CLINICAL MONOGRAPH · HORMONE OPTIMIZATION

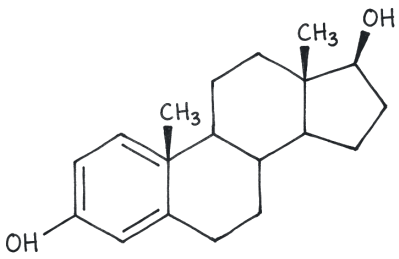
Estradiol

Bioidentical estrogen for hormone replacement

Estradiol is the main estrogen hormone your body makes, ovaries produce most of it before menopause, with smaller amounts coming from fat tissue and the adrenals [nams2022]. After menopause, ovarian estradiol falls sharply, and that drop drives hot flashes, night sweats, vaginal dryness and painful sex, sleep disruption, and accelerated bone loss.

Doctors prescribe estradiol to relieve those menopausal symptoms, protect bone in selected patients, and, for transgender women and gender-diverse people, as the principal hormone in feminizing therapy [nams2022; stuenkel2015endo; rossouw2002whi]. The FDA has approved many estradiol products: pills (Estrace), skin patches (Climara, Vivelle-Dot, Minivelle), gels (Divigel, EstroGel, Elestrin), a topical spray (Evamist), vaginal creams and tablets (Estrace Cream, Vagifem), vaginal rings (Estring, Femring), a low-dose vaginal softgel (Imvexxy), and long-acting injections (Delestrogen, Depo-Estradiol).

RonanRx compounds bioidentical estradiol when a patient needs something the manufactured products do not provide, a custom transdermal cream strength, an allergen-free vehicle, a pellet (no FDA-approved estradiol pellet exists in the US), vaginal preparations at non-commercial doses, or feminizing-therapy doses for gender-affirming care. The 2020 National Academies report [nasem2020] criticized broad marketing claims that compounded bioidentical hormones are safer or more 'natural' than FDA-approved products, RonanRx does not make those claims [fda_essentially_a_copy]. Estradiol is contraindicated in pregnancy, in women with a history of estrogen-sensitive cancer, and in those with prior venous thromboembolism; transdermal and vaginal routes carry lower clot risk than oral [canonico2007esther] [hodis2016elite].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

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

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FOR CLINICIANS

Estradiol is the principal endogenous estrogen and the molecule of choice when bioidentical estrogen replacement is indicated. FDA-approved indications across the manufactured product range include moderate-to-severe vasomotor symptoms of menopause, moderate-to-severe vulvovaginal atrophy and dyspareunia (vaginal products), prevention of postmenopausal osteoporosis in appropriate candidates, hypoestrogenism due to primary ovarian insufficiency or surgical menopause, and palliation of metastatic estrogen-responsive breast cancer and androgen-dependent prostate cancer. Diagnostic and prescribing standard per the Endocrine Society 2015 guideline [stuenkel2015endo] and the 2022 NAMS Hormone Therapy Position Statement [nams2022].

Pivotal evidence: the Women's Health Initiative reported harm with conjugated equine estrogens plus medroxyprogesterone in older women initiating therapy a decade past menopause [rossouw2002whi], while the estrogen-alone arm in women with prior hysterectomy showed a different risk profile with reduced breast cancer incidence [anderson2004whi]. The 18-year follow-up [manson2017whi] did not show excess all-cause mortality with either regimen. The timing hypothesis, that initiating estrogen near menopause produces a different risk/benefit profile than initiating it a decade later, is supported by ELITE [hodis2016elite] for carotid atherosclerosis surrogates, by KEEPS [miller2019keeps] for cardiovascular surrogates, and by KEEPS-Cog [gleason2015keepscog] for cognition.

Route-specific safety matters. Transdermal and vaginal estradiol bypass first-pass hepatic effects on coagulation; observational evidence from the ESTHER case-control study [canonico2007esther], the large QResearch / CPRD nested case-control [vinogradova2019bmj], and a systematic review of oral versus transdermal estrogen [mohammed2015orvtrans] consistently show lower VTE risk with non-oral routes. The E3N cohort [fournier2008e3n] reported that estradiol combined with micronized progesterone or dydrogesterone carried lower breast cancer risk than estradiol combined with synthetic progestins. Compounded estradiol occupies a legitimate 503A niche, custom strengths, allergen-free vehicles, pellets (no FDA-approved estradiol pellet exists in the US), vaginal preparations at non-commercial concentrations, and gender-affirming feminizing doses [hembree2017transgender], [coleman2022wpath], but NASEM 2020 [nasem2020] cautioned against broad superiority marketing of compounded preparations.

Why Personalized Estradiol

The FDA-approved estradiol products were built around averages: a patch that releases roughly 0.05 mg per day, a gel pump that delivers a fixed metered dose, an oral tablet at 0.5, 1, or 2 mg. Those strengths were calibrated for symptom relief in trial populations, not for your baseline estradiol level, your uterine status, your VTE history, your skin's response to patch adhesives, the specific vasomotor or genitourinary symptoms you are still having on a commercial dose, or whether you are receiving feminizing therapy that needs serum levels the menopausal product line was never designed to produce.

That is what compounding adds. The molecule is the same 17-beta-estradiol the FDA reviewed; what changes is the delivery. A transdermal cream can be made at a strength that sits between two commercial gel doses. A vaginal preparation can be made without the propylene glycol or paraben preservatives a patient reacts to. A subcutaneous pellet can be prepared at a strength no FDA-approved estradiol pellet provides, because no FDA-approved estradiol pellet exists in the US. A feminizing-therapy patient can be dosed to a target serum estradiol outside the menopausal label range. Each of these is a patient-specific prescription written by a licensed prescriber, prepared for that named patient, dispensed after pharmacist review.

This is the older arrangement, the one that predates mass-manufactured tablets and metered gels. A clinician writes the order, a pharmacist prepares the preparation for that patient, the label carries the patient's name. Modern state inspection, USP standards, and recall infrastructure keep it honest.

Quick Facts About Estradiol

Category: Endogenous estrogen (bioidentical steroid hormone)

Active ingredient: 17β-estradiol (bioidentical), also esterified as estradiol valerate, estradiol cypionate, and estradiol hemihydrate in various commercial products

FDA-approved branded products: Numerous: Estrace (oral and vaginal cream), Climara / Vivelle-Dot / Minivelle / Alora (transdermal patch), Divigel / Elestrin / EstroGel (transdermal gel), Estrasorb (topical emulsion), Estring / Femring (vaginal ring), Vagifem / Yuvafem (vaginal tablet), Imvexxy (vaginal softgel insert), Delestrogen (IM estradiol valerate), Depo-Estradiol (IM estradiol cypionate)

Routes studied in humans: Oral, transdermal (patch / gel / spray / cream), vaginal (cream / tablet / ring / softgel), intramuscular (valerate, cypionate), subcutaneous pellet (compounded)

Evidence posture: FDA-approved manufactured products are well-studied; landmark trials include WHI (Rossouw 2002; Anderson 2004), ELITE (Hodis 2016), KEEPS (Miller 2019; Gleason 2015), the WHIMS cognition substudies, and the E3N cohort on route- and progestogen-specific breast cancer risk

FDA-approval status: Multiple FDA-approved manufactured products for vasomotor symptoms, moderate-to-severe vulvovaginal atrophy / dyspareunia, hypoestrogenism, prevention of postmenopausal osteoporosis, and (in oncology) palliation of advanced breast and prostate cancer. Compounded variants are not FDA-approved but address patient-specific needs (custom strengths, allergen-free vehicles, pellets, gender-affirming dosing) the manufactured market does not provide.

Compounded under: 503A, patient-specific prescription only

Compounded role: Patient-specific compounding addresses needs the manufactured market does not meet: custom transdermal cream strengths between commercial gel doses; allergen-free formulations for patients with patch-adhesive reactions; subcutaneous pellets (no FDA-approved estradiol pellet exists in the US, Testopel is testosterone only); vaginal estradiol at non-commercial concentrations; and gender-affirming feminizing doses outside approved product labels. NASEM 2020 explicitly criticized broad cBHRT marketing claims, and RonanRx does not endorse them; compounding is justified by documented patient-specific clinical need.

Schedule: Not a controlled substance. Pregnancy category X, contraindicated in pregnancy.

SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY

Estradiol 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 Estradiol?

Estradiol (17β-estradiol; 1,3,5(10)-estratrien-3,17β-diol) is the principal endogenous estrogen in humans [stuenkel2015endo]. In premenopausal women, granulosa cells of the developing ovarian follicle produce most circulating estradiol from androgenic precursors via the aromatase enzyme (CYP19A1). Smaller amounts come from peripheral aromatization of androgens in adipose tissue, bone, brain, and skin. In men, estradiol arises mainly from peripheral aromatization of testosterone and contributes to bone, lipid, and reproductive physiology.

Bioidentical estradiol, the same chemical entity as endogenous human estradiol, has been available pharmaceutically since the 1930s, when Doisy isolated crystalline estrone and estradiol from urine and Inhoffen synthesized estradiol from cholesterol [stuenkel2015endo]. Replacement therapy has been in continuous use since the 1940s, initially with conjugated equine estrogens and increasingly with bioidentical estradiol in oral, transdermal, vaginal, intramuscular, and pellet forms.

The molecule itself is delivered in many forms: oral micronized estradiol; transdermal patches, gels, sprays, and emulsions; vaginal creams, tablets, softgel inserts, and rings; intramuscular ester depots (estradiol valerate, estradiol cypionate); and, exclusively as compounded preparations in the US, subcutaneous pellets. Each formulation is a different solution to the same delivery challenge: producing physiologic serum or local-tissue estradiol exposure while managing the first-pass hepatic effects on coagulation and binding globulins that drive much of estradiol's route-specific safety profile [canonico2007esther], [vinogradova2019bmj] [stuenkel2015endo].

How Estradiol Works

Estradiol acts at two nuclear estrogen receptors, ERα and ERβ, expressed in reproductive tract, breast, bone, brain, cardiovascular tissue, liver, and adipose. Ligand binding triggers receptor dimerization, nuclear translocation, and transcription of estrogen-responsive genes. ERα predominates in uterus, mammary epithelium, and liver; ERβ predominates in vascular endothelium, lung, prostate, and parts of the central nervous system. Beyond classical genomic signaling, estradiol also activates membrane-associated estrogen receptors (GPER and membrane-localized ERα) that drive rapid, nongenomic signaling through MAPK, PI3K/Akt, and nitric oxide synthase cascades.

Replacement therapy raises serum estradiol toward the premenopausal physiologic range, with downstream effects on vasomotor stability, vaginal and urethral epithelium, bone resorption (estradiol suppresses osteoclast activity), lipid metabolism, mood, and cognition. The Endocrine Society [stuenkel2015endo] and NAMS [nams2022] frame these effects as the basis for the established menopausal symptom and osteoporosis-prevention indications. The 'timing hypothesis' [hodis2016elite], that estradiol's vascular effects depend on when after menopause therapy starts, is supported by ELITE's carotid intima-

media thickness data showing benefit when therapy was initiated within 6 years of menopause but not after 10+ years.

