013progestogens]. NAMS 2022 [nams2022ht], the Endocrine Society 2015 [stuenkel2015endo], and NASEM 2020 [nasem2020bht] frame this as informing choice of progestogen in combined HRT, while noting the lack of head-to-head randomized data.

Cardiovascular safety of combined HRT including progesterone WELL STUDIED

Well-studied; ELITE provides randomized evidence on early-vs-late initiation.

The cardiovascular signal from WHI [rossouw2002whi] in women a decade or more past menopause produced a generation of caution about combined HRT. The KEEPS [harman2014keeps] and ELITE [hodis2016elite] trials addressed the 'timing hypothesis', that initiation closer to the menopause transition might produce different cardiovascular outcomes. ELITE in particular randomized 643 postmenopausal women to oral estradiol plus cyclic vaginal progesterone vs placebo and found reduced progression of carotid intima-media thickness when therapy was initiated within 6 years of menopause but not when initiated 10+ years out [manson2017whi]. KEEPS-Cog [keeps2014cog] examined cognitive outcomes. Neither trial was powered for hard CV events.

Catamenial epilepsy WELL STUDIED

Off-label; randomized evidence supports subgroup with perimenstrually-exacerbated seizures.

Catamenial epilepsy, seizures clustered around the perimenstrual or periovulatory phases of the cycle, is mechanistically linked to fluctuations in allopregnanolone, the GABA-A-modulating progesterone metabolite [schumacher2014progesterone] [guennoun2015allopreg]. The Herzog 2012 NIH-sponsored RCT [herzog2012epilepsy] was overall negative for unselected women with epilepsy but pre-specified a perimenstrually-exacerbated catamenial subgroup that showed benefit. Herzog 2014 [herzog2014allopreg] showed that allopregnanolone levels track seizure reduction, supporting the mechanism. Progesterone is not a first-line antiseizure drug; this is a specialty neurology indication.

Perimenopausal vasomotor symptoms WELL STUDIED

Off-label; modest randomized evidence supports a role.

Hitchcock and Prior's 2012 placebo-controlled RCT [hitchcock2012vms] of oral micronized progesterone 300 mg at bedtime in healthy postmenopausal women showed reduction in vasomotor symptom severity vs placebo, without rebound on discontinuation. Prior's 2023 phase 3 Canada-wide RCT [prior2023vms] in perimenopausal women supported night sweat reduction. NAMS 2022 [nams2022ht] does not list progesterone monotherapy as a first-line VMS therapy but acknowledges the evidence base.

Sleep disturbance in perimenopause and postmenopause WELL STUDIED

Off-label; modest randomized evidence for bedtime oral progesterone.

Caufriez 2011 [caufriez2011sleep] randomized 8 postmenopausal women in a crossover trial of oral micronized progesterone 300 mg vs placebo at bedtime and showed improved sleep architecture (reduced wake after sleep onset) along with modulation of GH, TSH, and melatonin. The sleep benefit is mechanistically attributed to allopregnanolone's GABA-A action [schumacher2014progesterone]. This is the basis for the recommendation that oral progesterone be dosed at bedtime in combined HRT regimens, converting somnolence from an adverse effect into a therapeutic effect [guennoun2015allopreg].

Off-Label Uses of Progesterone

Premenstrual syndrome / premenstrual dysphoric disorder EMERGING

Not supported by Cochrane review or systematic review, efficacy not established.

Wyatt 2001 [wyatt2001pms] systematic review and the Ford 2012 Cochrane review [ford2012pms] concluded that neither progesterone nor synthetic progestogens are effective for PMS. Despite continued prescribing in some practice settings, the evidence does not support efficacy. SSRIs, dietary measures, and ovulation suppression have stronger evidence bases for PMDD.

First-trimester threatened miscarriage WELL STUDIED

Off-label; PRISM 2019 was overall negative with a possible subgroup signal.

The PRISM trial [coomarasamy2019prism] randomized 4153 women with bleeding in early pregnancy to vaginal micronized progesterone 400 mg BID or placebo. The primary endpoint (live birth ≥34 weeks) showed no significant overall benefit. A pre-specified subgroup analysis suggested benefit in women with prior miscarriages, with effect size increasing with number of prior losses. The trial does not support routine progesterone for unselected early-pregnancy bleeding but is part of the rationale some clinicians cite for selective use in recurrent pregnancy loss.

Recurrent preterm birth (singleton, prior preterm birth) WELL STUDIED

17-OHPC (Makena) withdrawn from market 2023 after PROLONG confirmatory trial failure; vaginal progesterone retains evidence.

Meis 2003 [meis2003ohpc] reported reduction in recurrent preterm birth with weekly IM 17-α-hydroxyprogesterone caproate in women with a prior preterm birth, leading to FDA accelerated approval of Makena. PROLONG 2020 [blackwell2020prolong] was the FDA-required confirmatory trial and was negative. Makena was withdrawn from the US market in 2023. Vaginal micronized progesterone for women with both prior preterm birth and a short cervix retains evidence per the EPPPIC IPD meta-analysis [epppic2021ipd] [dodd2013cochrane].

Gender-affirming feminizing hormone therapy EMERGING

Limited evidence; not routinely included in major guidelines.

Some clinicians add bioidentical progesterone to feminizing hormone therapy regimens (estradiol ± anti-androgen) with the goals of breast development, mood support, libido modulation, and sleep. Evidence is limited and the Endocrine Society 2017 guideline [hembree2017transgender] does not include progesterone as standard, while WPATH SOC 8 [coleman2022wpath] acknowledges its use within shared decision-making frameworks. RonanRx compounds bioidentical progesterone in this context only on a patient-specific prescription from a knowledgeable clinician.

Traumatic brain injury PRECLINICAL

ProTECT III was negative, no clinical indication.

Decades of preclinical data suggested neuroprotective effects of progesterone after TBI. The ProTECT III randomized trial [wright2014protect3] of IV progesterone in severe TBI was negative; a parallel European trial (SyNAPSe) was also negative. There is no clinical indication for progesterone in TBI.

Postpartum depression FDA APPROVED

Bioidentical oral progesterone is not the validated mechanism; IV allopregnanolone (brexanolone) is FDA-approved.

Allopregnanolone, the GABA-A-modulating metabolite of progesterone, is the validated mechanism for postpartum depression treatment. IV brexanolone (Zulresso) was FDA-approved in 2019 on the basis of Meltzer-Brody's phase 3 program [meltzerbrody2018brexanolone]. Oral allopregnanolone analog zuranolone followed in 2023. Oral bioidentical progesterone itself has not been shown effective for postpartum depression in randomized trials; the brexanolone evidence supports the mechanism, not the use of oral progesterone for this indication. This is the clearest clinical proof that the neurosteroid pathway distinguishes bioidentical progesterone from synthetic progestins (which do not reliably generate allopregnanolone) [schumacher2014progesterone; guennoun2015allopreg].

FDA-Approved Uses of Progesterone

Brand	Indication	Year	Route
Prometrium	Endometrial protection in postmenopausal women receiving estrogen; secondary amenorrhea	1998	Oral (micronized progesterone in peanut oil)
Crinone	Luteal support in assisted reproductive technology; secondary amenorrhea	1997	Vaginal gel (4% and 8%)
Endometrin	Luteal support in assisted reproductive technology	2007	Vaginal insert (100 mg)
Progesterone in oil (generic)	Luteal support in ART; secondary amenorrhea	Pre-1962 / grandfathered	Intramuscular (progesterone in sesame or other oil)

Three principal FDA-approved manufactured products contain bioidentical progesterone: Prometrium (oral micronized in peanut oil, 1998), Crinone (vaginal gel, 1997), and Endometrin (vaginal insert, 2007). Generic intramuscular progesterone in oil has been in clinical use since before the modern FDA approval framework [stuenkel2015endo]. 17-α-hydroxyprogesterone caproate (Makena), which is not bioidentical

progesterone but a chemically distinct 17-OH-progesterone caproate ester, was withdrawn from the US market in 2023 after the PROLONG confirmatory trial [blackwell2020prolong] failed to replicate the Meis 2003 [meis2003ohpc] preterm-birth-prevention benefit.

Each FDA-approved product is indicated for narrow specific use: Prometrium for endometrial protection in combined HRT and for secondary amenorrhea, Crinone/Endometrin for luteal support in ART [pepi1996endometrium; vanderlinden2011luteal]. Crinone also has a labeling indication for secondary amenorrhea. Use of these products for vaginal preterm-birth prevention, perimenopausal vasomotor symptoms, sleep, catamenial epilepsy, or other off-label indications relies on the published evidence summarized in clinical_contexts and off_label_uses [stuenkel2015endo; nams2022ht].

