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Menopausal hormone therapy after the boxed warning: benefit, risk and the neurokinin antagonists

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Abstract

The Women's Health Initiative (WHI) trials of 2002 and 2004, and the class-wide boxed warning that the US Food and Drug Administration (FDA) placed on estrogen-containing products from 2003, cut the use of menopausal hormone therapy (MHT) by more than half. This review restates what the WHI showed and synthesizes the evidence accumulated since by age at initiation, time since menopause, route, progestogen, dose, duration and endpoint: coronary disease, stroke, venous thromboembolism (VTE), breast, endometrial and ovarian cancer, dementia, fracture and mortality. Started before age 60 or within 10 years of menopause, MHT has not been shown to increase coronary events or all-cause mortality and reduces fractures; oral estrogen raises the risk of VTE and stroke, whereas low-dose transdermal estradiol has not been so associated in observational studies; combined therapy raises breast cancer incidence in proportion to duration, less so with micronized progesterone or dydrogesterone; low-dose vaginal estrogen has not been associated with systemic risk. In November 2025 the FDA announced removal of the boxed-warning language on cardiovascular disease, breast cancer and probable dementia, and the first revised labels were approved in February 2026; European Union product information keeps the class warnings worded by the Pharmacovigilance Risk Assessment Committee in 2020. The neurokinin 3 receptor antagonist fezolinetant and the dual neurokinin 1 and 3 receptor antagonist elinzanetant, authorized in the European Union in 2023 and 2025, outperform paroxetine, desvenlafaxine and gabapentin in indirect comparisons, with liver monitoring required for fezolinetant. We close with a prescribing framework for the European clinician.

Keywords: menopausal hormone therapy, Women's Health Initiative, boxed warning, fezolinetant, elinzanetant, vasomotor symptoms

Introduction

The estrogen-plus-progestin trial of the Women's Health Initiative (WHI) was stopped in May 2002 and its results were published that July; in February 2026 the first US labels for menopausal hormone therapy (MHT) without a class-wide boxed warning were approved. In between, use of MHT by postmenopausal American women fell by more than three quarters while the evidence moved the other way: long-term follow-up of the WHI cohorts, randomized trials in recently menopausal women, European cohorts with detail on route and progestogen, and, most recently, a new class of non-hormonal drugs acting on hypothalamic neurokinin receptors [1,2].

This review restates what the WHI showed in 2002 and 2004, what the 2003 boxed warning of

the US Food and Drug Administration (FDA) said and what both did to prescribing; synthesizes the evidence accumulated since, by age at initiation, time since menopause, route, progestogen, dose, duration and endpoint; explains the regulatory reversal of 2025–2026 and where the European Medicines Agency (EMA), the UK Medicines and Healthcare products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE) and the European, international and North American menopause societies stand; and places fezolinetant and elinzanetant among the older non-hormonal options for vasomotor symptoms (VMS). It closes with a prescribing framework for the European clinician and what remains unresolved. Hormonal contraception, osteoporosis pharmacotherapy other than the fracture effect of MHT, testosterone and compounded products are treated only in passing.

We searched PubMed on 7 September 2026 for English-language randomized trials, individual-participant and other meta-analyses, large cohort and nested case-control studies, position statements and guidelines published from 1995 to September 2026, using the terms menopausal hormone therapy, hormone replacement therapy, Women's Health Initiative, estrogen, progestogen, transdermal, venous thromboembolism, stroke, breast cancer, endometrial cancer, dementia, fracture, vaginal estrogen, fezolinetant, elinzanetant, neurokinin, vasomotor symptoms, paroxetine, venlafaxine, escitalopram, gabapentin and oxybutynin, together with the names of the trials listed in Table 1. Regulatory documents were taken from the FDA, EMA, MHRA and NICE websites on the same date. We gave preference to primary trials, individual-participant meta-analyses, current guidelines and regulatory texts, checked every PubMed record for errata, retractions and expressions of concern (no source is retracted or under an expression of concern; the eight records with published errata carry the erratum note in the reference list), and used no preprints.