Importantly, exogenous estradiol in the absence of a progestogen causes endometrial proliferation and increases the risk of endometrial hyperplasia and adenocarcinoma in women with an intact uterus. This is why estradiol monotherapy is contraindicated in women with an intact uterus and why combined estradiol-plus-progestogen regimens are standard in that population. The PEPI trial [pepi1996bone] characterized this endometrial-protective role of cyclic and continuous progestogen across regimens, while bone-density benefit was maintained.

Biological Role of Estradiol

Estradiol is the principal mediator of female sexual development and adult reproductive physiology. During puberty in females, it drives breast development, uterine and vaginal maturation, the pubertal growth spurt, epiphyseal closure, and adult bone-density accrual. In adult premenopausal women, cyclical estradiol secretion from the developing ovarian follicle drives endometrial proliferation in the follicular phase, the mid-cycle LH surge that triggers ovulation, and physiologic preparation of cervical mucus and vaginal epithelium for reproduction.

Beyond reproduction, estradiol has major effects on bone (suppression of osteoclastic resorption, the abrupt loss of estradiol at menopause drives the acute postmenopausal phase of bone loss), cardiovascular tissue (vasodilation, favorable lipid effects, endothelial nitric oxide signaling), the central nervous system (mood, cognition, thermoregulation, the loss of estradiol-driven thermoregulatory tone underlies vasomotor symptoms), and the urogenital tract (epithelial maturation, mucus production, urethral function) [stuenkel2015endo].

Estradiol is also a normal physiologic hormone in men, where it derives mainly from aromatization of testosterone in adipose tissue, bone, and brain. The Finkelstein 2013 gonadal-suppression study established that a substantial fraction of testosterone's effects on bone density, fat mass, and some sexual function in men is mediated by aromatization to estradiol rather than by testosterone itself, establishing that estradiol is a physiologic hormone in male biology, not just a side effect of high testosterone exposure [nams2022; pepi1996bone].

Detailed Mechanism of Estradiol

Estrogen receptor structure and isoforms. The classical estrogen receptors ERα (encoded by ESR1 on chromosome 6) and ERβ (encoded by ESR2 on chromosome 14) are nuclear hormone receptors with a modular domain organization shared across the superfamily, N-terminal activation function-1 (AF-1) domain, central DNA-binding domain with two zinc-finger motifs that recognize estrogen-response elements, hinge region, and C-terminal ligand-binding domain that houses AF-2 [nams2022]. Unliganded

receptors are complexed with heat-shock chaperones; ligand binding induces conformational change, dimerization, nuclear translocation, and recruitment of coactivator complexes that drive transcription of estrogen-responsive genes.

Genomic versus nongenomic signaling. The genomic pathway operates on a transcriptional timescale of hours and underlies most of estradiol's chronic effects on tissue growth, gene expression, and homeostasis. The nongenomic pathway operates on a seconds-to-minutes timescale through plasma-membrane-associated complexes: a fraction of ERα localizes to caveolae and signals through Gαi, src, MAPK, and PI3K/Akt; a separate G protein-coupled receptor GPER (GPR30) drives rapid kinase cascades and endothelial nitric oxide synthase activation. Nongenomic signaling is implicated in estradiol's acute vasodilatory effects and in some neuroprotective and metabolic actions [hodis2016elite].

Tissue selectivity. The same circulating estradiol produces tissue-specific effects depending on the local ERα/ERβ ratio, coregulator complement, and the presence of metabolizing enzymes. Uterus, mammary epithelium, and liver are ERα-dominant; vascular endothelium, lung, and parts of the CNS are ERβ-dominant [hodis2016elite]. The selective estrogen receptor modulator (SERM) class, tamoxifen, raloxifene, bazedoxifene, exploits this tissue selectivity by acting as an agonist in some tissues (bone) and antagonist in others (breast).

First-pass hepatic effects and route-dependence. Oral estradiol is extensively metabolized to estrone (E1) and estrone sulfate (E1S) on first pass through the liver, producing a markedly different metabolite profile than endogenous ovarian secretion. The hepatic exposure that follows oral dosing also induces synthesis of sex hormone-binding globulin (SHBG), thyroid-binding globulin, corticosteroid-binding globulin, angiotensinogen, and several coagulation factors, driving the higher VTE and stroke risk seen with oral versus transdermal estradiol in observational studies [canonico2007esther], [vinogradova2019bmj], [mohammed2015orvtrans] [hodis2016elite]. Transdermal, vaginal, and subcutaneous pellet routes largely bypass first-pass, producing serum estradiol exposure closer to the premenopausal physiologic profile and a more favorable hepatic-coagulation signature [renoux2010transdermal].

Metabolism. Estradiol is metabolized hepatically by CYP1A2, CYP3A4, and other isoforms to 2-hydroxyestradiol, 4-hydroxyestradiol, and 16α-hydroxyestrone, with subsequent methylation by COMT and conjugation by SULT and UGT [hodis2016elite]. The catechol estrogens and their semiquinones have been studied as putative carcinogenic intermediates in breast tissue. Excretion is mostly urinary as glucuronide and sulfate conjugates.

Endometrial proliferation and progestogen co-therapy. Unopposed estradiol drives endometrial epithelial proliferation through ERα; in women with an intact uterus, this produces dose- and duration-dependent increases in endometrial hyperplasia (including atypia) and adenocarcinoma. Cyclic or continuous progestogen administration opposes this effect by downregulating endometrial estrogen receptors and inducing decidualization. The PEPI trial [pepi1996bone] established that all four common combined regimens (CEE alone in hysterectomized women, CEE + cyclic MPA, CEE + continuous MPA, CEE + cyclic micronized progesterone) preserved bone density relative to placebo while combined regimens prevented

endometrial hyperplasia. Compounded bioidentical estradiol delivered with micronized progesterone is widely used in postmenopausal women with an intact uterus, with the E3N cohort [fournier2008e3n] providing the largest observational signal that micronized progesterone or dydrogesterone produces lower breast cancer risk than synthetic progestins when paired with estradiol [stuenkel2015endo; hodis2016elite].

Estradiol Research History

Estradiol was isolated and characterized in the 1930s. Doisy isolated crystalline estrone from pregnancy urine in 1929 and crystalline estradiol from sow ovaries in 1935; Inhoffen and Hohlweg synthesized estradiol from cholesterol in 1938. Doisy shared the 1943 Nobel Prize in Physiology or Medicine for the discovery of vitamin K, with his estrogen work cited among his major contributions. Oral and parenteral estradiol preparations entered clinical use through the 1940s, with conjugated equine estrogens (Premarin, FDA-approved in 1942) becoming the dominant prescription form for several decades.

Transdermal delivery emerged in the 1980s with the Estraderm reservoir patch, providing the first route that avoided first-pass hepatic metabolism. Matrix patches (Climara, Vivelle, Vivelle-Dot, Minivelle, Alora) and transdermal gels (EstroGel, Divigel, Elestrin) followed in the 1990s and 2000s, each refining adhesion, dosing flexibility, and serum-level stability. Vaginal estradiol preparations expanded from the long-standing creams (Estrace Cream, Premarin Cream) to low-dose tablets (Vagifem; ultra-low 10 microgram dosing), rings (Estring for local effect, Femring for systemic effect), and a low-dose vaginal softgel (Imvexxy, FDA-approved 2018) [constantine2017imvexxy], [imvexxy2018paton].

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial in the 1990s [pepi1996bone] established the bone-density benefit of postmenopausal estrogen across regimens and the endometrial-protective role of progestogen co-therapy in women with an intact uterus. The Estrogen in the Prevention of Atherosclerosis Trial (EPAT) [hodis2001epat] was an early randomized controlled study suggesting estradiol slowed carotid intima-media thickness progression in postmenopausal women not previously treated for coronary disease.

The Women's Health Initiative (WHI), the largest randomized hormone-therapy program ever conducted, fundamentally reshaped clinical practice. The combined CEE + medroxyprogesterone acetate arm was stopped early in 2002 [rossouw2002whi] for an excess of breast cancer plus modest increases in coronary heart disease, stroke, and venous thromboembolism that crossed a pre-specified global safety index. The estrogen-alone (CEE in hysterectomized women) arm continued through 2004 [anderson2004whi] and showed a different risk profile, with reduced breast cancer incidence. The Manson 2013 [manson2013whi] follow-up and the Manson 2017 18-year cumulative analysis [manson2017whi] confirmed no excess all-cause mortality in either arm during the extended follow-up.

Substudies refined the picture. WHIMS [shumaker2004whims], [espeland2004whims], [rapp2003whims] reported excess dementia and global cognitive decline in women aged 65+ on CEE ± MPA. WHIMS-Y [vaughan2013whimsy] later examined younger women. Bone outcomes were favorable for combined

therapy [cauley2003whi]. Stefanick 2006 [stefanick2006whi] showed reduced mammographic abnormalities and breast cancer in the CEE-alone arm. Cushman 2004 [cushman2004whivte] quantified the VTE excess on combined therapy. Pradhan 2002 [pradhan2002whi] characterized inflammatory biomarker changes.

Post-WHI, the field re-evaluated WHI's relevance to younger, recently menopausal women, the population for whom hormone therapy is now most commonly recommended. KEEPS [miller2019keeps] randomized recently menopausal women to oral conjugated equine estrogens, transdermal estradiol, or placebo for 4 years; arterial imaging surrogates were neutral but symptom and bone effects favored active therapy. KEEPS-Cog [gleason2015keepscog] showed no cognitive harm with hormone therapy initiated near menopause, in contrast to the WHIMS signal in older women. ELITE [hodis2016elite] randomized women stratified by time since menopause and reported less carotid intima-media thickness progression on oral estradiol when initiated within 6 years of menopause, but not when initiated 10+ years out, the most direct test of the 'timing hypothesis.' Salpeter 2006 [salpeter2006chd] and Salpeter 2009 [salpeter2009mortality] meta-analyses had earlier suggested that younger women initiating therapy near menopause had lower coronary and all-cause mortality.

Route-specific safety became a major theme. The French ESTHER case-control study [canonico2007esther], the population-based Renoux study [renoux2010transdermal], the QResearch / CPRD nested case-control [vinogradova2019bmj], and a systematic review and meta-analysis [mohammed2015orvtrans] consistently reported lower VTE risk with transdermal versus oral estrogen. The E3N cohort [fournier2008e3n] reported that micronized progesterone and dydrogesterone, when paired with estradiol, produced lower breast cancer risk than synthetic progestins. The Million Women Study [beral2003mws] reported elevated breast cancer risk with combined therapy across regimens.

Vaginal and local estradiol preparations were studied separately. The Cochrane review of local vaginal estrogen [suckling2006cochrane] established the efficacy of vaginal estrogen across formulations for genitourinary syndrome of menopause. The TX-004HR (Imvexxy) trials [constantine2017imvexxy], [kingsberg2017tx004hr] supported the low-dose vaginal softgel. Mitchell 2018 [mitchell2018vagest] compared vaginal estradiol tablets, moisturizer, and placebo in postmenopausal women with bothersome vulvovaginal symptoms. Bhupathiraju 2018 [bhupathiraju2018vagne] and Crandall 2018 [crandall2018vagest] examined chronic disease outcomes in long-term vaginal estrogen users.