Compounded Progesterone (503A)

Compounded bioidentical progesterone occupies a circumscribed but legitimate role under 503A [fda503a]. The manufactured market provides Prometrium at 100 mg and 200 mg only, Crinone at 4% and 8% only, and Endometrin at 100 mg only. Patient-specific compounding addresses needs the manufactured market does not, intermediate oral strengths (50 mg, 75 mg, 150 mg) for titration, troche dosage forms for patients who cannot tolerate the peanut-oil excipient in Prometrium (peanut allergy is the most common reason), vaginal suppositories at strengths or in vehicles not available manufactured, and rectal suppositories in select clinical scenarios. The NASEM 2020 report [nasem2020bht] is the consensus document on this scope.

RonanRx is explicit about one specific limitation: compounded transdermal progesterone creams produce serum levels that are inadequate to reliably oppose estrogen-induced endometrial proliferation [fda503a]. They should not be used as the progestogen arm of a combined estrogen-plus-progestogen regimen for endometrial protection. NASEM 2020 [nasem2020bht], NAMS 2022 [nams2022ht], and the Endocrine Society 2015 [stuenkel2015endo] all flag this point. Compounded creams may be appropriate in specific, documented patient-specific scenarios that do not depend on serum-level-mediated endometrial action, but as endometrial-protection therapy they are not adequate.

Routine substitution of compounded oral progesterone for Prometrium without a documented clinical reason (such as peanut-oil allergy, need for a non-100/200 mg strength, or a documented excipient sensitivity) is not consistent with FDA guidance on compounded copies of approved drugs [fda_essentially_a_copy]. RonanRx's pharmacist review documents the patient-specific clinical reason for each compounded prescription [fda503a].

Progesterone Formulations and Routes

Form	Concentration	Description
Oral micronized progesterone capsule (compounded)	Custom, typical 25, 50, 75, 100, 150, 200 mg	Bioidentical micronized progesterone in oil (often olive, MCT, or other oils as alternatives to the peanut-oil excipient in manufactured Prometrium). Indicated for patients with peanut-oil sensitivity, those needing strengths between or outside the manufactured 100/200 mg range, or those requiring excipient substitution.
Oral progesterone troche / sublingual lozenge (compounded)	Custom, typical 25, 100 mg per troche	Slow-dissolve buccal/sublingual troche. Partially bypasses first-pass hepatic metabolism. Often selected for patients with GI absorption concerns or peanut-oil sensitivity. Pharmacokinetics differ from oral capsule, serum profile is more pulsatile.
Vaginal progesterone suppository (compounded)	Custom, typical 100, 200, 400 mg	Compounded suppositories in polyethylene glycol, cocoa butter, or other vehicles. Used for luteal support, endometrial protection (when oral route is not tolerated), and at 200 mg/day for preterm birth prevention in women with short cervix [hassan2011shortcervix]. Vaginal route exploits the first uterine pass effect [deziegler1997firstpass] for preferential uterine delivery.
Rectal progesterone suppository (compounded)	Custom, typical 100, 400 mg	Alternative route for select clinical scenarios when neither oral nor vaginal route is appropriate. Less first-pass than oral; less uterine-targeted than vaginal.
Transdermal / topical progesterone cream (compounded)	Custom, typical 20, 100 mg per gram	Topical cream for application to skin. Inadequate for endometrial protection in combined estrogen HRT regimens; serum levels do not reliably reach the threshold associated with secretory transformation of estrogen-primed endometrium [nasem2020bht]. May be appropriate for narrow, documented patient-specific scenarios that do not depend on serum-level-mediated systemic effect.
Intramuscular progesterone in oil	50 mg/mL standard manufactured strength; custom strengths compounded	Progesterone in sesame, cottonseed, or other oil vehicle for IM injection. Used principally for luteal support in ART. Custom strengths or alternative-oil compounding addresses sesame-oil sensitivity.

Routes used in published literature: oral, vaginal, rectal, intramuscular, topical, transdermal, sublingual, troche.

Progesterone Dosing

Route	Population	Range	Duration	Study type
Oral	Postmenopausal women on combined HRT, endometrial protection	100 mg at bedtime daily (continuous-combined regimen) OR 200 mg at bedtime for 12 days each month (cyclic-sequential regimen)	Indefinite while clinically beneficial; reassess periodically per NAMS 2022 and Endocrine Society 2015	PEPI randomized trial; NAMS 2022 position statement; Endocrine Society 2015 guideline
Oral	Adult women, secondary amenorrhea (induction of withdrawal bleed)	400 mg/day for 10 days	10 days	Prometrium labeled regimen
Vaginal (gel, Crinone)	ART luteal support	90 mg (Crinone 8%) once daily; in some protocols once or twice daily depending on fresh vs frozen-embryo cycle	From oocyte retrieval through ~10 weeks gestation if pregnancy occurs, then physician-directed taper	FDA-labeled regimen; Cochrane review by van der Linden 2011
Vaginal (insert, Endometrin)	ART luteal support	100 mg vaginal insert two or three times daily	From oocyte retrieval through ~10 weeks gestation if pregnancy occurs	FDA-labeled regimen
Vaginal (compounded suppository)	Pregnant women with sonographic short cervix (≤25 mm in mid-trimester), preterm birth prevention	200 mg vaginally at bedtime daily	From identification of short cervix through 36 0/7 weeks gestation or delivery	Hassan 2011 PREGNANT trial; Romero 2018 IPD meta-analysis; EPPPIC 2021 IPD meta-analysis
Intramuscular (progesterone in oil)	ART luteal support	50, 100 mg IM daily	From oocyte retrieval through ~10 weeks gestation	Long-standing ART protocol; Cochrane review by van der Linden 2011
Oral (off-label)	Perimenopausal women, vasomotor symptoms	300 mg at bedtime daily (Hitchcock 2012 trial regimen)	3, 4 months trial; reassess	Hitchcock 2012 placebo-controlled RCT; Prior 2023

Route	Population	Range	Duration	Study type
				Canada-wide phase 3 RCT
Oral (off-label)	Women with catamenial epilepsy, perimenstrual exacerbation subgroup	200 mg three times daily during luteal phase (Herzog 2012 trial regimen, cycle days 14, 28 with taper)	Cycle-locked; reassess at 3 months	Herzog 2012 NIH-sponsored RCT, overall negative, perimenstrually-exacerbated subgroup positive

Doses listed reflect FDA-labeled regimens and published clinical-trial protocols, not RonanRx prescribing recommendations [nams2022ht]. The prescribing clinician selects formulation, route, and dose based on indication, clinical context, prior tolerability, and shared decision-making.

Practical considerations: oral micronized progesterone is dosed at bedtime to use the somnolence effect therapeutically rather than as an adverse effect, and because the allopregnanolone surge after oral absorption peaks within 1, 4 hours, a window that overlaps natural sleep latency [schumacher2014progesterone]. Vaginal progesterone produces lower serum levels than oral or IM at comparable doses but concentrates in the uterus via the first uterine pass effect [deziegler1997firstpass], making vaginal the route of choice when uterine action is the goal (luteal support, endometrial protection in women with adequate vaginal absorption, short-cervix prophylaxis) [pepi1996endometrium]. IM progesterone produces high stable serum levels but is uncomfortable and is generally reserved for ART protocols where vaginal route is contraindicated or inadequate. Transdermal cream is inadequate for endometrial protection, this is a guideline-level point, not an opinion [nasem2020bht] [stuenkel2015endo].

Combined HRT regimen choice: continuous-combined estrogen + progesterone 100 mg/day produces amenorrhea after a transition period and is preferred by most postmenopausal women [pepi1996endometrium]. Cyclic-sequential estrogen + progesterone 200 mg × 12 days/month produces a withdrawal bleed each cycle and is sometimes preferred by women in early postmenopause or those who prefer a predictable bleed pattern [nams2022ht].

Progesterone Safety

Bioidentical progesterone has a favorable safety profile relative to synthetic progestins, with the most common on-therapy effects being dose-dependent somnolence and mild dizziness after oral dosing (an allopregnanolone-mediated GABA-A effect) [3][5]. Bedtime dosing converts somnolence from an adverse effect into a therapeutic effect. Mood lability, breast tenderness, and bloating are also reported.

Cardiovascular and breast safety: the WHI [2][3] used medroxyprogesterone acetate, not bioidentical progesterone, and its breast and CV signals cannot be cleanly attributed to either component. The E3N

observational cohort [6] reported a smaller breast-cancer signal with estrogen-plus-bioidentical-progesterone than with estrogen-plus-synthetic-progestin combined HRT. Randomized head-to-head comparison of bioidentical vs synthetic progestogen for breast safety in combined HRT does not exist. NAMS 2022 [11], the Endocrine Society 2015 [10], and the NASEM 2020 report [12] frame this distinction as informing choice rather than as a randomized safety claim.