What the Women's Health Initiative showed and what happened next

The WHI hormone trials randomized 27,347 postmenopausal women aged 50 to 79 years, mean age 63, to a single regimen each: 16,608 women with a uterus to conjugated equine estrogens (CEE) 0.625 mg with medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo, and 10,739 hysterectomized women to CEE 0.625 mg alone or placebo. The trials were designed to test prevention of chronic disease, not treatment of symptoms, and most participants had been postmenopausal for more than a decade [1,3,4]. The estrogen-plus-progestin trial was stopped on the monitoring board's recommendation in May 2002, after a mean of 5.2 years, because invasive breast cancer crossed its monitoring boundary and a global index favored harm. Hazard ratios (HRs) with nominal 95% confidence intervals (CIs) were 1.29 (1.02–1.63) for coronary heart disease (CHD), 1.41 (1.07–1.85) for stroke, 2.13 (1.39–3.25) for pulmonary embolism, 1.26 (1.00–1.59) for invasive breast cancer, 0.63 (0.43–0.92) for colorectal cancer and 0.66 (0.45–0.98) for hip fracture. In absolute terms, per 10,000 women-years, this was 7 more coronary events, 8 more strokes, 8 more pulmonary emboli and 8 more breast cancers, against 6 fewer colorectal cancers and 5 fewer hip fractures [3]. The estrogen-alone trial ran until February 2004 (average follow-up 6.8 years) and looked different: CHD 0.91 (0.75–1.12), breast cancer 0.77 (0.59–1.01), stroke 1.39 (1.10–1.77), pulmonary embolism 1.34 (0.87–2.06) and hip fracture 0.61 (0.41–0.91), that is, 12 additional strokes and 6 fewer hip fractures per 10,000 women-years [4]. Both regimens reduced fractures, estrogen plus progestin reduced incident diabetes, both increased gallbladder disease, and combined therapy did not increase endometrial cancer (HR 0.81, 0.48–1.36) [30-34]. In the ancillary memory study of women aged 65 or older, estrogen plus progestin doubled probable dementia (HR 2.05, 1.21–3.48; 45 versus 22 cases per 10,000 women-years), and the pooled estimate with the nonsignificant estrogen-alone result was 1.76 (1.19–2.60) [6,7].

The FDA's answer, from 2003, was class labeling: a boxed warning, extended in steps to every estrogen and estrogen-progestogen product, naming cardiovascular disorders, invasive breast cancer and probable dementia, together with the instruction to use the lowest effective dose for the shortest duration [35]. The warning made no distinction of dose, route, formulation or age, and it was applied to low-dose vaginal products [36]. Relative to the first half of 2002, US prescriptions in the first half of 2003 declined by 66% for the CEE-MPA combination and by 33% for CEE [37]; the prevalence of oral hormone use among postmenopausal American women fell from 22.4% in 1999–2000 to 11.9% in 2003–2004 and 4.7% in 2009–2010 [2]. By the FDA's own utilization review, about 2 million of the roughly 41 million American women aged 45 to 64 received a prescription for systemic MHT in 2020 [35].

After treatment stopped, most risks and benefits of both regimens dissipated; a modest excess of breast cancer persisted with CEE-MPA and a deficit with CEE alone, and neither regimen changed all-cause mortality [8]. At 18 years, all-cause mortality was 27.1% with hormone therapy and 27.6% with placebo (HR 0.99, 0.94–1.03); the ratio of hazard ratios for women aged 50–59 versus 70–79 was 0.61 (0.43–0.87) during the in-

Table 1. Principal randomized trials, individual-participant meta-analyses and large cohorts of menopausal hormone therapy, by endpoint.