Gender-affirming feminizing therapy uses estradiol as the principal hormone. The Endocrine Society 2017 guideline [hembree2017transgender] and WPATH Standards of Care Version 8 [coleman2022wpath] define current best practice for estradiol dosing, monitoring, and shared decision-making in transgender women and gender-diverse people. Estradiol valerate IM, estradiol cypionate IM, transdermal estradiol patches, oral estradiol, and (in compounded practice) subcutaneous pellets are all used in this population.

The 2020 National Academies of Sciences, Engineering, and Medicine consensus report on compounded bioidentical hormone therapy [nasem2020] reviewed the clinical utility, safety, and marketing of compounded hormones. It found insufficient evidence to support broad claims of safety or efficacy

advantages over FDA-approved manufactured products and recommended restricting compounded preparations to documented patient-specific clinical needs, the framework RonanRx follows.

Estradiol Timeline

1929 • Doisy isolates crystalline estrone (theelin) from pregnancy urine, first pure isolation of a human estrogen

1935 • Doisy isolates crystalline estradiol from sow ovaries

1938 • Inhoffen and Hohlweg synthesize estradiol from cholesterol, basis for industrial pharmaceutical production

1942 • FDA approves Premarin (conjugated equine estrogens), dominant prescription estrogen for several decades

1986 • FDA approves Estraderm, the first transdermal estradiol patch, establishes the non-oral route that avoids first-pass hepatic metabolism

1996 • PEPI trial reports bone-density preservation with postmenopausal estrogen across regimens and endometrial-protective effect of progestogen co-therapy [pepi1996bone]

2001 • Hodis et al publish the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) in Annals of Internal Medicine, early randomized evidence that oral estradiol slows carotid intima-media thickness in postmenopausal women without prior CHD [hodis2001epat]

2002 • Writing Group for the Women's Health Initiative publishes the principal results of the combined CEE + MPA trial in JAMA, trial stopped early for excess breast cancer, CHD, stroke, and VTE crossing the global safety index [rossouw2002whi]

2003 • Manson et al publish WHI estrogen plus progestin and coronary heart disease in NEJM; Cauley et al publish bone-fracture results in JAMA; Beral et al publish Million Women Study breast cancer results in Lancet; Rapp et al publish WHIMS global cognitive results in JAMA [manson2003chd; cauley2003whi; beral2003mws; rapp2003whims]

2004 • Anderson et al publish WHI CEE-alone (hysterectomy) results in JAMA, different risk profile from combined arm, with reduced breast cancer incidence; Shumaker and Espeland publish WHIMS dementia and cognition substudies in JAMA; Cushman publishes WHI VTE substudy in JAMA [anderson2004whi; shumaker2004whims; espeland2004whims; cushman2004whivte]

2006 • Stefanick et al publish WHI CEE-alone breast cancer and mammography results in JAMA; Suckling et al publish Cochrane review of local vaginal estrogen for vaginal atrophy [stefanick2006whi; suckling2006cochrane]

2006 • Salpeter et al publish meta-analysis suggesting reduced coronary heart disease events on hormone therapy in younger women initiating therapy near menopause [salpeter2006chd]

2007 • Canonico et al publish ESTHER case-control study in Circulation, transdermal estradiol carries lower VTE risk than oral; progestogen type also matters [canonico2007esther]

2008 • Fournier et al publish E3N cohort breast cancer results in Breast Cancer Research and Treatment, estradiol plus micronized progesterone or dydrogesterone carried lower breast cancer risk than estradiol plus synthetic progestins [fournier2008e3n]

2009 • Salpeter et al publish Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women in American Journal of Medicine [salpeter2009mortality]

2010 • Renoux et al publish population-based study of HRT and VTE risk in Journal of Thrombosis and Haemostasis, confirms route differential [renoux2010transdermal]

2011 • Files, Ko, and Pruthi publish 'Bioidentical hormone therapy' in Mayo Clinic Proceedings, widely cited critical review of the bioidentical-hormone marketing landscape [files2011bioidentical]

2013 • Manson et al publish WHI health outcomes during intervention and extended poststopping phases in JAMA; Vaughan et al publish WHIMS-Y baseline characteristics in Brain Research [manson2013whi; vaughan2013whimsy]

2015 • Gleason et al publish KEEPS-Cog results in PLoS Medicine, no cognitive harm with hormone therapy initiated near menopause, contrasting WHIMS in older women; Stuenkel et al publish Endocrine Society 2015 menopause guideline in JCEM; Boardman et al publish Cochrane review of hormone therapy for cardiovascular disease prevention; Mohammed et al publish JCEM meta-analysis of oral vs transdermal estrogen vascular events [gleason2015keepscog; stuenkel2015endo; boardman2015cochranecv; mohammed2015orvtrans]

2016 • Hodis et al publish ELITE in NEJM, oral estradiol initiated within 6 years of menopause slowed carotid intima-media thickness progression; not so when initiated 10+ years out, strongest randomized support of the timing hypothesis [hodis2016elite]

2017 • Manson et al publish 18-year cumulative WHI mortality analysis in JAMA, no excess all-cause or cause-specific mortality in either WHI arm during extended follow-up; Constantine and Kingsberg publish TX-004HR (Imvexxy) trial data; Hembree et al publish Endocrine Society guideline on endocrine treatment of gender-dysphoric/gender-incongruent persons in JCEM [manson2017whi; constantine2017imvexxy; kingsberg2017tx004hr; hembree2017transgender]

2018 • FDA approves Imvexxy (estradiol vaginal softgel insert); Mitchell et al publish vaginal estradiol vs moisturizer vs placebo RCT in JAMA Internal Medicine; Bhupathiraju and Crandall analyze long-term vaginal estrogen safety in NHS and WHI [imvexxy2018paton; mitchell2018vagest; bhupathiraju2018vagne; crandall2018vagest]

2019 • Miller et al publish KEEPS overview ('what have we learned') in Menopause; Vinogradova et al publish QResearch / CPRD nested case-control of HRT and VTE in BMJ, confirms route differential at scale [miller2019keeps; vinogradova2019bmj]

2020 • National Academies of Sciences, Engineering, and Medicine publish 'The Clinical Utility of Compounded Bioidentical Hormone Therapy' consensus report, finds insufficient evidence for broad safety/efficacy claims over FDA-approved products and recommends restricting compounded preparations to documented patient-specific clinical needs [nasem2020]

2022 • NAMS publishes the 2022 Hormone Therapy Position Statement in Menopause, current consensus framework for menopausal hormone therapy; Coleman et al publish WPATH Standards of Care Version 8 [nams2022; coleman2022wpath]

Clinical Contexts for Estradiol

Moderate-to-severe vasomotor symptoms of menopause FDA APPROVED

FDA-approved indication across the oral, transdermal, and systemic-dose vaginal-ring estradiol product range.

Estradiol is FDA-approved for moderate-to-severe vasomotor symptoms (hot flashes, night sweats) due to menopause. The Endocrine Society 2015 guideline [stuenkel2015endo] and NAMS 2022 Position Statement [nams2022] frame systemic estradiol (with progestogen in women with an intact uterus) as the most effective therapy for moderate-to-severe vasomotor symptoms in appropriate candidates initiating therapy within 10 years of menopause and under age 60. The Cochrane review of long-term hormone therapy [marjoribanks2018cochrane] and the Boardman 2015 Cochrane review of hormone therapy for cardiovascular disease prevention [boardman2015cochranecv] provide the systematic-review framing.

Branded product: Estrace, Climara, Vivelle-Dot, Minivelle, Divigel, EstroGel, Elestrin, Femring, Delestrogen, Depo-Estradiol

Moderate-to-severe vulvovaginal atrophy / genitourinary syndrome of menopause

FDA APPROVED

FDA-approved indication for vaginal estradiol products.

Vaginal estradiol, creams, tablets, softgels, and rings, is FDA-approved for moderate-to-severe vulvovaginal atrophy and dyspareunia due to menopause [imvexxy2018paton]. The Cochrane review [suckling2006cochrane], the TX-004HR (Imvexxy) trials [constantine2017imvexxy], [kingsberg2017tx004hr], the JAMA Internal Medicine RCT comparing vaginal estradiol tablets, moisturizer, and placebo [mitchell2018vagest], and the long-term safety analyses in NHS [bhupathiraju2018vagne] and WHI [crandall2018vagest] together provide a strong evidence base for local vaginal estrogen. Systemic absorption is minimal at recommended doses, and observational data support a favorable safety profile.

Branded product: Estrace Cream, Vagifem, Yuvafem, Imvexxy, Estring, Premarin Cream

Prevention of postmenopausal osteoporosis FDA APPROVED

FDA-approved indication for systemic estradiol in appropriate candidates.

Systemic estradiol is FDA-approved for prevention of postmenopausal osteoporosis in women at significant risk and for whom non-estrogen therapies are unsuitable. The PEPI trial [pepi1996bone] established bone-density preservation across CEE-based regimens; WHI [cauley2003whi] confirmed reduced hip and clinical fractures with combined therapy in older women. Current NAMS [nams2022] and Endocrine Society [stuenkel2015endo] framing positions estradiol as a reasonable bone-preserving choice for symptomatic women within 10 years of menopause, with non-estrogen alternatives preferred when osteoporosis is the sole indication in older women given WHI's broader risk profile in that age stratum.

Branded product: Climara, Vivelle-Dot, Minivelle, Estrace

Hypoestrogenism (primary ovarian insufficiency, surgical menopause, hypopituitarism)

FDA APPROVED

FDA-approved indication for systemic estradiol.

Estradiol replacement is FDA-approved and clinically standard for hypoestrogenism due to primary ovarian insufficiency, bilateral oophorectomy, or hypogonadotropic hypogonadism, with goals of preserving bone density, ameliorating vasomotor symptoms, and supporting cardiovascular health to physiologic-age expectations. The Endocrine Society guideline [stuenkel2015endo] and NAMS 2022 [nams2022] frame this population as a clear long-duration indication, distinct from age-typical menopausal hormone therapy decisions.

Branded product: Estrace, Climara, Vivelle-Dot, Divigel, EstroGel

Cardiovascular safety and the 'timing hypothesis' WELL STUDIED

Addressed by ELITE, KEEPS, and WHI subgroup analyses.

The 'timing hypothesis', that initiating estradiol near menopause produces a different cardiovascular risk/benefit profile than initiating it a decade later, is supported by ELITE [hodis2016elite] for carotid intima-media thickness, by KEEPS [miller2019keeps] for symptom and surrogate endpoints, and by the WHI age-stratified reanalyses. The Boardman 2015 Cochrane review [boardman2015cochranecv] integrates the randomized evidence base. Hodis EPAT [hodis2001epat] was an early supporting RCT. Salpeter 2006 [salpeter2006chd] and 2009 [salpeter2009mortality] meta-analyses suggested reduced CHD events and lower all-cause mortality in younger initiators. Route also matters: transdermal estradiol carries lower VTE and stroke risk than oral in observational data [canonico2007esther], [vinogradova2019bmj], [mohammed2015orvtrans], [renoux2010transdermal].