Pregnancy: vaginal and IM progesterone for luteal support in ART and for short-cervix preterm-birth prophylaxis [21] [23] have favorable safety profiles in the established randomized literature. No teratogenicity signal is established for bioidentical progesterone at the doses used clinically. 17-α-hydroxyprogesterone caproate (Makena) was withdrawn from market in 2023 after PROLONG failed confirmatory replication, but vaginal progesterone retains evidence [24] [25].

Transdermal cream-specific caution: progesterone creams do not produce serum levels adequate to oppose estrogen-induced endometrial proliferation. They are not appropriate as the progestogen arm of combined estrogen HRT for women with an intact uterus [12] [10].

Contraindications

Bioidentical progesterone (oral, vaginal, IM, or compounded) is contraindicated in: known hypersensitivity to progesterone or formulation excipients (Prometrium contains peanut oil, peanut allergy is a contraindication to that specific manufactured product; compounded preparations in alternative oils address this); known or suspected breast cancer (relative, discuss with oncology); active thrombophlebitis or thromboembolic disorders; cerebrovascular disease; severe hepatic impairment; undiagnosed abnormal genital bleeding; known or suspected pregnancy when not being used specifically to support pregnancy (e.g., not appropriate as menopausal HT when pregnancy is possible); missed abortion as a diagnostic test of choice (use other methods).

Relative cautions per NAMS 2022 [11] and Endocrine Society 2015 [10]: prior personal history of breast cancer (oncology-shared decision-making), prior personal history of VTE or known thrombophilia (oral progesterone has minimal VTE signal compared with synthetic progestins; route choice matters), and active liver disease.

Transdermal cream is contraindicated as the sole progestogen arm of combined estrogen HRT in women with an intact uterus, because serum levels are inadequate for endometrial protection [12].

Drug interactions

Progesterone is metabolized primarily by CYP3A4 in the liver. Strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St John's wort) can lower serum progesterone concentrations; strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, grapefruit juice in large quantities) can raise them. In women on combined HRT, this can affect the adequacy of endometrial protection. In women using progesterone for catamenial epilepsy, concomitant enzyme-inducing antiepileptics can reduce the allopregnanolone-mediated benefit [32] [35].

CNS-depressant drugs (benzodiazepines, opioids, alcohol, sedating antihistamines) may have additive effects with the allopregnanolone-mediated sedation of oral progesterone, particularly relevant for the bedtime dosing common in combined HRT [35]. Patients should be counseled about additive sedation if combining [10].

Adverse events

The most common on-therapy adverse events of oral micronized progesterone are dose-dependent somnolence and mild dizziness (allopregnanolone GABA-A effect) [35]. Bedtime dosing makes these therapeutic rather than burdensome. Breast tenderness, mild bloating, mood lability, and headache are also reported. Vaginal preparations produce local effects: vaginal discharge, itching, and burning are most common; partner exposure during intercourse is generally minimal in clinical reports. IM progesterone in oil produces local injection-site pain, occasional sterile abscess, and rare allergic reactions to the oil vehicle.

Pregnancy-related: in the large randomized vaginal-progesterone preterm-birth trials [21] [22] [23] [24], safety signals were limited to local vaginal effects without an established teratogenic, neonatal, or long-term developmental signal at the doses studied. The PROLONG trial of 17-OHPC [25] (a different molecule from bioidentical progesterone) showed no efficacy signal but also no major safety signal.

Site-specific adverse events vary by route: oral, somnolence, dizziness, headache, breast tenderness; vaginal, local irritation, discharge; IM, injection-site pain, oil-vehicle local reactions; transdermal cream, minimal systemic effects (consistent with the inadequate serum levels that also make it inadequate for endometrial protection [12]).

↗ Monitoring Progesterone Therapy

Combined HRT monitoring per NAMS 2022 [nams2022ht] and Endocrine Society 2015 [stuenkel2015endo]: baseline review of indications, contraindications, breast and endometrial cancer risk factors; periodic reassessment of indication, dose, and route at least annually; investigation of any abnormal uterine bleeding on a regimen designed to produce amenorrhea (continuous-combined) or unexpected bleeding pattern on a cyclic regimen. Mammography and breast clinical exam per age-appropriate screening guidelines. Serum progesterone levels are not routinely used to titrate menopausal HT, the clinical endpoint is symptom control and absence of abnormal bleeding [hassan2011shortcervix].

ART luteal support: monitoring is for the pregnancy outcome, not for serum progesterone level. Most US protocols use vaginal or IM progesterone through ~10 weeks gestation, then taper [hassan2011shortcervix].

Short-cervix preterm-birth prophylaxis: vaginal progesterone 200 mg nightly from identification of short cervix through 36 0/7 weeks [hassan2011shortcervix]. Ultrasound follow-up for cervical length and obstetric monitoring per OB protocols.

Catamenial epilepsy: cycle-locked dosing requires careful menstrual cycle tracking; allopregnanolone level monitoring is research-grade not routine [herzog2014allopreg]; seizure frequency is the clinical endpoint [hassan2011shortcervix].

Progesterone in Special Populations

Progesterone Evidence Quality

Evidence for bioidentical progesterone is anchored by three randomized programs and one large observational cohort [prior2023vms]. PEPI [pepi1996endometrium] established endometrial protection equivalence with MPA. The vaginal-progesterone preterm-birth program, Da Fonseca 2003 [dafonseca2003preterm], Fonseca 2007 [fonseca2007shortcervix], Hassan 2011 [hassan2011shortcervix], Norman OPPTIMUM 2016 [norman2016opptimum], Romero 2018 IPD [romero2018ipd], EPPPIC 2021 IPD [epppic2021ipd], established benefit in the short-cervix subgroup with negative or null findings in unselected populations. The Cochrane review of luteal support in ART [vanderlinden2011luteal] supports the FDA-approved ART use.

The E3N observational cohort [fournier2008e3n] is the principal source of the bioidentical-vs-synthetic-progestogen breast-cancer signal. WHI [rossouw2002whi] [stefanick2006wbi] [manson2017whi] used MPA and does not directly inform the bioidentical-progesterone safety question. The 'timing hypothesis' randomized trials KEEPS [harman2014keeps] [keeps2014cog] and ELITE [hodis2016elite] used micronized progesterone in their combined-HRT arms [prior2023vms].

Off-label evidence is mixed: positive in perimenopausal vasomotor symptoms [hitchcock2012vms], positive in sleep [caufriez2011sleep], positive in a perimenstrually-exacerbated catamenial epilepsy subgroup [herzog2012epilepsy], negative in unselected PMS/PMDD [wyatt2001pms], and negative in traumatic brain injury (ProTECT III [wright2014protect3]). The brexanolone phase 3 program for postpartum depression [meltzerbrody2018brexanolone] is the clinical proof of the allopregnanolone GABA-A mechanism that mechanistically distinguishes bioidentical progesterone from synthetic progestins [ford2012pms].

The Stanczyk 2013 [stanczyk2013progestogens], Schindler 2003 [schindler2003classification], and Campagnoli 2005 [campagnoli2005breast] reviews are the standard references for progestogen pharmacology and the bioidentical-vs-synthetic distinction [prior2023vms]. Schumacher 2014 [schumacher2014progesterone] and Guennoun 2015 [guennoun2015allopreg] are the standard references for neurosteroid biology. NAMS 2022 [nams2022ht], Endocrine Society 2015 [stuenkel2015endo], and NASEM 2020 [nasem2020bht] are the consensus position statements that frame the clinical role of compounded bioidentical hormone therapy.