Study [reference]	Population and regimen	Follow-up	Principal results (95% CI)
WHI estrogen plus progestin [3]	16,608 women with a uterus, aged 50–79 (mean 63); CEE 0.625 mg + MPA 2.5 mg daily vs placebo	5.2 y, stopped 2002	CHD HR 1.29 (1.02–1.63), +7/10,000 wy; stroke 1.41 (1.07–1.85), +8; PE 2.13 (1.39–3.25), +8; breast cancer 1.26 (1.00–1.59), +8; colorectal cancer 0.63 (0.43–0.92), −6; hip fracture 0.66 (0.45–0.98), −5
WHI estrogen alone [4]	10,739 hysterectomized women; CEE 0.625 mg daily vs placebo	6.8 y, stopped 2004	CHD 0.91 (0.75–1.12); stroke 1.39 (1.10–1.77), +12/10,000 wy; PE 1.34 (0.87–2.06); breast cancer 0.77 (0.59–1.01); hip fracture 0.61 (0.41–0.91), −6
WHI venous thromboembolism [5]	Estrogen-plus-progestin trial	5.2 y	VTE HR 2.06 (1.57–2.70); 3.5 vs 1.7 per 1,000 wy; excess greater with age, obesity and factor V Leiden
WHI Memory Study [6,7]	4,532 (E+P) and 2,947 (CEE) women aged 65–79	4–5 y	Probable dementia: E+P HR 2.05 (1.21–3.48), 45 vs 22/10,000 wy; CEE 1.49 (0.83–2.66); pooled 1.76 (1.19–2.60)
WHI extended follow-up [8-10]	Both trials	13 y cumulative; 18 y mortality; 20 y breast cancer	Most effects dissipated after stopping; all-cause mortality HR 0.99 (0.94–1.03); CEE alone: breast cancer incidence 0.78 (0.65–0.93), mortality 0.60 (0.37–0.97); CEE-MPA: incidence 1.28 (1.13–1.45), mortality 1.35 (0.94–1.95)
WHI by timing [11]	Both trials pooled, by years since menopause	—	CHD HR 0.76 (0.50–1.16) <10 y, 1.10 (0.84–1.45) 10–19 y, 1.28 (1.03–1.58) ≥20 y; −6, +4, +17/10,000 wy; stroke 1.32 (1.12–1.56) at all ages
HERS [12]	2,763 women with CHD, mean age 67; CEE + MPA vs placebo	4.1 y	CHD events relative hazard 0.99 (0.80–1.22); early excess, later deficit
DOPS [13]	1,006 women aged 45–58; open-label estradiol ± norethisterone acetate	10 y (16 y follow-up)	Death, heart failure or MI HR 0.48 (0.26–0.87); no excess cancer, VTE or stroke
KEEPS [14]	727 women within 3 y of menopause; oral CEE 0.45 mg or transdermal estradiol 50 μg + cyclic micronized progesterone	4 y	No change in carotid intima-media thickness progression or coronary calcium

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tervention phase but 0.87 (0.76–1.00) over the full 18 years, so the advantage of early initiation was largely confined to the treatment period [9]. At 20 years, CEE alone had reduced breast cancer incidence (HR 0.78, 0.65–0.93) and breast cancer mortality (HR 0.60, 0.37–0.97), while CEE-MPA had increased incidence (HR 1.28, 1.13–1.45) without a significant effect on breast cancer death (HR 1.35, 0.94–1.95) [10]. The WHI investigators' 2024 summary and the Cochrane review of long-term hormone therapy, last updated in September 2026 with searches to September 2024, which draws about 70% of its data from the WHI and the Heart and Estrogen/progestin Replacement Study (HERS) and in which only about 30% of participants were aged 50–59, reach the same reading: the trials answer the question of chronic-disease prevention in older women and have limited applicability to the woman who starts treatment at 51 for hot flashes [1,17]. Table 1 lists the principal trials and analyses by endpoint.

Cardiovascular disease and the timing hypothesis

In HERS, CEE-MPA did not prevent recurrent coronary events in 2,763 women with established disease (relative hazard 0.99, 0.80–1.22) and increased them in the first year [12]. The timing hypothesis, that estrogen slows atherogenesis in healthy arteries and destabilizes established plaque, is supported but not proven by four lines

Table 1 (continued). Principal randomized trials, individual-participant meta-analyses and large cohorts of menopausal hormone therapy, by endpoint.