Breast cancer risk on estradiol-based hormone therapy WELL STUDIED

Well-studied; risk depends on regimen, route, progestogen, and time since menopause.

WHI [rossouw2002whi] reported elevated invasive breast cancer on CEE + medroxyprogesterone in older women, but the CEE-alone arm in hysterectomized women [anderson2004whi], [stefanick2006whi] showed reduced breast cancer incidence. The E3N cohort [fournier2008e3n] reported that micronized progesterone or dydrogesterone, paired with estradiol, produced lower breast cancer risk than estradiol plus synthetic progestins. The Million Women Study [beral2003mws] reported elevated breast cancer risk with combined therapy across regimens. Long-term WHI follow-up [chlebowski2020whilongterm], [manson2017whi] refined the cumulative incidence and mortality picture across the two regimens. The current consensus [nams2022] frames breast cancer risk as a function of regimen (combined > estrogen-alone), progestogen type (synthetic progestins > micronized progesterone), duration, and baseline risk.

Cognition and dementia risk WELL STUDIED

Time-of-initiation dependent; WHIMS in older women showed harm; KEEPS-Cog and WHIMS-Y do not show harm in younger initiators.

WHIMS [shumaker2004whims], [espeland2004whims] reported excess probable dementia and global cognitive decline on CEE ± MPA in women aged 65+. Rapp 2003 [rapp2003whims] reported the global cognitive function findings in JAMA. WHIMS-Y [vaughan2013whimsy] examined younger women. KEEPS-Cog [gleason2015keepscog] randomized recently menopausal women and reported no cognitive harm, and possible mood benefit, over 4 years of oral or transdermal therapy. The current consensus [nams2022] positions hormone therapy as not indicated for cognitive protection but acceptable from a cognition-safety standpoint in symptomatic recently menopausal women.

Off-Label Uses of Estradiol

Gender-affirming feminizing hormone therapy WELL STUDIED

Standard-of-care per Endocrine Society and WPATH guidelines; no estradiol product carries this specific FDA indication.

Estradiol is the principal hormone of feminizing hormone therapy in transgender women and gender-diverse people. The Endocrine Society 2017 guideline [hembree2017transgender] and WPATH Standards of Care Version 8 [coleman2022wpath] define current best practice for estradiol dosing (oral, transdermal patch, transdermal gel, sublingual, IM valerate or cypionate, and compounded pellet), monitoring (serum estradiol and total testosterone, with co-administered anti-androgen as appropriate), and shared decision-making. RonanRx compounded estradiol is dispensed in this context only on a patient-specific prescription from the patient's clinician; this page does not substitute for those guidelines.

Compounded bioidentical hormone therapy (cBHRT) EMERGING

Not recommended as broadly safer or more effective than FDA-approved products per NASEM 2020 and NAMS.

Marketing of compounded bioidentical hormone therapy as broadly safer, more 'natural,' or more effective than FDA-approved products is not supported by the evidence base reviewed in the 2020 National Academies consensus report [nasem2020] [nams2022]. NASEM recommended restricting compounded preparations to documented patient-specific clinical needs, allergen sensitivity, dose customization, alternative routes, and not as a general-purpose substitute for FDA-approved products. The Files 2011 Mayo Clinic Proceedings review [files2011bioidentical] articulated the same critique earlier. RonanRx follows this framework: compounded estradiol is dispensed for documented patient-specific reasons, not as a marketing claim of superiority.

Palliative therapy in advanced prostate cancer (high-dose estradiol) EMERGING

Historically used as androgen-suppression; largely replaced by GnRH analogues. Mentioned here for completeness only.

High-dose oral estrogens (diethylstilbestrol, ethinyl estradiol) were a historical mainstay of androgen-deprivation therapy in advanced prostate cancer through the 1970s. The cardiovascular and VTE burden led to their replacement by GnRH analogues and antagonists. Transdermal estradiol has been studied in this context as a route that may avoid the first-pass hepatic coagulation burden of oral estrogens. This page focuses on menopausal and feminizing indications; prostate-cancer hormonal therapy is outside the typical 503A compounding context for estradiol [stuenkel2015endo].

FDA-Approved Uses of Estradiol

Brand	Indication	Year	Route
Estrace (oral)	Vasomotor symptoms, vulvovaginal atrophy, hypoestrogenism, prevention of postmenopausal osteoporosis	1975	Oral micronized estradiol tablet
Estrace Cream	Moderate-to-severe vulvovaginal atrophy	—	Vaginal cream (0.01% estradiol)
Climara	Vasomotor symptoms, vulvovaginal atrophy, hypoestrogenism, prevention of postmenopausal osteoporosis	1994	Transdermal patch (weekly)
Vivelle-Dot / Vivelle	Vasomotor symptoms, vulvovaginal atrophy, hypoestrogenism, prevention of postmenopausal osteoporosis	1999	Transdermal patch (twice weekly)
Minivelle	Vasomotor symptoms, prevention of postmenopausal osteoporosis	2012	Transdermal patch (twice weekly)
Alora	Vasomotor symptoms, vulvovaginal atrophy, hypoestrogenism, prevention of postmenopausal osteoporosis	1996	Transdermal patch (twice weekly)
Divigel	Moderate-to-severe vasomotor symptoms	2007	Transdermal gel sachet
EstroGel	Moderate-to-severe vasomotor symptoms, vulvovaginal atrophy	2004	Transdermal gel pump
Elestrin	Moderate-to-severe vasomotor symptoms	2006	Transdermal gel pump
Estrasorb	Moderate-to-severe vasomotor symptoms	2003	Topical emulsion
Evamist	Moderate-to-severe vasomotor symptoms	2007	Transdermal spray
Vagifem / Yuvafem	Moderate-to-severe vulvovaginal atrophy / atrophic vaginitis	1999	Vaginal tablet (10 microgram)
Imvexxy	Moderate-to-severe dyspareunia due to vulvar and vaginal atrophy	2018	Vaginal softgel insert (4 or 10 microgram)
Estring	Moderate-to-severe urogenital symptoms of postmenopausal atrophy	1996	Vaginal ring (low-dose, local effect)
Femring	Moderate-to-severe vasomotor and vulvovaginal symptoms	2003	

Brand	Indication	Year	Route
			Vaginal ring (systemic dose)
Delestrogen	Vasomotor symptoms, hypoestrogenism, palliation of advanced breast cancer, palliation of advanced prostate cancer	—	Intramuscular estradiol valerate in oil
Depo-Estradiol	Vasomotor symptoms, hypoestrogenism	—	Intramuscular estradiol cypionate in oil

Numerous FDA-approved estradiol products are available across oral, transdermal patch, transdermal gel and spray, vaginal cream and tablet and ring and softgel insert, and intramuscular ester routes. Approved indications across the product range include moderate-to-severe vasomotor symptoms of menopause, moderate-to-severe vulvovaginal atrophy and dyspareunia (vaginal products), prevention of postmenopausal osteoporosis in appropriate candidates, hypoestrogenism due to primary ovarian insufficiency or castration, and, for selected IM products, palliation of advanced estrogen-responsive breast cancer and advanced prostate cancer [constantine2017imvexxy].

The Endocrine Society 2015 guideline [stuenkel2015endo] and NAMS 2022 Hormone Therapy Position Statement [nams2022] frame the diagnostic and prescribing standard. Compounded estradiol preparations are not FDA-approved; they are dispensed under 503A on a patient-specific prescription when the manufactured product range does not meet a documented clinical need [constantine2017imvexxy].

Compounded Estradiol (503A)

Compounded estradiol occupies a meaningful 503A niche, distinct from typical 'essentially-a-copy' compounding [files2011bioidentical]. The manufactured market is broad but not exhaustive: it offers oral micronized estradiol at limited strengths, transdermal patches and gels at fixed strengths, vaginal preparations at fixed local doses, and IM esters at fixed concentrations. The manufactured market does not offer FDA-approved estradiol pellets, the only marketed pellet product (Testopel) is testosterone, so any estradiol pellet preparation in US practice is inherently compounded.

Patient-specific compounding addresses needs the manufactured market does not provide: custom transdermal cream strengths between commercial gel doses, allergen-free formulations for patients who react to patch adhesives or to specific gel vehicles, subcutaneous pellets at clinician-specified doses, vaginal estradiol at non-commercial concentrations (for example, ultra-low-dose preparations below Vagifem's 10 microgram strength or above for selected refractory atrophy), and gender-affirming feminizing-therapy doses that fall outside the labeled ranges of approved menopausal products [hembree2017transgender], [coleman2022wpath] [files2011bioidentical].

Per FDA guidance on compounded copies of approved drugs [fda_essentially_a_copy], the prescribing clinician documents the patient-specific clinical reason [files2011bioidentical]. For estradiol the documented reasons are typically formulation/route the manufactured market does not provide (pellet, custom transdermal cream strength), allergen/excipient sensitivity (alternative vehicle), strength outside the manufactured range, or gender-affirming-care dosing outside the menopausal label. Routine substitution of compounded for manufactured product without a documented reason is not the appropriate framing.

The 2020 NASEM report on compounded bioidentical hormone therapy [nasem2020] explicitly criticized broad marketing claims that compounded estradiol is safer, more effective, or more 'natural' than FDA-approved bioidentical estradiol, claims that conflate the molecule (which is identical) with the manufacturing pathway [files2011bioidentical; nams2022]. RonanRx does not endorse those marketing claims. Compounded estradiol is bioidentical to FDA-approved estradiol; the case for compounding is a patient-specific clinical need, not a superiority claim.

Estradiol Formulations and Routes

Form	Concentration	Description
Oral micronized estradiol tablet	Manufactured: 0.5, 1, 2 mg (Estrace); compounded capsules at custom strengths	Daily oral dosing. Extensive first-pass hepatic conversion to estrone produces a higher E1:E2 ratio than non-oral routes. Hepatic exposure drives SHBG induction and the higher VTE and stroke risk seen with oral versus transdermal estrogen in observational data.
Transdermal patch	Manufactured: 0.025, 0.0375, 0.05, 0.075, 0.1 mg/day (Climara, Vivelle-Dot, Minivelle, Alora)	Weekly or twice-weekly application. Avoids first-pass hepatic metabolism; serum estradiol and metabolite profile approximate premenopausal physiologic. Patch-adhesive reactions in some patients motivate compounded alternatives.
Transdermal gel or spray	Manufactured: Divigel 0.25, 0.5, 0.75, 1.0 mg/sachet; EstroGel 0.06%; Elestrin 0.06%; Evamist 1.53 mg/spray; compounded creams at custom percentages	Daily application. Like patches, avoids first-pass. Custom compounded transdermal creams provide strengths between commercial pump doses; useful for titration.
Vaginal cream	Manufactured: Estrace Cream 0.01%; compounded creams at custom strengths	Intravaginal application for genitourinary syndrome of menopause. Local effect on vaginal epithelium, urethra, and bladder trigone. Systemic absorption is dose-dependent; recommended low-dose regimens produce minimal systemic exposure.