Major Progesterone Clinical Studies

Study	Design	Participants	Duration	Finding
PEPI, Effects of Hormone Replacement Therapy on Endometrial Histology in Postmenopausal Women (PEPI Writing Group 1996 JAMA)	3-year multicenter randomized placebo-controlled trial, 5 arms including conjugated estrogen plus cyclic micronized progesterone vs estrogen plus MPA vs estrogen alone vs placebo	596	3 years	Oral micronized progesterone 200 mg/day for 12 days/month protected estrogen-primed endometrium at a rate equivalent to MPA; both produced rates of hyperplasia indistinguishable from placebo, while estrogen alone produced ~34% hyperplasia [pepi1996endometrium]
WHI, Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women (Rossouw 2002 JAMA)	Randomized double-blind placebo-controlled trial of CEE + MPA vs placebo in postmenopausal women with intact uterus	16608	Mean 5.2 years (stopped early)	Increased coronary heart disease, breast cancer, stroke, and VTE; reduced fractures and colorectal cancer; overall risk-benefit unfavorable in the population studied. Used MPA, not bioidentical progesterone [rossouw2002whi].
WHI Estrogen-Only Arm, Effects of CEE on Breast Cancer (Stefanick 2006 JAMA)	Randomized trial of CEE alone vs placebo in postmenopausal women with prior hysterectomy	10739	Mean 7.1 years	No increase in breast cancer (non-significant reduction); reinforces interpretation that the progestogen (MPA) component of the combined arm contributed substantially to that arm's breast-cancer signal [stefanick2006wbi]
WHI Long-Term Follow-Up, Menopausal Hormone Therapy and All-Cause Mortality (Manson 2017 JAMA)	Long-term follow-up of both WHI hormone therapy trials	27347	Cumulative 18 years	No significant increase in all-cause, cardiovascular, or cancer mortality over 18-year cumulative follow-up, contextualizes the original 2002 stopping decision [manson2017whi]
HERS, Estrogen Plus Progestin for Secondary	Randomized placebo-controlled secondary-prevention trial in	2763	Mean 4.1 years	No overall reduction in CHD events; early increase in events; informed FDA labeling on use in

Study	Design	Participants	Duration	Finding
Prevention of CHD (Hulley 1998 JAMA)	postmenopausal women with established CHD			secondary CV prevention [hulley1998hers]. Used CEE + MPA.
E3N Cohort, Unequal Risks for Breast Cancer Associated with Different HRTs (Fournier 2008)	Prospective cohort of French postmenopausal women	Over 80,000 women	Mean 8 years follow-up	Estrogen plus bioidentical progesterone HRT not associated with increased breast cancer risk vs never-use; estrogen plus synthetic progestins associated with increased risk, principal observational evidence for the bioidentical-vs-synthetic distinction [fournier2008e3n]
ELITE, Vascular Effects of Early vs Late Postmenopausal Treatment with Estradiol (Hodis 2016 NEJM)	Randomized placebo-controlled trial of oral estradiol plus cyclic vaginal progesterone in early vs late postmenopausal women	643	Median 5 years	Reduced progression of carotid intima-media thickness in women starting within 6 years of menopause; no effect in women starting 10+ years out, supports the timing hypothesis; used micronized progesterone vaginally [hodis2016elite]
KEEPS, Kronos Early Estrogen Prevention Study (Harman 2014)	Randomized placebo-controlled trial of oral CEE or transdermal estradiol, each with cyclic oral micronized progesterone, in early postmenopausal women	727	4 years	No effect on progression of subclinical atherosclerosis; modest favorable effects on symptoms and some metabolic measures; KEEPS-Cog analyzed cognitive outcomes [harman2014keeps; keeps2014cog]
Da Fonseca 2003, Vaginal Progesterone Suppository for Preterm Birth Prevention	Randomized placebo-controlled trial of vaginal progesterone 100 mg/day suppository in women at increased preterm-birth risk	142	From 24 weeks to 34 weeks gestation	Reduced spontaneous preterm birth before 37 weeks, foundational early evidence for vaginal progesterone in preterm-birth prophylaxis [dafonseca2003preterm]
Meis 2003, 17-OHPC for Recurrent Preterm Birth (NEJM)	Randomized placebo-controlled trial of weekly IM 17-α-hydroxyprogesterone	463	From 16, 20 weeks through 36	Reduced recurrent preterm birth, basis for FDA accelerated approval of Makena; later failed

Study	Design	Participants	Duration	Finding
	caproate in women with prior preterm birth		weeks gestation	confirmatory replication in PROLONG [meis2003ohpc]
Fonseca 2007, Progesterone and Risk of Preterm Birth in Women with Short Cervix (NEJM)	Randomized placebo-controlled trial of vaginal progesterone 200 mg/day in women with sonographic short cervix	250	From mid-trimester through 34 weeks	Reduced spontaneous preterm birth before 34 weeks in women with a short cervix [fonseca2007shortcervix]
Hassan 2011 PREGNANT, Vaginal Progesterone for Short Cervix	Multicenter randomized double-blind placebo-controlled trial of vaginal progesterone gel 90 mg/day in women with sonographic short cervix	458	From 19, 24 weeks through 36 weeks	Reduced preterm birth before 33 weeks by 45%; reduced neonatal morbidity [hassan2011shortcervix]
Norman OPPTIMUM 2016, Vaginal Progesterone in Heterogeneous-Risk Women (Lancet)	UK multicenter randomized placebo-controlled trial of vaginal progesterone 200 mg/day in women at increased preterm-birth risk	1228	From 22, 24 weeks through 34 weeks	No significant effect on composite obstetric or neonatal primary outcome; short-cervix subgroup small and underpowered [norman2016opptimum]
Romero 2018 IPD Meta-Analysis, Vaginal Progesterone for Short Cervix	Individual-patient-data meta-analysis of randomized trials of vaginal progesterone in women with sonographic short cervix	Approximately 974 women across 5 trials	Per-trial	Vaginal progesterone reduces preterm birth before 33 weeks and improves neonatal outcomes in women with a sonographic short cervix [romero2018ipd]
EPPPIC 2021 IPD Meta-Analysis, Evaluating Progestogens for Preventing	Individual-patient-data meta-analysis spanning vaginal progesterone, 17-OHPC, and oral progesterone trials	Approximately 11,644 women across 31 trials	Pooled randomized data	Vaginal progesterone reduces preterm birth and adverse perinatal outcomes in women with a short cervix or prior preterm birth; 17-OHPC and oral progesterone do not show

Study	Design	Participants	Duration	Finding
Preterm Birth (Lancet)				consistent benefit [epppic2021ipd]
PROLONG 2020, 17-OHPC Confirmatory Trial (Blackwell, Am J Perinatol)	Phase 4 multicenter international randomized placebo-controlled trial	1708	Through 37 weeks	No significant effect on preterm birth before 35 weeks or on neonatal morbidity, failed to replicate Meis 2003; basis for FDA withdrawal of Makena in 2023 [blackwell2020prolong]
Dodd 2013 Cochrane Review, Antenatal Progesterone for Preterm Birth Prevention	Cochrane systematic review and meta-analysis of randomized trials	—	Pooled randomized data	Progesterone reduces preterm birth in selected populations (prior preterm birth, short cervix); route and dose matter [dodd2013cochrane]
Cochrane Luteal Phase Support in ART (van der Linden 2011)	Cochrane systematic review of luteal phase support in IVF/ICSI	—	Pooled randomized data	Luteal phase support with progesterone (vaginal, IM, or oral) improves clinical pregnancy and ongoing pregnancy rates [vanderlinden2011luteal]
PRISM, Progesterone for Bleeding in Early Pregnancy (Coomarasamy 2019 NEJM)	Randomized double-blind placebo-controlled trial of vaginal micronized progesterone 400 mg BID	4153	From bleeding to 16 weeks	No significant effect on live birth ≥34 weeks overall; subgroup with prior miscarriages showed possible benefit, particularly with ≥3 prior losses [coomarasamy2019prism]
Hitchcock 2012, Oral Micronized Progesterone for Vasomotor Symptoms	Randomized double-blind placebo-controlled trial of oral progesterone 300 mg at bedtime	133	12 weeks	Reduced vasomotor symptom severity vs placebo; no rebound on discontinuation [hitchcock2012vms]
Prior 2023, Oral Micronized Progesterone for Perimenopausal Night Sweats and Hot Flushes	Phase 3 Canada-wide multicenter randomized placebo-controlled trial	—	4 months	Reduced perimenopausal night sweats and hot flushes, extends Hitchcock 2012 evidence to perimenopausal population [prior2023vms]
Caufriez 2011, Progesterone for	Randomized crossover trial of oral	8	Per-arm	Reduced wakefulness, modulated GH/TSH/melatonin; basis for the