Study [reference]	Population and regimen	Follow-up	Principal results (95% CI)
ELITE [15]	643 women <6 y or ≥10 y since menopause; oral estradiol 1 mg (+ vaginal progesterone)	Median 5 y	Intima-media progression 0.0044 vs 0.0078 mm/y in the early stratum (p=0.008); no effect late; no effect on coronary CT
Cochrane 2015 [16]	19 trials, 40,410 women	—	Overall: stroke RR 1.24 (1.10–1.41), VTE 1.92 (1.36–2.69); started <10 y after menopause: mortality 0.70 (0.52–0.95), CHD 0.52 (0.29–0.96), VTE 1.74 (1.11–2.73)
Cochrane 2026 [17]	24 studies, 45,660 women, ≥1 y of therapy; searches to Sep 2024	—	Combined: stroke RR 1.39 (1.09–2.09), breast cancer 1.27 (1.03–1.56), gallbladder surgery 1.64 (1.30–2.06), fractures 0.78 (0.71–0.86); estrogen-only: stroke 1.33 (1.06–1.67), VTE 1.32 (1.00–1.74), breast cancer 0.79 (0.61–1.01), fractures 0.73 (0.65–0.80)
Collaborative Group 2019 [18]	Individual-participant data; 108,647 breast cancers in prospective follow-up	—	Current use, years 1–4: E+P RR 1.60 (1.52–1.69), E-only 1.17 (1.10–1.26); years 5–14: 2.08 (2.02–2.15) and 1.33 (1.28–1.37); 5 y from age 50: 20-y incidence 6.3% to about 8.3%; no excess with vaginal estrogen
E3N [19]	80,377 French women; by progestogen	8.1 y	E + micronized progesterone RR 1.00 (0.83–1.22); E + dydrogesterone 1.16 (0.94–1.43); E + other progestins 1.69 (1.50–1.91); E alone 1.29 (1.02–1.65)
UK primary care, breast cancer [20]	Nested case-control, QResearch and CPRD	Recent use, ≥5 y	Estrogen-only OR 1.15 (1.09–1.21); combined 1.79 (1.73–1.85); dydrogesterone 1.24 (1.03–1.48); 3–8 and 9–36 extra cases/10,000 wy
UK primary care, VTE [21]	Nested case-control, >80,000 women with VTE	—	Oral OR 1.58 (1.52–1.64); CEE + MPA 2.10 (1.92–2.31); estradiol + dydrogesterone 1.18 (0.98–1.42); transdermal 0.93 (0.87–1.01)
ESTHER [22]	France, 271 idiopathic VTE cases, 610 controls	—	Oral OR 4.2 (1.5–11.6); transdermal 0.9 (0.4–2.1); norpregnanes 3.9 (1.5–10.0); micronized progesterone and pregnanes null
UK stroke by route and dose [23]	Nested case-control, 15,710 strokes	—	Oral rate ratio 1.28 (1.15–1.42); transdermal ≤50 µg 0.81 (0.62–1.05); transdermal >50 µg 1.89 (1.15–3.11)

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of evidence. In the pooled WHI trials, the HR for CHD was 0.76 (0.50–1.16) in women within 10 years of menopause, 1.10 (0.84–1.45) at 10–19 years and 1.28 (1.03–1.58) at 20 years or more (p for trend 0.02), corresponding to −6, +4 and +17 events per 10,000 women-years; stroke, by contrast, was increased at every age (HR 1.32, 1.12–1.56) [11]. In the Cochrane review of 19 trials with 40,410 women, hormone therapy conferred no protection against mortality, cardiovascular death or myocardial infarction overall and increased stroke (relative risk [RR] 1.24, 1.10–1.41) and venous thromboembolism (VTE) (RR 1.92, 1.36–2.69); but women who started within 10 years of menopause had lower mortality (RR 0.70, 0.52–0.95) and fewer coronary events (RR 0.52, 0.29–0.96), with VTE still increased (RR 1.74, 1.11–2.73) and no clear effect on stroke [16]. In the Early versus Late Intervention Trial with Estradiol (ELITE), oral estradiol 1 mg daily, with vaginal progesterone in women with a uterus, slowed progression of carotid intima-media thickness when started within 6 years of menopause (0.0044 versus 0.0078 mm per year, p=0.008) but not when started 10 or more years after it, with no effect on coronary computed tomography measures in either stratum [15]. In the Kronos Early Estrogen Prevention Study (KEEPS), four years of low-dose oral CEE

Table 1 (continued). Principal randomized trials, individual-participant meta-analyses and large cohorts of menopausal hormone therapy, by endpoint.

Study [reference]	Population and regimen	Follow-up	Principal results (95% CI)
Danish dementia study [24]	Nationwide nested case-control	—	Estrogen-progestogen HR 1.24 (1.17–1.33); >12 y 1.74 (1.45–2.10); treated ≤55 y 1.24 (1.11–1.40)
Dementia meta-analysis 2025 [25]	10 studies, 1,016,055 participants	—	No association with mild cognitive impairment or dementia by timing, duration or type
WHI ovarian and endometrial cancer [26]	Both trials	20 y	CEE alone: ovarian cancer HR 2.04 (1.14–3.65), 35 vs 17 cases, and higher ovarian cancer mortality; CEE-MPA: ovarian cancer 1.14 (0.82–1.59), endometrial cancer 0.72 (0.56–0.92)
Danish mortality cohort [27]	876,805 women followed from age 45; 104,086 MHT users	Median 14.3 y	All-cause mortality HR 0.96 (0.93–0.98); no unequivocal difference in cause-specific mortality
Vaginal estrogen after breast cancer [28,29]	Denmark, 8,461 early ER-positive cases; Scotland and Wales, 49,237 cases	—	Denmark: recurrence RR 1.08 (0.89–1.32), 1.39 (1.04–1.85) with aromatase inhibitors; all-cause mortality HR 0.78 (0.71–0.87). Scotland and Wales: breast cancer-specific mortality HR 0.77 (0.63–0.94)

CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; CPRD, Clinical Practice Research Datalink; CT, computed tomography; DOPS, Danish Osteoporosis Prevention Study; E, estrogen; E+P, estrogen plus progestogen; ELITE, Early versus Late Intervention Trial with Estradiol; ER, estrogen receptor; HERS, Heart and Estrogen/progestin Replacement Study; HR, hazard ratio; KEEPS, Kronos Early Estrogen Prevention Study; MI, myocardial infarction; MPA, medroxyprogesterone acetate; OR, odds ratio; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism; WHI, Women's Health Initiative; wy, women-years; y, years.

(0.45 mg) or transdermal estradiol (50 µg) with cyclic micronized progesterone, started within three years of menopause, did not change intima-media progression or coronary calcium [14]. The open-label Danish Osteoporosis Prevention Study (1,006 women aged about 50, estradiol with or without norethisterone acetate for 10 years) reported a halving of death, heart failure and myocardial infarction combined (HR 0.48, 0.26–0.87; 16 versus 33 events) without excess cancer, VTE or stroke, but its design and few events limit its weight [13].

The reading shared by the WHI investigators and the European and North American societies is that, for appropriately selected symptomatic women younger than 60 or within 10 years of menopause, the early-initiation analyses show no clear increase in coronary events or all-cause mortality and the overall balance is favorable, without establishing cardiovascular protection, whereas later initiation, or established atherosclerosis, carries an early excess of coronary and cerebrovascular events [1,38-40]. MHT is not indicated for prevention of cardiovascular disease or stroke at any age; the timing data define when symptom treatment carries no demonstrated cardiovascular excess, not a reason to treat [16,38,40].

Venous thromboembolism and stroke: route and dose

Route matters most for VTE, and European data have been decisive. Oral estrogen undergoes first-pass hepatic metabolism and shifts hemostatic proteins toward coagulation; in the WHI it doubled VTE (HR 2.06, 1.57–2.70; 3.5 versus 1.7 events per 1,000 women-years), with an absolute excess that rose steeply with age, body mass index and factor V Leiden [5]. Transdermal estradiol bypasses the liver. In the French Estrogen and Thromboembolism Risk (ESTHER) case-control study, the odds ratio (OR) for VTE was 4.2 (1.5–11.6) with oral and 0.9 (0.4–2.1) with transdermal estrogen; micronized progesterone and pregnane derivatives carried no excess, norpregnane derivatives did (OR 3.9, 1.5–10.0) [22]. The UK QResearch and Clinical Practice Research Datalink databases, with more than 80,000 women with VTE, showed oral therapy associated with VTE (OR 1.58, 1.52–1.64), estradiol with lower risk than CEE, CEE with MPA highest (2.10, 1.92–2.31) and estradiol with dydrogesterone lowest (1.18, 0.98–1.42), and no association with transdermal preparations of any type (0.93, 0.87–1.01) [21]. Meta-analysis confirms the pattern: oral estrogen-only RR 1.48 (1.39–1.58), transdermal 0.97 (0.87–1.09); transdermal estradiol

with micronized progesterone 0.93 (0.65–1.33); oral estrogen with MPA 2.77 (2.33–3.30) [41]. The European Menopause and Andropause Society (EMAS) drew the practical conclusion in 2011: a personal or family history of VTE, especially with a prothrombotic mutation, contraindicates oral therapy, but transdermal estrogen can be considered after individual assessment and is the first choice in overweight and obese women [42]. The European Union (EU) core product information for hormone replacement therapy nevertheless lists previous or current VTE and known thrombophilic disorders as contraindications for systemic products of any route [43], and the 2025 European Society of Endocrinology (ESE) guideline, endorsed by EMAS, recommends low-dose transdermal estrogen when treatment is indicated in a woman with previous VTE after individual risk-benefit assessment [40]; such use is a guideline-supported departure from the product license and should be documented as one.