Form	Concentration	Description
Vaginal tablet or softgel insert	Manufactured: Vagifem 10 microgram; Yuvafem 10 microgram; Imvexxy 4 or 10 microgram softgel	Low-dose intravaginal release for vulvovaginal atrophy. Imvexxy supported by TX-004HR clinical program.
Vaginal ring	Estring (low-dose, local effect, 7.5 microgram/day for 90 days); Femring (systemic dose, 0.05 or 0.1 mg/day for 90 days)	Three-month intravaginal ring. Estring delivers a local dose with minimal systemic exposure; Femring delivers a systemic dose that treats both genitourinary and vasomotor symptoms.
Intramuscular estradiol ester in oil	Delestrogen 10, 20, 40 mg/mL (estradiol valerate); Depo-Estradiol 5 mg/mL (estradiol cypionate); compounded variants at custom concentrations	Long-acting depot for systemic estradiol. Commonly used in gender-affirming feminizing therapy and in selected menopausal contexts where other routes are not feasible. Peak-trough serum estradiol variability over the dosing interval is wider than with transdermal continuous delivery.
Subcutaneous estradiol pellet (compounded)	Custom, typical 12.5, 25, 37.5, 50 mg per pellet, often co-implanted with testosterone pellet in selected practice	Implanted in the subcutaneous fat of the hip or buttock; releases estradiol over 3, 6 months. No FDA-approved estradiol pellet exists in the United States, Testopel is testosterone only, so any estradiol pellet preparation is inherently compounded. The published safety and pharmacokinetic evidence for estradiol pellets is limited; long-term outcome data are largely observational from specialty pellet-therapy clinics.
Sublingual / troche (compounded)	Custom, typical 0.5, 2 mg per troche	Sublingual or buccal slow-dissolve troche. Bypasses first-pass metabolism with rapid absorption and peak serum estradiol within 1, 2 hours; trough levels fall within 6, 8 hours. Used by some clinicians for menopausal symptoms or gender-affirming feminizing therapy.

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

Estradiol Dosing

Route	Population	Range	Duration	Study type
Oral	Postmenopausal women, vasomotor symptoms or	Estradiol 0.5, 2 mg orally once daily; with progestogen co-therapy in women with an	Typically reassessed annually; lowest	Endocrine Society 2015 guideline;

Route	Population	Range	Duration	Study type
	osteoporosis prevention	intact uterus (typically micronized progesterone 100, 200 mg/day or cyclic 200 mg for 12, 14 days/ month)	effective dose for the shortest duration consistent with treatment goals	NAMS 2022 Position Statement
Transdermal patch	Postmenopausal women, vasomotor symptoms or osteoporosis prevention	0.025, 0.1 mg/day; weekly (Climara) or twice-weekly (Vivelle-Dot, Minivelle, Alora) application; with progestogen co-therapy in women with an intact uterus	Reassessed annually; route preferred over oral when VTE / stroke risk concerns are present	FDA-labeled regimens; route-specific safety supported by ESTHER (Canonico 2007), Renoux 2010, Vinogradova 2019, and Mohammed 2015 systematic review
Transdermal gel or spray	Postmenopausal women, vasomotor symptoms	EstroGel 0.75 mg/day (1 pump) to 1.5 mg/day (2 pumps); Divigel 0.25, 1.0 mg/day sachet; Elestrin 0.52 mg/day (1 pump) to 1.04 mg/day (2 pumps); Evamist 1, 3 sprays daily	Reassessed annually	FDA-labeled regimens
Vaginal	Postmenopausal women, moderate-to-severe vulvovaginal atrophy / dyspareunia	Estrace Cream 2, 4 g intravaginally daily for 1, 2 weeks, then 1 g 1, 3 times weekly; Vagifem / Yuvafem 10 microgram tablet intravaginally daily for 2 weeks, then twice weekly; Imvexxy 4 or 10 microgram softgel insert daily for 2 weeks, then twice weekly; Estring inserted for 90 days	Indefinite while clinically beneficial; minimal systemic exposure at recommended doses	Cochrane review (Suckling 2006); TX-004HR pivotal program; Mitchell 2018 JAMA Internal Medicine RCT
Intramuscular	Postmenopausal hypoestrogenism or gender-affirming feminizing therapy	Estradiol valerate (Delestrogen): 10, 20 mg IM every 1, 4 weeks in menopausal use; in feminizing therapy, often 2, 10 mg IM weekly or 5, 20 mg IM every 2 weeks per	Indefinite while clinically beneficial; titrated to target serum estradiol	FDA-labeled regimens; Endocrine Society 2017 (Hembree); WPATH SOC v8 (Coleman 2022)

Route	Population	Range	Duration	Study type
		Endocrine Society and WPATH guidelines. Estradiol cypionate (Depo-Estradiol): 1, 5 mg IM every 3, 4 weeks in menopausal use; 2, 10 mg IM every 1, 2 weeks in feminizing therapy		
Subcutaneous pellet (compounded)	Postmenopausal women or gender-affirming feminizing therapy	Typical 12.5, 50 mg estradiol pellet implanted every 3, 6 months, often individualized; published PK and safety evidence is limited and largely observational	Per implant interval; replaced when serum estradiol drops below the prescriber-defined target	Observational pellet-clinic series; no FDA-approved estradiol pellet exists in the US
Compounded transdermal cream or troche	Postmenopausal women or gender-affirming feminizing therapy, patient-specific	Custom strengths per clinician prescription; target physiologic serum estradiol	Reassessed at the same interval as for manufactured products	Patient-specific 503A compounding under documented clinical reason

Doses listed reflect FDA-labeled regimens and published clinical-trial protocols, not RonanRx prescribing recommendations. The prescribing clinician selects formulation, route, and starting dose based on the patient's clinical context (indication, time since menopause, uterine status, VTE and breast cancer risk, formulation preference, and shared decision-making) [stuenkel2015endo].

Practical considerations across routes: oral estradiol carries higher VTE and stroke risk than transdermal in observational data [canonico2007esther], [vinogradova2019bmj], [mohammed2015orvtrans], [renoux2010transdermal] and is generally avoided in women with elevated thrombotic risk [stuenkel2015endo]. Transdermal patches and gels are first-line for women with metabolic syndrome, obesity, smoking, migraine with aura, hypertriglyceridemia, or prior VTE. Vaginal estradiol at recommended low doses produces minimal systemic exposure and is acceptable across most contraindications to systemic therapy [bhupathiraju2018vagne], [crandall2018vagest]. IM and pellet routes are most common in gender-affirming feminizing therapy or in patients who prefer infrequent administration.

In women with an intact uterus, progestogen co-therapy is required to prevent endometrial hyperplasia and adenocarcinoma. Micronized progesterone is the bioidentical option; the E3N cohort [fournier2008e3n] reported lower breast cancer risk with estradiol plus micronized progesterone or dydrogesterone than with estradiol plus synthetic progestins. Target the lowest effective dose for the shortest duration consistent with treatment goals, with annual reassessment per NAMS 2022 [nams2022] [stuenkel2015endo].

Estradiol Safety

Estradiol safety has been characterized in some of the largest randomized hormone-therapy programs ever conducted, supplemented by extensive observational pharmacoepidemiology. The most clinically important adverse events on systemic estradiol-based therapy are venous thromboembolism, ischemic stroke, gallbladder disease, and, when combined with a progestogen, breast cancer (regimen-, progestogen-, and duration-dependent) [37]. Endometrial hyperplasia and adenocarcinoma are prevented by progestogen co-therapy in women with an intact uterus.

WHI [1] reported, on CEE + medroxyprogesterone in women aged 50, 79 (mean age 63) initiating therapy a decade past menopause, an excess of invasive breast cancer, coronary heart disease, stroke, and VTE that crossed a pre-specified global safety index [37]. The CEE-alone arm in hysterectomized women [2], [7] showed a different risk profile, with reduced breast cancer incidence and a more favorable overall summary in younger women. The 18-year cumulative WHI follow-up [3] did not show excess all-cause mortality in either arm. Subsequent randomized programs in younger, recently menopausal women, KEEPS [18] and ELITE [17], have shaped current guidance that the risk profile depends heavily on time since menopause, age at initiation, and route.

Route-specific safety: transdermal and vaginal estradiol carry lower VTE and stroke risk than oral, based on consistent observational evidence from ESTHER [20], Renoux 2010 [22], QResearch/CPRD [23], and a JCEM systematic review [24] [37]. Vaginal low-dose preparations produce minimal systemic exposure and are associated with favorable long-term safety in observational cohorts [34], [35].

Breast cancer: regimen, progestogen, and duration matter [37]. E3N [25] reported lower breast cancer risk with estradiol plus micronized progesterone or dydrogesterone than with estradiol plus synthetic progestins. The Million Women Study [26] reported elevated risk across combined regimens. The WHI long-term follow-up [8] refined cumulative incidence. Other considerations include gallbladder disease (more common with oral estrogen), exacerbation of migraine with aura, and the absolute contraindications detailed in the next section.

Contraindications

Estradiol is contraindicated in: known, suspected, or history of breast cancer (and other estrogen-sensitive neoplasia); active or recent (within 1 year) arterial thromboembolic disease such as stroke or myocardial infarction; active or history of venous thromboembolism (DVT or pulmonary embolism) unless on therapeutic anticoagulation with carefully weighed risk/benefit and preference for a transdermal route; known thrombophilia (factor V Leiden, antiphospholipid antibody syndrome, protein C/S deficiency) without anticoagulation; known hepatic dysfunction or disease; known hypersensitivity to estradiol or any product excipient; pregnancy (category X, teratogenic; in particular, masculinization concerns for a female fetus); and undiagnosed abnormal genital bleeding [2023].

Relative contraindications and cautions per the Endocrine Society 2015 guideline [36] and NAMS 2022 [37] include uncontrolled hypertension, hypertriglyceridemia (oral estradiol can elevate triglycerides further), migraine with aura (especially for oral estradiol given stroke risk), gallbladder disease, hereditary angioedema, severe hypertriglyceridemia, and an intact uterus without progestogen co-therapy (endometrial cancer risk) [20]. Transdermal and vaginal routes are preferred over oral in patients with several of these relative cautions.

Drug interactions

Estradiol is metabolized hepatically by CYP1A2 and CYP3A4, with conjugation by UGT and SULT. Strong CYP3A4 inducers (rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John's wort) reduce serum estradiol and may compromise efficacy. Strong CYP3A4 inhibitors (clarithromycin, itraconazole, ketoconazole, ritonavir-boosted regimens, grapefruit juice in high intake) raise estradiol exposure. Oral estradiol induces hepatic SHBG and binding globulins, which can affect interpretation of thyroid function tests (raises TBG and total T4 / total T3 while free hormone usually remains stable) and adrenal cortisol-binding globulin [37].

Estradiol can attenuate the response to lamotrigine (estrogen induces lamotrigine glucuronidation); cyclic oral estrogen regimens can produce cyclical breakthrough seizures in women on lamotrigine monotherapy. Concomitant tamoxifen, raloxifene, or aromatase inhibitors are not generally co-administered with estradiol given mechanistic opposition. Transdermal estradiol largely bypasses first-pass hepatic effects on thyroid and adrenal binding globulins, making it preferable in patients on complex thyroid replacement or with adrenal disease [36].