Study	Design	Participants	Duration	Finding
Sleep in Postmenopausal Women	progesterone 300 mg at bedtime vs placebo			recommendation to dose oral progesterone at bedtime [caufriez2011sleep]
Herzog 2012, Progesterone for Catamenial Epilepsy (NIH-Sponsored RCT)	Randomized placebo-controlled trial of oral progesterone in women with intractable focal epilepsy	294	3 months	Overall negative on the primary endpoint; pre-specified perimenstrually-exacerbated catamenial subgroup showed seizure reduction [herzog2012epilepsy]
Herzog 2014, Allopregnanolone Levels in Progesterone-Treated Epilepsy	Post-hoc analysis of Herzog 2012 trial	—	Per-trial	Allopregnanolone levels track seizure-frequency reduction, supports the GABA-A neurosteroid mechanism [herzog2014allopreg]
Wright 2014 ProTECT III, Progesterone for Severe Traumatic Brain Injury (NEJM)	Randomized placebo-controlled trial of IV progesterone in severe TBI	882	30 days to 6 months	No significant effect on Glasgow Outcome Scale-Extended at 6 months; ended an active translational hypothesis [wright2014protect3]
Meltzer-Brody 2018, Brexanolone (IV Allopregnanolone) for Postpartum Depression (Lancet)	Two multicenter phase 3 randomized placebo-controlled trials	Approximately 246 women across both trials	60-hour IV infusion with follow-up to 30 days	Significant reduction in Hamilton Depression Rating Scale at 60 hours and 30 days; basis for FDA approval (2019), clinical proof of GABAergic-neurosteroid mechanism that distinguishes bioidentical progesterone from synthetic progestins [meltzerbrody2018brexanolone]
Wyatt 2001, Progesterone for PMS (BMJ Systematic Review)	Systematic review of randomized trials of progesterone and progestogens in PMS	—	Pooled randomized data	No evidence of efficacy of progesterone or progestogens for PMS [wyatt2001pms]
Ford 2012, Progesterone for PMS (Cochrane Review)	Cochrane systematic review of randomized trials	—	Pooled randomized data	Insufficient evidence to support progesterone for PMS; SSRIs and other approaches preferred [ford2012pms]
		—	Lifespan	

Study	Design	Participants	Duration	Finding
Mulac-Jericevic 2000, PR-B Isoform-Selective Knockout Mouse (Science)	Mouse knockout study			Separated function of PR-A and PR-B isoforms, PR-A required for uterine and ovarian function; PR-B required for mammary alveologenesis [mulac2000prb]
Conneely 2001, Lessons from Progesterone Receptor Isoform Knockout Mice	Review	—	Synthesis	Consolidated the isoform-selective biology of PR-A and PR-B and its implications for reproductive and breast physiology [conneely2001isoforms]
Stanczyk 2013, Progestogens Used in Postmenopausal HT	Review	—	Synthesis	Standard reference for the pharmacology of progestogen heterogeneity, receptor binding, metabolite spectrum, intracellular actions, and clinical effects across bioidentical progesterone, MPA, norethindrone, levonorgestrel, drospirenone, and others [stanczyk2013progestogens]
Schindler 2003, Classification and Pharmacology of Progestins	Review	—	Synthesis	Standard reference framework for classifying progestogens by chemical class (progesterone-derived, 17-OH-progesterone-derived, 19-nortestosterone-derived) and clinical receptor profile [schindler2003classification]
Campagnoli 2005, Progestins and Progesterone in HRT and Breast Cancer Risk	Review	—	Synthesis	Argues, on the basis of E3N and mechanistic data, that synthetic progestins drive most of the breast-cancer signal in combined HRT and that bioidentical progesterone may be a lower-risk choice [campagnoli2005breast]
Schumacher 2014, Progesterone and Allopregnanolone in the Nervous	Review	—	Synthesis	Standard reference for the neurosteroid biology of progesterone and allopregnanolone, GABA-A modulation, myelination,

Study	Design	Participants	Duration	Finding
System (Prog Neurobiol)				neuroprotection, mood, sleep, and seizure threshold [schumacher2014progesterone]
Guennoun 2015, Progesterone and Allopregnanolone CNS Response to Injury	Review	—	Synthesis	Mechanistic synthesis of progesterone/allopregnanolone neuroprotection literature; updated through the era of failed clinical TBI trials [guennoun2015allopreg]
Hargrove 1989, Absorption of Oral Progesterone Influenced by Vehicle and Particle Size	Pharmacokinetic study in healthy women	—	Per-dose	Micronization plus oil vehicle substantially improves oral progesterone absorption, pharmaceutical basis for Prometrium [hargrove1989oral]
De Ziegler & Bulletti 1997, The First Uterine Pass Effect	Review of pharmacokinetic and tissue-distribution data	—	Synthesis	Vaginal progesterone preferentially concentrates in the uterus relative to serum, the pharmacokinetic basis for vaginal route's efficacy in luteal support and short-cervix prophylaxis [deziegler1997firstpass]
Cicinelli 1998, Higher Uterine-Artery Than Radial-Artery Progesterone After Vaginal Administration	Pharmacokinetic study in oophorectomized women	—	Per-dose	Direct demonstration of preferential uterine vascular delivery of vaginal progesterone, confirmatory mechanism for the first uterine pass effect [cicinelli1998uterine]
NASEM 2020, Compounded Bioidentical Hormone Therapy Report	Consensus committee report	—	Synthesis	Acknowledged the legitimate role of compounded BHRT for documented patient-specific need; explicitly criticized routine substitution of compounded for FDA-approved products without clinical rationale and the use of transdermal progesterone creams for endometrial protection [nasem2020bht]

Study	Design	Participants	Duration	Finding
NAMS 2022 Hormone Therapy Position Statement	Society position statement	—	Synthesis	Current consensus framework for menopausal HT including selection of progestogen for endometrial protection; references micronized progesterone as a reasonable choice with the caveat that head-to-head randomized data vs synthetic progestins are limited [nams2022ht]
Endocrine Society 2015 Treatment of Symptoms of the Menopause (Stuenkel)	Clinical practice guideline	—	Synthesis	Diagnostic and therapeutic framework for menopausal HT including discussion of progestogen choice [stuenkel2015endo]

Progesterone Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Unmodified oral progesterone has very low bioavailability because of extensive first-pass hepatic metabolism [delignieres2000pd]. Micronization plus an oil vehicle (Prometrium uses peanut oil; compounded preparations can use olive, MCT, or other oils) substantially improves oral absorption [hargrove1989oral]. After oral micronized progesterone, serum levels peak at 1, 4 hours and decline over 8, 12 hours; substantial 5α-reduction to allopregnanolone in the gut wall and liver produces the characteristic somnolence within 1, 2 hours of oral dosing.

Vaginal progesterone produces lower peak serum levels than oral or IM at comparable mg dose but concentrates in the uterus via the first uterine pass effect [deziegler1997firstpass] [delignieres2000pd]. Cicinelli demonstrated that progesterone concentrations are higher in the uterine artery than in the radial artery after vaginal administration [cicinelli1998uterine], direct evidence of preferential uterine vascular delivery. This makes the vaginal route ideal when uterine action (luteal support, short-cervix prophylaxis) is the goal.

IM progesterone in oil produces high stable serum levels and is the historical standard for ART luteal support in protocols where vaginal route is contraindicated or inadequate [delignieres2000pd]. Half-life of IM progesterone is approximately 7 hours but the depot release from oil extends pharmacodynamic effect to 24 hours or more.

Transdermal cream produces low and variable serum levels, orders of magnitude lower than oral or vaginal at typical compounded strengths, which is the pharmacokinetic basis for the position that creams are inadequate for endometrial protection [nasem2020bht] [stuenkel2015endo] [delignieres2000pd].

Pharmacodynamics

Pharmacodynamic effects are tissue-specific and route-dependent [stanczyk2013progestogens]. Endometrial action requires adequate serum or local concentration to produce secretory transformation, achieved at 100, 200 mg oral or 90, 200 mg vaginal daily in combined HRT [pepi1996endometrium]. CNS effects (somnolence, anxiolysis, anticonvulsant) are dose-dependent and mediated by 5α-reduced metabolite allopregnanolone, concentrated in the first hours after oral dosing [schumacher2014progesterone] [guennoun2015allopreg].

Breast tissue: PR-A/PR-B isoform-selective signaling [mulac2000prb] [conneely2001isoforms] underlies the tissue-specific effects on breast that are functionally distinct from synthetic progestins. The observational evidence [fournier2008e3n] supports the interpretation that bioidentical progesterone has a more favorable breast safety signal than MPA and other synthetic progestins in combined HRT, though randomized head-to-head data do not exist [stanczyk2013progestogens].

↓↑ Comparing Progesterone Formulations

Choice of formulation balances indication, prior tolerability, and patient preference. For endometrial protection in combined HRT, oral Prometrium (or compounded oral capsule) at 100 mg continuous or 200 mg cyclic is the standard. For ART luteal support, vaginal gel (Crinone) or insert (Endometrin) is most common in US practice; IM progesterone in oil is an alternative for protocols with contraindication or inadequate response to vaginal [vanderlinden2011luteal]. For short-cervix preterm-birth prophylaxis, vaginal compounded suppository 200 mg/day or vaginal gel is supported by the EPPPIC IPD meta-analysis [epppic2021ipd]. For perimenopausal vasomotor symptoms and sleep, oral micronized progesterone at bedtime [hitchcock2012vms] [caufriez2011sleep] is the route used in the randomized literature.

Compounded preparations expand the route palette: troches and alternative-oil oral capsules address peanut-oil sensitivity to Prometrium; intermediate-strength oral capsules (50, 75, 150 mg) address titration needs; compounded vaginal suppositories address strengths not provided by Crinone or Endometrin [fda_essentially_a_copy]. Transdermal cream is not appropriate as the progestogen arm of combined HRT for endometrial protection [nasem2020bht].

RonanRx compounds these preparations on patient-specific prescription [fda_essentially_a_copy]. The pharmacist review confirms the prescribed formulation is responsive to a documented patient-specific need and is not routine substitution for a manufactured product.

Progesterone Storage and Handling

Compounded oral progesterone capsules in oil are stored at controlled room temperature (USP definition 20, 25°C, with allowed excursions 15, 30°C) protected from light. Vaginal suppositories and troches may require refrigeration depending on the base used (e.g., cocoa-butter suppositories soften at room temperature in warm climates and are typically refrigerated). Compounded creams are stored per the dispensing label.

Beyond-use dating follows USP <795> for non-sterile compounded preparations and USP <797> for sterile preparations (e.g., compounded IM progesterone if dispensed) [usp_797; usp_795].

Progesterone Compounding & Operations

503A compounding

RonanRx compounds bioidentical progesterone preparations under 503A on patient-specific prescriptions. Non-sterile preparations (oral capsules, troches, vaginal/rectal suppositories, creams) follow USP General Chapter <795>. Sterile preparations (compounded IM progesterone, if dispensed) follow USP General Chapter <797> with documented active-ingredient sourcing (USP/NF grade), sterility and endotoxin testing per applicable risk-level requirements, gravimetric/volumetric verification, and full lot traceability [usp_795; usp_797; nasem2020bht].

Progesterone is not a controlled substance. Standard prescription handling applies. Each prescription is verified for prescriber registration and patient identity before dispensing [fda503a].

Pharmacist review

Each prescription for compounded progesterone undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason for the compounded preparation (peanut-oil sensitivity to Prometrium; need for a strength not provided manufactured; need for a route not provided manufactured; documented excipient sensitivity); appropriate indication framework (combined HRT endometrial protection, luteal support, short-cervix prophylaxis, catamenial epilepsy specialty management, or other documented clinical context); absence of contraindications [fda_essentially_a_copy].

Critical pharmacist-review boundary: RonanRx does not fill prescriptions for transdermal progesterone cream when the prescription documents endometrial-protection intent in a woman on systemic estrogen with an intact uterus. The serum levels produced by cream are inadequate for that purpose [nasem2020bht] [stuenkel2015endo]. In such cases the pharmacist contacts the prescriber to discuss an oral or vaginal alternative [nams2022ht].

Quality and traceability

Progesterone API is sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, and dispensing pharmacist of record. Sterile preparations carry sterility and endotoxin test documentation per USP <797> risk-level requirements [usp_797; usp_795].

Cold chain

Most compounded progesterone preparations are not cold-chain products. Oral capsules and creams ship at controlled room temperature. Cocoa-butter-based vaginal suppositories may require refrigerated shipping in warm seasons or climates; shipping instructions are determined per preparation. Patients are instructed to follow the dispensing-label storage instructions and to contact the pharmacy if shipping temperature integrity is in doubt.

Frequently Asked Questions About Progesterone

Is compounded progesterone the same as Prometrium?

No. Prometrium is an FDA-approved manufactured product (oral micronized progesterone in peanut oil at 100 mg or 200 mg). Compounded preparations are pharmacy-prepared on patient-specific prescription and are not FDA-approved [fda_essentially_a_copy; nasem2020bht]. They are dispensed when a documented patient-specific clinical need is not met by Prometrium or another manufactured product, for example, peanut-oil sensitivity (requiring an alternative oil vehicle), a strength between 100 and 200 mg (such as 50, 75, or 150 mg), a troche or vaginal suppository at a strength the manufactured market does not provide, or a documented excipient sensitivity [fda503a].

Why does my doctor want me to take progesterone at bedtime?

Oral micronized progesterone is converted in the gut and liver to allopregnanolone, a metabolite that activates the GABA-A receptor in the brain (the same receptor system that benzodiazepines and alcohol act on) [schumacher2014progesterone]. This produces predictable somnolence and mild dizziness within 1, 2 hours of dosing, which is a side effect during the day but a therapeutic effect at bedtime. Caufriez 2011 showed that bedtime oral progesterone improves sleep architecture in postmenopausal women, and this is the standard recommendation in combined HRT [caufriez2011sleep].

Is bioidentical progesterone safer than the progestins in WHI?

Maybe. The WHI used medroxyprogesterone acetate (MPA), not bioidentical progesterone [stanczyk2013progestogens]. The E3N observational cohort suggested that combined HRT with bioidentical progesterone carries a smaller breast-cancer signal than combined HRT with synthetic progestins [fournier2008e3n]. NAMS and the Endocrine Society reference this when discussing progestogen choice

[nams2022ht; stuenkel2015endo]. But there is no head-to-head randomized trial of bioidentical progesterone vs MPA for combined-HRT safety endpoints, so the bioidentical advantage is observational rather than randomized [rossouw2002whi].

Why is RonanRx unwilling to dispense progesterone cream for combined HRT?

Progesterone creams produce serum levels that are inadequate to reliably oppose estrogen-induced endometrial proliferation. Using a cream as the progestogen arm of combined estrogen HRT in a woman with an intact uterus puts her at risk of endometrial hyperplasia and adenocarcinoma. The NASEM 2020 report, NAMS 2022, and the Endocrine Society 2015 guideline all flag this [nasem2020bht; nams2022ht; stuenkel2015endo]. Oral micronized progesterone or vaginal progesterone are the appropriate routes for endometrial protection.

Will progesterone help with my hot flashes?

The Hitchcock 2012 placebo-controlled trial and the Prior 2023 phase 3 Canada-wide trial show modest reduction in vasomotor symptoms with oral micronized progesterone 300 mg at bedtime [hitchcock2012vms; prior2023vms]. NAMS 2022 does not list progesterone monotherapy as a first-line vasomotor-symptom therapy but acknowledges the evidence [nams2022ht]. For women who cannot or prefer not to take estrogen, oral micronized progesterone is one of several options worth discussing with the prescriber.

Why did Makena (17-OHPC) get withdrawn?

Makena was 17-α-hydroxyprogesterone caproate, a synthetic progestin, not bioidentical progesterone. The Meis 2003 trial showed reduction in recurrent preterm birth, leading to FDA accelerated approval [meis2003ohpc; blackwell2020prolong; epppic2021ipd]. The PROLONG 2020 confirmatory trial failed to replicate that benefit. FDA initiated withdrawal in 2023. Vaginal bioidentical progesterone for women with a sonographic short cervix retains evidence and remains in use, that's a different molecule and a different indication.

Does progesterone treat postpartum depression?

Oral progesterone has not been shown effective for postpartum depression in randomized trials [meltzerbrody2018brexanolone]. The validated mechanism is intravenous allopregnanolone (brexanolone, Zulresso, FDA-approved 2019), which is the GABA-A-modulating 5α-reduced metabolite of progesterone [schumacher2014progesterone]. This is the strongest clinical proof that the neurosteroid pathway distinguishes bioidentical progesterone from synthetic progestins, but it does not support oral progesterone as a treatment for postpartum depression.

Does RonanRx sell progesterone directly to patients?

No. Compounded progesterone is dispensed only on a patient-specific prescription written by a licensed prescriber for an identified patient, with pharmacist review before dispensing. RonanRx is not a direct-to-consumer storefront [fda503a].