Adverse events

Common adverse events on systemic estradiol include breast tenderness, breakthrough bleeding (more frequent in the first months of combined therapy), nausea (oral), headache, mood changes, fluid retention, and application-site reactions (transdermal patch, adhesive irritation; gel, local erythema) [1]. Vaginal estradiol commonly causes vaginal discharge or local irritation in the first weeks of therapy.

Serious adverse events with systemic estradiol-based hormone therapy, per WHI and observational pharmacoepidemiology: venous thromboembolism (DVT, pulmonary embolism, higher with oral than transdermal per ESTHER [20], Renoux 2010 [22], QResearch/CPRD [23], and Mohammed 2015 [24]); ischemic stroke (also route-dependent); gallbladder disease and cholecystectomy; breast cancer (with combined regimens, progestogen- and duration-dependent, E3N [25], Million Women [26], WHI long-term follow-up [8]); endometrial hyperplasia and adenocarcinoma in women with an intact uterus not receiving adequate progestogen co-therapy; and probable dementia in women aged 65+ initiating CEE ± MPA per WHIMS [9] [12].

Vaginal low-dose estradiol at recommended regimens does not show consistent excess of breast cancer, endometrial cancer, or cardiovascular events in long-term observational cohorts [34], [35], reflecting the minimal systemic exposure at low local doses [33] [1].

Monitoring Estradiol Therapy

Baseline assessment per the Endocrine Society 2015 guideline [stuenkel2015endo] and NAMS 2022 [nams2022]: history of breast or other estrogen-sensitive cancer; personal or family history of VTE; cardiovascular risk profile (blood pressure, lipids, smoking, diabetes, BMI); migraine history with attention to aura; uterine status (intact uterus mandates progestogen co-therapy); age-appropriate breast and pelvic exam, mammography per national screening guidance; baseline endometrial assessment by symptom and risk profile (TVUS or biopsy if abnormal bleeding); and shared decision-making about expected benefits and risks.

On-therapy monitoring: annual reassessment of indication and dose; ongoing breast cancer screening per national guidance; prompt evaluation of any post-menopausal bleeding on combined therapy (TVUS and/or endometrial biopsy as clinically indicated); review of cardiovascular and thrombotic risk profile annually; serum estradiol may be measured to confirm absorption and target range in transdermal, IM, and pellet regimens, particularly in gender-affirming feminizing therapy [hembree2017transgender], [coleman2022wpath].

For gender-affirming feminizing therapy, the Endocrine Society 2017 [hembree2017transgender] and WPATH SOC v8 [coleman2022wpath] frameworks recommend serum estradiol and total testosterone monitoring at 3-month intervals during the first year and at least annually thereafter, with targets of estradiol in the premenopausal female physiologic range and total testosterone in the female physiologic range.

Estradiol in Special Populations

Estradiol Evidence Quality

Evidence for estradiol in menopausal symptom management is among the largest in clinical medicine. WHI [rossouw2002whi], [anderson2004whi], [manson2013whi], [manson2017whi] is the foundational randomized program, with substudies addressing breast cancer [stefanick2006whi], [chlebowski2020whilongterm], bone [cauley2003whi], cognition [shumaker2004whims], [espeland2004whims], [rapp2003whims], VTE [cushman2004whivte], and inflammatory biomarkers [pradhan2002whi]. The Endocrine Society 2015 guideline [stuenkel2015endo] and the 2022 NAMS Position Statement [nams2022] provide the consensus framing.

The 'timing hypothesis', that initiating estradiol near menopause produces a different risk/benefit profile than initiating a decade later, is supported by ELITE [hodis2016elite] (oral estradiol slowed carotid IMT progression when started within 6 years of menopause but not when started 10+ years out), by KEEPS

[miller2019keeps] (no excess vascular harm in recently menopausal women over 4 years), and by KEEPS-Cog [gleason2015keepscog] (no cognitive harm and possible mood benefit in recently menopausal women, in contrast to WHIMS in women aged 65+). EPAT [hodis2001epat] was an early supporting RCT. Salpeter 2006 [salpeter2006chd] and Salpeter 2009 [salpeter2009mortality] meta-analyses had earlier suggested reduced CHD events and lower all-cause mortality in younger initiators.

Route-specific safety is supported by consistent observational pharmacoepidemiology, ESTHER [canonico2007esther], [canonico2008esther], Renoux 2010 [renoux2010transdermal], QResearch/CPRD [vinogradova2019bmj], and by the Mohammed 2015 JCEM systematic review and meta-analysis [mohammed2015orvtrans]. Transdermal and vaginal routes carry lower VTE and stroke risk than oral.

Vaginal estradiol evidence: Cochrane review [suckling2006cochrane] established cross-formulation efficacy. The TX-004HR (Imvexxy) clinical program [constantine2017imvexxy], [kingsberg2017tx004hr] supported the low-dose vaginal softgel. Mitchell 2018 [mitchell2018vagest] compared vaginal estradiol tablets, moisturizer, and placebo. Long-term observational safety in NHS [bhupathiraju2018vagne] and WHI [crandall2018vagest] cohorts does not show consistent excess of breast cancer, endometrial cancer, or cardiovascular events at recommended low doses.

For gender-affirming feminizing therapy, the Endocrine Society 2017 [hembree2017transgender] and WPATH SOC v8 [coleman2022wpath] frameworks define current best practice. For compounded bioidentical hormone therapy specifically, the 2020 NASEM consensus report [nasem2020] and Files 2011 [files2011bioidentical] are the principal critical reviews; they find insufficient evidence to support broad superiority claims and recommend restricting compounding to documented patient-specific clinical needs.

Compounded estradiol pellets have a limited published evidence base, pharmacokinetic and outcome data are largely observational from specialty pellet-therapy clinics. There is no FDA-approved estradiol pellet product in the United States.

Major Estradiol Clinical Studies

Study	Design	Participants	Duration	Finding
WHI Combined CEE + MPA Principal Results (Rossouw 2002 JAMA)	Randomized double-blind placebo-controlled trial of conjugated equine estrogens plus medroxyprogesterone acetate in postmenopausal women aged 50, 79	16608	Mean 5.2 years (stopped early)	Trial stopped early for excess invasive breast cancer, coronary heart disease, stroke, and VTE that crossed a pre-specified global safety index; bone fractures reduced [rossouw2002whi]
		10739		

Study	Design	Participants	Duration	Finding
WHI CEE-Alone (Hysterectomy) Results (Anderson 2004 JAMA)	Randomized double-blind placebo-controlled trial of conjugated equine estrogens alone in postmenopausal women with prior hysterectomy		Mean 6.8 years	No excess CHD; increased stroke and VTE; reduced hip fractures; trend toward reduced breast cancer that reached significance in subsequent follow-up [anderson2004whi]
WHI 18-Year Cumulative Follow-Up Mortality (Manson 2017 JAMA)	Extended observational follow-up of both WHI hormone therapy trials	27347	Cumulative 18 years	No statistically significant excess of all-cause mortality or cause-specific mortality (cardiovascular, cancer) in either WHI hormone-therapy arm vs placebo over 18-year cumulative follow-up [manson2017whi]
WHI Health Outcomes Intervention and Extended Phases (Manson 2013 JAMA)	Pooled analysis of both WHI hormone-therapy trials across intervention and post-intervention follow-up	—	Cumulative through 13 years post-randomization	Risk/benefit profile differed by age, time since menopause, and regimen; combined therapy carried more harm than estrogen-alone in older women; estrogen-alone had favorable profile in younger hysterectomized women [manson2013whi]
ELITE, Early versus Late Postmenopausal Estradiol (Hodis 2016 NEJM)	Randomized double-blind placebo-controlled trial of oral estradiol stratified by years since menopause (<6 years vs ≥10 years)	643	Median 5 years	Oral estradiol slowed progression of carotid intima-media thickness in women within 6 years of menopause but not in women 10+ years past menopause, strongest randomized support of the 'timing hypothesis' [hodis2016elite]
KEEPS, Kronos Early Estrogen Prevention Study Overview (Miller 2019 Menopause)	Synthesis of the 4-year randomized trial of oral CEE, transdermal estradiol, or placebo in recently menopausal women	—	4 years	No significant effect on carotid IMT or coronary artery calcification surrogates over 4 years; symptom benefit and bone effects favored active therapy; no excess vascular harm in this

Study	Design	Participants	Duration	Finding
				recently menopausal population [miller2019keeps]
KEEPS-Cog (Gleason 2015 PLoS Medicine)	Randomized double-blind placebo-controlled cognition substudy of KEEPS	—	4 years	No cognitive harm with oral CEE or transdermal estradiol initiated near menopause; possible mood benefit; in contrast to WHIMS findings in older women [gleason2015keepscog]
WHIMS Dementia and Cognition (Shumaker 2004 / Espeland 2004 JAMA; Rapp 2003 JAMA)	Randomized cognitive substudies of WHI in women aged 65+	—	Mean 4, 5 years	Excess probable dementia and decline in global cognitive function on CEE ± MPA in women aged 65+, basis for current guidance against initiating systemic hormone therapy primarily for cognitive protection in older women [shumaker2004whims; espeland2004whims; rapp2003whims]
WHIMS-Y Younger Women Memory Study (Vaughan 2013 Brain Research)	Long-term cognitive follow-up in women randomized to WHI hormone therapy at younger ages	—	—	Baseline characterization for cognitive follow-up of younger WHI participants [vaughan2013whimsy]
EPAT, Estrogen in the Prevention of Atherosclerosis Trial (Hodis 2001 Ann Intern Med)	Randomized double-blind placebo-controlled trial of oral micronized estradiol in postmenopausal women without prior CHD	—	2 years	Oral estradiol slowed progression of carotid intima-media thickness, early randomized support for vascular benefit in primary-prevention setting [hodis2001epat]
WHI VTE Substudy (Cushman 2004 JAMA)	Substudy of the WHI combined CEE + MPA trial	—	Mean 5.6 years	Combined hormone therapy approximately doubled VTE risk vs placebo, with greater absolute risk in older and obese participants [cushman2004whivte]
		—		