References

1. *[pepi1996endometrium]* The Writing Group for the PEPI Trial. *Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial*. JAMA. 1996. PMID 8569016. (accessed 2026-05-11)
2. *[rossouw2002whi]* Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. *Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial*. JAMA. 2002. PMID 12117397. (accessed 2026-05-11)
3. *[stefanick2006wbi]* Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, Lane DS, Hubbell FA, Assaf AR, Sarto GE, Schenken RS, Yasmeen S, Lessin L, Chlebowski RT; WHI Investigators. *Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy*. JAMA. 2006. PMID 16609086. (accessed 2026-05-11)
4. *[manson2017whi]* Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Chlebowski RT, Howard BV, Thomson CA, Margolis KL, Lewis CE, Stefanick ML, Jackson RD, Limacher MC, Black HR, Wenger NK, Stuenkel CA. *Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials*. JAMA. 2017. PMID 28898378. (accessed 2026-05-11)
5. *[hulley1998hers]* Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. *Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group*. JAMA. 1998. PMID 9718051. (accessed 2026-05-11)
6. *[fournier2008e3n]* Fournier A, Berrino F, Clavel-Chapelon F. *Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study*. Breast Cancer Research and Treatment. 2008. PMID 17333341. (accessed 2026-05-11)
7. *[hodis2016elite]* Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, Li Y, Feng M, Dustin L, Kono N, Stanczyk FZ, Selzer RH, Azen SP; ELITE Research Group. *Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol*. New England Journal of Medicine. 2016. PMID 27028912. (accessed 2026-05-11)
8. *[harman2014keeps]* Harman SM, Black DM, Naftolin F, Brinton EA, Budoff MJ, Cedars MI, Hopkins PN, Lobo RA, Manson JE, Merriam GR, Miller VM, Neal-Perry G, Santoro N, Taylor HS, Vittinghoff E, Yan M, Hodis HN. *Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial*. Annals of Internal Medicine. 2014. PMID 25069991. (accessed 2026-05-11)
9. *[keeps2014cog]* Wharton W, Gleason CE, Dowling NM, Carlsson CM, Brinton EA, Santoro MN, Neal-Perry G, Taylor H, Naftolin F, Lobo RA, Merriam G, Manson JE, Cedars MI, Miller VM, Black DM, Budoff M, Hodis HN, Harman SM, Asthana S. *The KEEPS-Cognitive and Affective Study: baseline associations between vascular risk factors and cognition*. Journal of Alzheimer's Disease. 2014. PMID 24430001. (accessed 2026-05-11)

10. *[stuenkel2015endo]* Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, Santen RJ. *Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline*. Journal of Clinical Endocrinology & Metabolism. 2015. PMID 26444994. (accessed 2026-05-11)
11. *[nams2022ht]* The North American Menopause Society. *The 2022 hormone therapy position statement of The North American Menopause Society*. Menopause. 2022. PMID 35797481. (accessed 2026-05-11)
12. *[nasem2020bht]* Pinkerton JV, Faubion SS, Kaunitz AM, Manson JE, Kingsberg SA, Liu JH, Iglesia CB, Santoro N, Stuenkel CA, Stanczyk FZ. *The National Academies of Science, Engineering, and Medicine (NASEM) Report on Compounded Bioidentical Hormone Therapy*. Menopause. 2020. PMID 33110032. (accessed 2026-05-11)
13. *[hargrove1989oral]* Hargrove JT, Maxson WS, Wentz AC. *Absorption of oral progesterone is influenced by vehicle and particle size*. American Journal of Obstetrics and Gynecology. 1989. PMID 2801843. (accessed 2026-05-11)
14. *[delignieres2000pd]* de Lignières B, Silberstein S. *Pharmacodynamics of oestrogens and progestogens*. Cephalalgia. 2000. PMID 10997774. (accessed 2026-05-11)
15. *[deziegler1997firstpass]* De Ziegler D, Bulletti C, De Monstier B, Jääskeläinen AS. *The first uterine pass effect*. Annals of the New York Academy of Sciences. 1997. PMID 9329850. (accessed 2026-05-11)
16. *[cicinelli1998uterine]* Cicinelli E, Cignarelli M, Sabatelli S, Romano F, Schonauer LM, Padovano R, Einer-Jensen N. *Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women*. Fertility and Sterility. 1998. PMID 9531879. (accessed 2026-05-11)
17. *[vanderlinden2011luteal]* van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. *Luteal phase support for assisted reproduction cycles*. Cochrane Database of Systematic Reviews. 2011. PMID 21975790. (accessed 2026-05-11)
18. *[dafonseca2003preterm]* da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. *Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study*. American Journal of Obstetrics and Gynecology. 2003. PMID 12592250. (accessed 2026-05-11)
19. *[meis2003ohpc]* Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, Spong CY, Hauth JC, Miodovnik M, Varner MW, Leveno KJ, Caritis SN, Iams JD, Wapner RJ, Conway D, O'Sullivan MJ, Carpenter M, Mercer B, Ramin SM, Thorp JM, Peaceman AM, Gabbe S; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate*. New England Journal of Medicine. 2003. PMID 12802023. (accessed 2026-05-11)
20. *[fonseca2007shortcervix]* Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH; Fetal Medicine Foundation Second Trimester Screening Group. *Progesterone and the risk of preterm birth among women with a short cervix*. New England Journal of Medicine. 2007. PMID 17671254. (accessed 2026-05-11)
21. *[hassan2011shortcervix]* Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, Vijayaraghavan J, Trivedi Y, Soma-Pillay P, Sambarey P, Dayal A, Potapov V, O'Brien J, Astakhov V, Yuzko O, Kinzler W, Dattel B, Sehdev H, Mazheika L, Manchulenko D, Gervasi MT, Sullivan L, Conde-Agudelo A, Phillips JA, Creasy GW; PREGNANT Trial. *Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial*. Ultrasound in Obstetrics & Gynecology. 2011. PMID 21472815. (accessed 2026-05-11)
22. *[norman2016opptimum]* Norman JE, Marlow N, Messow CM, Shennan A, Bennett PR, Thornton S, Robson SC, McConnachie A, Petrou S, Sebire NJ, Lavender T, Whyte S, Norrie J; OPPTIMUM Study Group. *Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial*. Lancet. 2016. PM ID 26921136. (accessed 2026-05-11)

23. *[romero2018ipd]* Romero R, Conde-Agudelo A, Da Fonseca E, O'Brien JM, Cetingoz E, Creasy GW, Hassan SS, Nicolaides KH. *Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data*. American Journal of Obstetrics and Gynecology. 2018. PMID 29157866. (accessed 2026-05-11)
24. *[epppic2021ipd]* EPPPIC Group. *Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials*. Lancet. 2021. PMID 33773630. (accessed 2026-05-11)
25. *[blackwell2020prolong]* Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, Chauhan SP, Hughes BL, Louis JM, Manuck TA, Miller HS, Das AF, Saade GR, Nielsen P, Baker J, Yuzko OM, Reznichenko GI, Reznichenko NY, Pekarev O, Tatarova N, Gudeman J, Birch R, Jozwiakowski M, Duncan M, Williams L, Krop J. *17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial*. American Journal of Perinatology. 2020. PMID 31652479. (accessed 2026-05-11)
26. *[dodd2013cochrane]* Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. *Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth*. Cochrane Database of Systematic Reviews. 2013. PMID 23903965. (accessed 2026-05-11)
27. *[coomarasamy2019prism]* Coomarasamy A, Devall AJ, Cheed V, Harb H, Middleton LJ, Gallos ID, Williams H, Eapen AK, Roberts T, Ogwulu CC, Goranitis I, Daniels JP, Ahmed A, Bender-Atik R, Bhatia K, Bottomley C, Brewin J, Choudhary M, Crosfill F, Deb S, Duncan WC, Ewer A, Hinshaw K, Holland T, Izzat F, Johns J, Kriedt K, Lumsden MA, Manda P, Norman JE, Nunes N, Overton CE, Quenby S, Rao S, Ross J, Shahid A, Underwood M, Vaithilingam N, Watkins L, Wykes C, Horne A, Jurkovic D. *A Randomized Trial of Progesterone in Women with Bleeding in Early Pregnancy*. New England Journal of Medicine. 2019. PMID 31067371. (accessed 2026-05-11)
28. *[hitchcock2012vms]* Hitchcock CL, Prior JC. *Oral micronized progesterone for vasomotor symptoms--a placebo-controlled randomized trial in healthy postmenopausal women*. Menopause. 2012. PMID 22453200. (accessed 2026-05-11)
29. *[prior2023vms]* Prior JC, Cameron A, Fung M, Hitchcock CL, Janssen P, Lee T, Singer J. *Oral micronized progesterone for perimenopausal night sweats and hot flushes a Phase III Canada-wide randomized placebo-controlled 4 month trial*. Scientific Reports. 2023. PMID 37277418. (accessed 2026-05-11)
30. *[caufriez2011sleep]* Caufriez A, Leproult R, L'Hermite-Balériaux M, Kerkhofs M, Copinschi G. *Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women*. Journal of Clinical Endocrinology & Metabolism. 2011. PMID 21289261. (accessed 2026-05-11)
31. *[herzog2012epilepsy]* Herzog AG, Fowler KM, Smithson SD, Kalayjian LA, Heck CN, Sperling MR, Liporace JD, Harden CL, Dworetzky BA, Pennell PB, Massaro JM; Progesterone Trial Study Group. *Progesterone vs placebo therapy for women with epilepsy: A randomized clinical trial*. Neurology. 2012. PMID 22649214. (accessed 2026-05-11)
32. *[herzog2014allopreg]* Herzog AG, Frye CA; Progesterone Trial Study Group. *Allopregnanolone levels and seizure frequency in progesterone-treated women with epilepsy*. Neurology. 2014. PMID 24944264. (accessed 2026-05-11)
33. *[wright2014protect3]* Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, Goldstein FC, Caveney AF, Howlett-Smith H, Bengelink EM, Manley GT, Merck LH, Janis LS, Barsan WG; NETT Investigators. *A clinical trial of progesterone for severe traumatic brain injury*. New England Journal of Medicine. 2014. PMID 25493978. (accessed 2026-05-11)
34. *[meltzerbrody2018brexanolone]* Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson CN, Deligiannidis KM, Rubinow DR, Li H, Sankoh AJ, Clemson C, Schacterle A, Jonas J, Kanes S. *Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials*. Lancet. 2018. PMID 30177236. (accessed 2026-05-11)

35. *[schumacher2014progesterone]* Schumacher M, Mattern C, Ghoumari A, Oudinet JP, Liere P, Labombarda F, Sitruk-Ware R, De Nicola AF, Guennoun R. *Revisiting the roles of progesterone and allopregnanolone in the nervous system: resurgence of the progesterone receptors*. Progress in Neurobiology. 2014. PMID 24172649. (accessed 2026-05-11)
36. *[guennoun2015allopreg]* Guennoun R, Labombarda F, Gonzalez Deniselle MC, Liere P, De Nicola AF, Schumacher M. *Progesterone and allopregnanolone in the central nervous system: response to injury and implication for neuroprotection*. Journal of Steroid Biochemistry and Molecular Biology. 2015. PMID 25196185. (accessed 2026-05-11)
37. *[mulac2000prb]* Mulac-Jericevic B, Mullinax RA, DeMayo FJ, Lydon JP, Conneely OM. *Subgroup of reproductive functions of progesterone mediated by progesterone receptor-B isoform*. Science. 2000. PMID 10976068. (accessed 2026-05-11)
38. *[conneely2001isoforms]* Conneely OM, Mulac-Jericevic B, Lydon JP, DeMayo FJ. *Reproductive functions of the progesterone receptor isoforms: lessons from knock-out mice*. Molecular and Cellular Endocrinology. 2001. PMID 11420134. (accessed 2026-05-11)
39. *[stanczyk2013progestogens]* Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. *Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects*. Endocrine Reviews. 2013. PMID 23238854. (accessed 2026-05-11)
40. *[schindler2003classification]* Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, Thijssen JH. *Classification and pharmacology of progestins*. Maturitas. 2003. PMID 14670641. (accessed 2026-05-11)
41. *[campagnoli2005breast]* Campagnoli C, Clavel-Chapelon F, Kaaks R, Peris C, Berrino F. *Progestins and progesterone in hormone replacement therapy and the risk of breast cancer*. Journal of Steroid Biochemistry and Molecular Biology. 2005. PMID 15908197. (accessed 2026-05-11)
42. *[sitrukware2006progestagens]* Sitruk-Ware R. *New progestagens for contraceptive use*. Human Reproduction Update. 2006. PMID 16291771. (accessed 2026-05-11)
43. *[wyatt2001pms]* Wyatt K, Dimmock P, Jones P, Obhrai M, O'Brien S. *Efficacy of progesterone and progestogens in management of premenstrual syndrome: systematic review*. BMJ. 2001. PMID 11588078. (accessed 2026-05-11)
44. *[ford2012pms]* Ford O, Lethaby A, Roberts H, Mol BW. *Progesterone for premenstrual syndrome*. Cochrane Database of Systematic Reviews. 2012. PMID 22419287. (accessed 2026-05-11)
45. *[hembree2017transgender]* Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline*. Journal of Clinical Endocrinology & Metabolism. 2017. PMID 28945902. (accessed 2026-05-11)

46. *[coleman2022wpath]* Coleman E, Radix AE, Bouman WP, Brown GR, de Vries ALC, Deutsch MB, Ettner R, Fraser L, Goodman M, Green J, Hancock AB, Johnson TW, Karasic DH, Knudson GA, Leibowitz SF, Meyer-Bahlburg HFL, Monstrey SJ, Motmans J, Nahata L, Nieder TO, Reisner SL, Richards C, Schechter LS, Tangpricha V, Tishelman AC, Van Trotsenburg MAA, Winter S, Ducheny K, Adams NJ, Adrián TM, Allen LR, Azul D, Bagga H, Başar K, Bathory DS, Belinky JJ, Berg DR, Berli JU, Bluebond-Langner RO, Bouman MB, Bowers ML, Brassard PJ, Byrne J, Capitán L, Cargill CJ, Carswell JM, Chang SC, Chelvakumar G, Corneil T, Dalke KB, De Cuypere G, de Vries E, Den Heijer M, Devor AH, Dhejne C, D'Marco A, Edmiston EK, Edwards-Leeper L, Ehrbar R, Ehrensaft D, Eisfeld J, Elaut E, Erickson-Schroth L, Feldman JL, Fisher AD, Garcia MM, Gijs L, Green SE, Hall BP, Hardy TLD, Irwig MS, Jacobs LA, Janssen AC, Johnson K, Klink DT, Kreukels BPC, Kuper LE, Kvach EJ, Malouf MA, Massey R, Mazur T, McLachlan C, Morrison SD, Mosser SW, Neira PM, Nygren U, Oates JM, Obedin-Maliver J, Pagkalos G, Patton J, Phanuphak N, Rachlin K, Reed T, Rider GN, Ristori J, Robbins-Cherry S, Roberts SA, Rodriguez-Wallberg KA, Rosenthal SM, Sabir K, Safer JD, Silva AB, Spencer K, St Amand C, Steensma TD, Strang JF, Taylor GB, Tilleman K, Tolentino TF, Vermeir E, Vlot M, Whelan E, Zwickl S. *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8*. International Journal of Transgender Health. 2022. PMID 36238954. (accessed 2026-05-11)

47. *[fda503a]* U.S. Food and Drug Administration. *Section 503A of the Federal Food, Drug, and Cosmetic Act*. 2024. https://www.fda.gov/drugs/human-drug-compounding/section-503a-federal-food-drug-and-cosmetic-act (accessed 2026-05-11)

48. *[fda_essentially_a_copy]* U.S. Food and Drug Administration. *Compounded Drug Products That Are Essentially Copies of Approved Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act — Guidance for Industry*. FDA Guidance for Industry. 2018. https://www.fda.gov/media/98973/download (accessed 2026-05-11)

49. *[usp_795]* United States Pharmacopeia. *USP General Chapter <795> Pharmaceutical Compounding — Nonsterile Preparations*. USP Compounding Compendium. 2024. https://www.usp.org/compounding/general-chapter-795 (accessed 2026-05-11)

50. *[usp_797]* United States Pharmacopeia. *USP General Chapter <797> Pharmaceutical Compounding — Sterile Preparations*. USP Compounding Compendium. 2024. https://www.usp.org/compounding/general-chapter-797 (accessed 2026-05-11)

How to Access Progesterone

Compounded Progesterone is dispensed under 503A on a patient-specific prescription. Depending on your role, the next step looks different.

FOR PRESCRIBING CLINICIANS

Offer this medication

A pharmacist will follow up within two business days. We'll cover state availability, supported formulations, and what integration looks like for your clinic.

ronanrx.com/request-partnership-call

PATIENT WITH A DOCTOR

Receive your prescription

If your doctor has prescribed Progesterone, sign up so we can prepare and ship your medication. The signup wizard collects intake and connects you to the prescribing workflow.

ronanrx.com/patients

PATIENT WITHOUT A DOCTOR

Find a partner clinic

RonanRx prescribes through partner clinics — we don't initiate prescriptions on this site. Read how the referral process works and how to find a partner clinic in your state.

ronanrx.com/find-clinic

Other compounds RonanRx makes

This monograph is one of many in the RonanRx formulary. Every compound below is prepared under 503A on a patient-specific prescription. Browse the full catalog at ronanrx.com/medications and ronanrx.com/peptides, or scan the codes at right for each index.

Medications Peptides

MEDICATIONS (40)

Alpha-Lipoic Acid (ALA) — Antioxidant & mitochondrial
Coenzyme Q10 (CoQ10) — Antioxidant & mitochondrial
Glutathione — Antioxidant & mitochondrial
NAD+ / NMN — Antioxidant & mitochondrial
Compounded Topical Anesthetics (BLT, LET) — Dermatology
Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
Compounded T3 (Liothyronine) — Thyroid
Compounded T3/T4 Combinations — Thyroid
Compounded T4 (Levothyroxine) — Thyroid

PEPTIDES (21)

Sermorelin — Available now

Tesamorelin — Available now

AOD-9604 — Growth-hormone axis (under FDA review)

CJC-1295 — Growth-hormone axis (under FDA review)

GHRP-2 / GHRP-6 — Growth-hormone axis (under FDA review)

Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)