Study	Design	Participants	Duration	Finding
WHI Fracture and Bone Density (Cauley 2003 JAMA)	Substudy of the WHI combined CEE + MPA trial		Mean 5.6 years	Combined hormone therapy reduced hip fractures, clinical vertebral fractures, and total fractures; increased BMD [cauley2003whi]
WHI CEE-Alone Breast Cancer and Mammography (Stefanick 2006 JAMA)	Substudy of the WHI estrogen-alone trial in hysterectomized women	—	Mean 7.1 years	CEE alone did not increase invasive breast cancer (trend toward reduction); increased need for short-interval mammography follow-up [stefanick2006whi]
WHI Long-Term Breast Cancer Mortality (Chlebowski 2020 JAMA)	Long-term follow-up of both WHI hormone-therapy trials for breast cancer outcomes	—	Cumulative 20+ years	CEE alone reduced breast cancer incidence and mortality in hysterectomized women; CEE + MPA increased breast cancer incidence and mortality during and after intervention [chlebowski2020whilongterm]
PEPI, Postmenopausal Estrogen/ Progestin Interventions (1996 JAMA)	Randomized placebo-controlled trial of four estrogen-progestin regimens vs placebo in postmenopausal women	—	3 years	All active regimens preserved bone density; cyclic and continuous progestogen prevented endometrial hyperplasia in women with intact uterus while preserving bone benefit [pepi1996bone]
Estrogen plus Progestin and Coronary Heart Disease (Manson 2003 NEJM)	Pre-specified WHI substudy of coronary heart disease outcomes	—	Mean 5.2 years	Increased CHD risk with combined CEE + MPA, with hazard concentrated in the first year of therapy [manson2003chd]
ESTHER, Hormone Therapy and VTE Route Differential (Canonico 2007 Circulation)	Multicenter case-control study of postmenopausal women with VTE vs controls	—	Index VTE event vs matched controls	Oral estrogen approximately quadrupled VTE risk; transdermal estrogen showed no significant excess vs no therapy; progestogen type also influenced risk (micronized progesterone and pregnane derivatives lower than norpregnane derivatives) [canonico2007esther]

Study	Design	Participants	Duration	Finding
ESTHER ABO Blood Group Interaction (Canonico 2008 Thromb Haemost)	ESTHER substudy on synergism between non-O blood group and oral estrogen	—	—	Non-O blood group amplified VTE risk of oral but not transdermal estrogen in postmenopausal women [canonico2008esther]
Renoux Population-Based HRT VTE Study (2010 J Thromb Haemost)	Population-based nested case-control study in UK general practice	—	—	Oral hormone replacement therapy increased VTE risk; transdermal therapy did not, replication of ESTHER in a separate population [renoux2010transdermal]
Vinogradova HRT and VTE Nested Case-Control (2019 BMJ)	Nested case-control studies in QResearch and CPRD UK primary-care databases	80396	—	Oral hormone replacement therapy associated with increased VTE risk; transdermal preparations did not increase VTE risk, definitive observational evidence at scale for the route differential [vinogradova2019bmj]
Oral vs Transdermal Estrogen Vascular Events Meta-Analysis (Mohammed 2015 JCEM)	Systematic review and meta-analysis	—	—	Pooled randomized and observational evidence supports lower VTE and stroke risk with transdermal versus oral estrogen in postmenopausal women [mohammed2015orvtrans]
E3N Cohort Breast Cancer by Progestogen (Fournier 2008 Breast Cancer Res Treat)	Prospective French cohort of postmenopausal women in the E3N study	80377	—	Estradiol plus micronized progesterone or dydrogesterone carried lower breast cancer risk than estradiol plus synthetic progestins, informs progestogen selection in combined estradiol regimens [fournier2008e3n]
Million Women Study Breast Cancer (Beral 2003 Lancet)	Large UK cohort study of breast cancer incidence on hormone therapy	1084110	—	Current use of combined hormone therapy substantially elevated breast cancer incidence and mortality; estrogen-only

Study	Design	Participants	Duration	Finding
				therapy showed a smaller increase [beral2003mws]
Salpeter Younger-Women CHD Meta-Analysis (Salpeter 2006 J Gen Intern Med)	Meta-analysis of randomized trials of hormone therapy and CHD events by age and time since menopause	—	—	Reduced CHD events in younger postmenopausal initiators; neutral or increased events in older initiators, quantitative support for the timing hypothesis [salpeter2006chd]
Salpeter Bayesian Mortality Meta-Analysis (Salpeter 2009 Am J Med)	Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women	—	—	Hormone therapy associated with lower total mortality in younger postmenopausal women across pooled randomized data [salpeter2009mortality]
Cochrane Local Vaginal Estrogen for Vaginal Atrophy (Suckling 2006)	Cochrane systematic review of local vaginal estrogen preparations	—	—	Vaginal estrogen, across cream, tablet, ring formulations, produced significant symptomatic improvement of vaginal atrophy with minimal systemic effects [suckling2006cochrane]
Cochrane Long-Term Hormone Therapy (Marjoribanks 2017/2018)	Updated Cochrane systematic review of long-term hormone therapy for perimenopausal and postmenopausal women	—	—	Quantified absolute risks and benefits across cardiovascular, breast cancer, fracture, and dementia endpoints by age at initiation [marjoribanks2018cochrane]
Boardman Cochrane Hormone Therapy for CV Disease Prevention (2015)	Cochrane systematic review of randomized hormone-therapy trials for cardiovascular disease prevention	—	—	Hormone therapy is not recommended for primary or secondary prevention of cardiovascular disease; subgroup analysis supports age-dependent risk profile [boardman2015cochranecv]
TX-004HR / Imvexxy Vaginal Estradiol Softgel	Phase 3 randomized double-blind placebo-controlled trials of low-	—	—	TX-004HR (4 and 10 microgram) improved most-bothersome symptom of

Study	Design	Participants	Duration	Finding
(Constantine 2017; Kingsberg 2017)	dose vaginal estradiol softgel insert in postmenopausal women with moderate-to-severe dyspareunia due to vulvar/vaginal atrophy			dyspareunia and vaginal physiology endpoints with minimal systemic absorption; basis for Imvexxy FDA approval (2018) [constantine2017imvexxy; kingsberg2017tx004hr; imvexxy2018paton]
Vaginal Estradiol vs Moisturizer vs Placebo (Mitchell 2018 JAMA Intern Med)	Randomized double-blind placebo-controlled trial in postmenopausal women with bothersome vulvovaginal symptoms	302	12 weeks	Both low-dose vaginal estradiol tablet and vaginal moisturizer improved symptoms similarly, with both modestly better than placebo; minimal systemic estradiol absorption [mitchell2018vagest]
Vaginal Estrogen and Chronic Disease Risk in NHS (Bhupathiraju 2018 Menopause)	Prospective observational analysis in the Nurses' Health Study	—	—	Long-term vaginal estrogen use was not associated with elevated risk of cardiovascular events or invasive cancer overall [bhupathiraju2018vagne]
Vaginal Estrogen Safety in WHI Observational Cohort (Crandall 2018 Menopause)	Observational follow-up of vaginal estrogen users in the WHI	—	—	Vaginal estrogen use was not associated with increased breast cancer, endometrial cancer, or cardiovascular events compared with non-users in this cohort [crandall2018vagest]
Files Bioidentical Hormone Therapy Review (Files 2011 Mayo Clin Proc)	Critical narrative review	—	—	Reviewed bioidentical hormone marketing claims and clinical evidence; concluded that compounded bioidentical hormones are not safer or more effective than FDA-approved bioidentical preparations, and that broad marketing claims of superiority are not supported by evidence [files2011bioidentical]
NAMS 2022 Hormone	Consensus position statement	—	—	Current consensus framework for menopausal hormone therapy:

Study	Design	Participants	Duration	Finding
Therapy Position Statement				most favorable risk/benefit in symptomatic women within 10 years of menopause and under age 60; route-, regimen-, and duration-specific guidance; not recommended for primary chronic disease prevention [nams2022]
Endocrine Society 2015 Menopause Guideline (Stuenkel)	Clinical practice guideline	—	—	Diagnostic, therapeutic, and monitoring recommendations for menopausal hormone therapy across the indication range [stuenkel2015endo]
Endocrine Society 2017 Gender-Dysphoric/ Gender-Incongruent Guideline (Hembree)	Clinical practice guideline	—	—	Feminizing hormone therapy recommendations including estradiol dosing across routes (oral, transdermal, IM ester, sublingual), monitoring (serum estradiol and total testosterone targets), and shared decision-making framework [hembree2017transgender]
WPATH Standards of Care Version 8 (Coleman 2022)	International multidisciplinary consensus guideline	—	—	Defines current best-practice framework for estradiol use in feminizing gender-affirming care across the lifespan [coleman2022wpath]
NASEM 2020 Compounded Bioidentical Hormone Therapy Report	Consensus report of the National Academies of Sciences, Engineering, and Medicine	—	—	Found insufficient evidence to support broad claims of safety or efficacy advantages of compounded bioidentical hormones over FDA-approved manufactured products; recommended restricting compounded preparations to documented patient-specific clinical needs [nasem2020]
Marjoribanks Cochrane Corner	Cochrane Corner narrative synthesis of	—	—	Quantified absolute risks for cardiovascular disease, VTE,

Study	Design	Participants	Duration	Finding
Long-Term Hormone Therapy (2018 Heart)	the long-term hormone therapy review			breast cancer, and fracture across age strata; informed contemporary risk communication [marjoribanks2018cochrane]
WHI Estrogen Plus Progestin and Inflammatory Biomarkers (Pradhan 2002 JAMA)	Prospective analysis within WHI	—	—	Combined CEE + MPA elevated CRP and other inflammatory biomarkers, mechanistic context for the early-stage CHD signal [pradhan2002whi]

Estradiol Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Oral estradiol has low and variable bioavailability (around 5%) due to extensive first-pass intestinal and hepatic metabolism to estrone and estrone sulfate. The first-pass exposure drives induction of hepatic SHBG, binding globulins, angiotensinogen, and coagulation factors, the mechanistic basis for the higher VTE and stroke risk seen with oral versus non-oral routes [canonico2007esther], [vinogradova2019bmj]. Peak serum estradiol occurs 1, 2 hours after oral dosing.

Transdermal patches deliver estradiol continuously through skin; serum levels reach near-steady-state within 24, 48 hours of patch application and are maintained throughout the wear interval (3.5 or 7 days depending on product). Transdermal gels and sprays produce steady-state within several days of daily application. Transdermal routes bypass first-pass and produce serum estradiol exposure closer to the premenopausal physiologic profile, with markedly lower hepatic SHBG and coagulation-factor induction [mohammed2015orvtrans], [renoux2010transdermal].

Vaginal estradiol at low local doses (Vagifem 10 microgram tablet, Imvexxy 4 microgram softgel, Estring 7.5 microgram/day ring) produces minimal systemic exposure, serum estradiol typically remains in the postmenopausal physiologic range or modestly above, well below systemic-replacement levels [mitchell2018vagest]. Higher-dose vaginal preparations (Estrace Cream at standard regimen, Femring at systemic dose) produce serum estradiol comparable to oral or transdermal systemic therapy.

Intramuscular estradiol esters (valerate, cypionate) produce peak serum estradiol several days after injection with gradual decline over 1, 4 weeks depending on ester and dose. Peak-trough variability is wider than with transdermal continuous delivery, which is relevant to symptom control and patient experience in both menopausal and gender-affirming use. Subcutaneous estradiol pellets release estradiol over 3, 6

months in observational PK series; the published PK literature is limited compared with testosterone pellets.

Pharmacodynamics

Pharmacodynamic effects are dose-dependent and route-dependent. Replacement to premenopausal physiologic serum estradiol relieves vasomotor symptoms, restores vaginal and urethral epithelial maturation, suppresses bone resorption and preserves bone density [pepi1996bone], [cauley2003whi], and produces favorable changes in lipid profile and endothelial function. Oral estradiol's hepatic exposure also induces SHBG, angiotensinogen, triglycerides, and coagulation factors, pharmacodynamic effects largely absent from transdermal and vaginal routes [canonico2007esther], [vinogradova2019bmj].

Endometrial pharmacodynamics: unopposed estradiol drives endometrial proliferation in women with an intact uterus and increases endometrial cancer risk; cyclic or continuous progestogen co-therapy opposes this effect [pepi1996bone]. Breast pharmacodynamics: estradiol stimulates breast epithelial proliferation; combined therapy with synthetic progestins amplifies breast cancer risk more than combined therapy with micronized progesterone or dydrogesterone [fournier2008e3n]. CNS pharmacodynamics: estradiol's effects on cognition and dementia depend on time of initiation, with neutral-to-favorable effects in recently menopausal women [gleason2015keepscog] and excess dementia in women aged 65+ on CEE ± MPA [shumaker2004whims].

↓↑ Comparing Estradiol Formulations

Choice of estradiol formulation balances patient preference, route-specific safety, indication (systemic vs local), and the manufactured-product range [fda_essentially_a_copy]. Oral estradiol (Estrace) is convenient and inexpensive but carries the highest VTE and stroke risk among the routes [canonico2007esther], [vinogradova2019bmj], [mohammed2015orvtrans]. Transdermal patches (Climara weekly; Vivelle-Dot, Minivelle, Alora twice-weekly) provide steady serum levels and lower thrombotic risk than oral, with patch-adhesive sensitivity as the main practical limitation. Transdermal gels (Divigel, EstroGel, Elestrin) and sprays (Evamist) offer dosing flexibility and avoid patch adhesives but require attention to inter-personal transfer.

Vaginal preparations are preferred when the indication is limited to genitourinary syndrome of menopause: low-dose tablets (Vagifem, Yuvafem 10 microgram), softgel insert (Imvexxy 4 or 10 microgram), low-dose ring (Estring), and cream (Estrace Cream) all produce minimal systemic exposure at recommended low-dose regimens [mitchell2018vagest], [bhupathiraju2018vagne] [fda_essentially_a_copy]. Higher-dose systemic vaginal rings (Femring) treat both systemic and local symptoms.

Intramuscular ester depots (Delestrogen, Depo-Estradiol) are most commonly used in feminizing gender-affirming therapy and selected menopausal contexts where infrequent dosing is preferred. Compounded preparations expand the route palette: custom transdermal cream strengths between manufactured gel

doses; allergen-free formulations for patch-adhesive-reactive patients; pellets (no FDA-approved estradiol pellet exists in the US); troches; and gender-affirming-specific strengths and vehicles [fda_essentially_a_copy]. RonanRx compounds these preparations on patient-specific prescription, with documented clinical reason for compounding. The pharmacist review confirms the prescribed formulation is responsive to a documented patient-specific need and is not routine substitution for a manufactured product.

Estradiol Storage and Handling

Compounded estradiol preparations are stored per the dispensing label. Sterile injectable preparations in oil (compounded estradiol valerate or cypionate) are stored at controlled room temperature (USP definition 20, 25°C, with allowed excursions 15, 30°C) protected from light; refrigeration may cause crystallization of higher-concentration ester-in-oil solutions. Beyond-use dating follows USP <797> for sterile compounded preparations [usp_797].

Non-sterile compounded forms, transdermal creams, troches, oral capsules, vaginal creams, are stored per the dispensing label at controlled room temperature with light-resistant packaging, with beyond-use dating per USP <795> non-sterile compounding standards [usp_795]. Estradiol pellets are stored per the supplier's storage instructions until implantation.

Estradiol Compounding & Operations

503A compounding

RonanRx compounds estradiol preparations under 503A on patient-specific prescriptions. Sterile injectable preparations (compounded estradiol valerate or cypionate in oil) follow USP General Chapter <797> for sterile pharmaceutical compounding, 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]. Non-sterile preparations (troches, transdermal creams, oral capsules, vaginal creams, suppositories) follow USP General Chapter <795>. Estradiol pellets are implanted only on documented patient-specific prescription with clinician-defined dose.

Estradiol is not a controlled substance, but its dispensing follows standard prescription-only handling, prescriber verification, and patient identification protocols. RonanRx does not dispense compounded estradiol on a direct-to-consumer basis [fda_essentially_a_copy].

Pharmacist review

Each prescription for compounded estradiol undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason for the compounded preparation (formulation/

route not in the manufactured market, custom strength, allergen sensitivity, or gender-affirming-care dose outside menopausal labeling); diagnostic basis consistent with the Endocrine Society 2015 [stuenkel2015endo], NAMS 2022 [nams2022], or Endocrine Society 2017 transgender guideline [hembree2017transgender] / WPATH SOC v8 [coleman2022wpath] framework as applicable; absence of contraindications (history of breast or other estrogen-sensitive cancer, active VTE or recent arterial event without anticoagulation, hepatic dysfunction, pregnancy, undiagnosed abnormal bleeding); confirmation of baseline monitoring (uterine status with progestogen co-therapy as indicated, breast and CV risk profile); and appropriate prescription elements.

RonanRx does not fill prescriptions for compounded estradiol that read as routine substitution for an available manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of approved drugs [fda_essentially_a_copy] and the NASEM 2020 framework on compounded bioidentical hormone therapy [nasem2020].

Quality and traceability

Estradiol 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]. Non-sterile preparations carry compounding-record documentation per USP <795> [usp_795].

Cold chain

Most compounded estradiol preparations are not cold-chain products. Injectable ester-in-oil preparations, transdermal creams, troches, capsules, and vaginal creams are shipped at controlled room temperature. Patients are instructed to store at room temperature in tightly closed light-resistant containers and to contact the pharmacy if shipping temperature integrity is in doubt.

Frequently Asked Questions About Estradiol

Is compounded estradiol the same molecule as Estrace or Climara?

Yes, the active ingredient (17β-estradiol) is the same bioidentical molecule. The difference is the manufacturing pathway and the FDA approval status. Estrace, Climara, Vivelle-Dot, Vagifem, Imvexxy, Estring, Femring, Delestrogen, Depo-Estradiol, and other branded estradiol products are FDA-approved manufactured products. Compounded preparations are pharmacy-prepared on a patient-specific prescription and are not FDA-approved. The 2020 NASEM consensus report (nasem2020) found insufficient evidence to support broad claims that compounded bioidentical hormones are safer or more effective than FDA-approved bioidentical preparations [nasem2020; fda_essentially_a_copy; files2011bioidentical].

When does compounded estradiol make clinical sense?

Common documented reasons include: a route or strength the manufactured market does not provide (estradiol pellet, there is no FDA-approved estradiol pellet in the US; custom transdermal cream strength between commercial gel doses; ultra-low or above-label vaginal strength for selected refractory atrophy); allergen sensitivity to a manufactured product's adhesive or vehicle; or a gender-affirming-care dose outside the labeled ranges of approved menopausal products per the Endocrine Society 2017 and WPATH SOC v8 frameworks [fda_essentially_a_copy; hembree2017transgender]. Routine substitution of compounded for manufactured product without a documented reason is not appropriate [coleman2022wpath].

Is transdermal estradiol really safer than oral?

For venous thromboembolism (DVT, pulmonary embolism) and stroke, the consistent observational evidence, ESTHER (Canonico 2007), Renoux 2010, and the large QResearch/CPRD nested case-control (Vinogradova 2019), summarized in the Mohammed 2015 JCEM systematic review, shows lower risk with transdermal than oral estradiol [canonico2007esther; vinogradova2019bmj; mohammed2015orvtrans]. The mechanism is straightforward: oral estradiol passes through the liver first and induces coagulation factors and SHBG; transdermal estradiol largely bypasses first-pass. For symptom relief and bone benefit, both routes are effective [renoux2010transdermal].

What did the WHI actually show, and does it still apply?

WHI (Rossouw 2002) randomized older postmenopausal women (mean age 63, average a decade past menopause) to conjugated equine estrogens plus medroxyprogesterone or placebo, and reported an excess of breast cancer, CHD, stroke, and VTE that stopped the trial early [rossouw2002whi; anderson2004whi; stefanick2006whi]. The estrogen-alone arm in hysterectomized women (Anderson 2004; Stefanick 2006) showed a different profile, with reduced breast cancer. The 18-year follow-up (Manson 2017) showed no excess all-cause mortality in either arm. Subsequent randomized programs in recently menopausal women, ELITE (Hodis 2016) and KEEPS (Miller 2019), have shaped current guidance that age and time since menopause matter substantially, and that transdermal routes and bioidentical progesterone may further refine the risk profile [manson2017whi; hodis2016elite; miller2019keeps].

What about breast cancer risk?

Risk depends on regimen, progestogen, duration, and baseline risk. The combined estrogen-plus-progestogen regimens elevate breast cancer risk in WHI and the Million Women Study, with synthetic progestins carrying higher risk than micronized progesterone or dydrogesterone per the E3N cohort (Fournier 2008) [fournier2008e3n; beral2003mws]. The estrogen-alone arm in WHI in hysterectomized women showed reduced breast cancer incidence [rossouw2002whi; anderson2004whi]. Vaginal low-dose estradiol does not show consistent breast cancer signal in long-term observational cohorts (Bhupathiraju 2018; Crandall 2018) [bhupathiraju2018vagne; crandall2018vagest].

Are estradiol pellets FDA-approved?

No. There is no FDA-approved estradiol pellet product in the United States, the only marketed pellet (Testopel) is testosterone. Any estradiol pellet preparation in US practice is inherently compounded under 503A on a patient-specific prescription [fda_essentially_a_copy]. The published evidence base for estradiol pellets is more limited than for transdermal patches, gels, or vaginal preparations; the prescribing clinician and patient discuss the trade-offs [nasem2020].

Is compounded bioidentical hormone therapy safer or more 'natural' than FDA-approved products?

The 2020 National Academies consensus report (nasem2020) found insufficient evidence to support broad claims of safety, efficacy, or 'naturalness' advantages of compounded bioidentical hormone therapy over FDA-approved bioidentical preparations [nasem2020; files2011bioidentical; nams2022]. The Files 2011 Mayo Clinic Proceedings review made the same point. The molecule (17β-estradiol) is identical between compounded and FDA-approved bioidentical products. The case for compounding is patient-specific clinical need, a formulation, route, strength, or vehicle the manufactured market does not provide, not broad marketing superiority.

What about estradiol for gender-affirming feminizing therapy?

Estradiol is the principal hormone of feminizing therapy. The Endocrine Society 2017 guideline (Hembree) and WPATH Standards of Care Version 8 (Coleman 2022) define current best practice for dosing across oral, sublingual, transdermal patch and gel, intramuscular valerate or cypionate, and compounded pellet routes; monitoring (serum estradiol and total testosterone with co-administered anti-androgen as appropriate); and shared decision-making [hembree2017transgender; coleman2022wpath]. RonanRx compounded estradiol in this context is dispensed only on a patient-specific prescription from the patient's clinician.

Does RonanRx sell estradiol directly to patients?

No. Estradiol is a prescription-only product dispensed 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 [fda_essentially_a_copy].

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How to Access Estradiol

Compounded Estradiol 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 Estradiol, 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)