Stroke follows the same logic with a dose threshold. In the WHI, stroke increased with both regimens and at all ages [4,11]; in the 2026 Cochrane update the RR was 1.33 (1.06–1.67) with estrogen alone [17]. In a UK nested case-control study of 15,710 strokes, current oral therapy increased stroke (rate ratio 1.28, 1.15–1.42) at low and high doses, whereas transdermal therapy overall did not (0.95, 0.75–1.20); the excess was confined to high-dose patches, above 50 µg estradiol daily (1.89, 1.15–3.11), and absent with low-dose patches (0.81, 0.62–1.05) [23]. In a French nested case-control study of 3,144 ischemic strokes and 12,158 controls aged 51–62, identified through the national health insurance database, stroke was associated with oral (OR 1.58, 1.01–2.49) but not transdermal estrogen (0.83, 0.56–1.24), and with norpregnane progestogens (2.25, 1.05–4.81) but not with progesterone or pregnanes [44]. Observational and confounded as they are, these findings are consistent and large, and they underlie the European preference for transdermal estradiol at 50 µg or less, with micronized progesterone or dydrogesterone, in any woman with vascular risk factors [39,42].

Breast cancer: progestogen, dose, duration

The randomized evidence on breast cancer is narrow: CEE-MPA and CEE alone, at one dose, in women whose average age was 63, with the 20-year results given above [10] and an original absolute excess with combined therapy of 8 cases per 10,000 women-years [3].

The individual-participant meta-analysis of the Collaborative Group on Hormonal Factors in Breast Cancer (108,647 women with breast cancer during prospective follow-up) is the most comprehensive estimate. Every type of systemic MHT except vaginal estrogen carried an excess risk that increased steadily with duration and was greater with estrogen-progestogen than with estrogen alone: in current users the RR was 1.60 (1.52–1.69) for combined and 1.17 (1.10–1.26) for estrogen-only therapy during years 1–4, and 2.08 (2.02–2.15) and 1.33 (1.28–1.37) during years 5–14. Daily progestogen carried more risk than intermittent (2.30 versus 1.93), the excess was similar for women starting at 40–59 years and attenuated after 60 and in obese women, and some excess persisted for more than 10 years after stopping. The authors estimated that five years of combined therapy started at age 50 would raise the 20-year cumulative incidence from 6.3% to about 8.3%, one extra case in 50 for daily progestogen, one in 70 for intermittent progestogen and one in 200 for estrogen alone [18].

Progestogen type modifies this risk. In the French E3N (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) cohort of 80,377 women, estrogen with micronized progesterone carried no excess (RR 1.00, 0.83–1.22), estrogen with dydrogesterone a small nonsignificant excess (1.16, 0.94–1.43) and estrogen with other synthetic progestins a clear one (1.69, 1.50–1.91), against 1.29 (1.02–1.65) for estrogen alone [19]. In the UK primary-care databases, recent long-term combined use was associated with an OR of 1.79 (1.73–1.85), highest with norethisterone (1.88) and lowest with dydrogesterone (1.24, 1.03–1.48), which translated into 9 to 36 extra cases per 10,000 women-years for combined therapy and 3 to 8 for estrogen alone [20]. A 2025 Finnish registry analysis found larger excesses (combined therapy for 5–9 years, OR 1.82; estrogen-only 1.61), again smaller with dydrogesterone (1.32, 1.12–1.55) and tibolone (1.30), persisting 5–10 years after cessation [45]. The advantage of micronized progesterone and dydrogesterone is consistent across cohorts but observational, untested in a randomized trial, and relative rather than absolute. The excess rises with each year of use and is measurable within the first four years [18]; the 2020 review by the Pharmacovigilance Risk Assessment Committee (PRAC) accordingly added to EU product information that risk may remain increased for 10 years or more after stopping if treatment lasted more than five years [46]. What the data do not show is an excess of breast cancer death with contemporary regimens started early; the only randomized mortality data are the WHI's [10].

Endometrial protection is the reason progestogens are given at all. Unopposed CEE produced simple, complex and atypical hyperplasia in 27.7%, 22.7% and 11.8% of women over three years in the Postmenopausal Estrogen/Progestin Inter-

ventions trial, against 0.8%, 0.8% and 0% with placebo, whereas the three progestogen regimens matched placebo [47]; endometrial cancer risk with unopposed estrogen rises with duration and persists for years after stopping [48]. In the Million Women Study, continuous combined therapy reduced endometrial cancer (RR 0.71, 0.56–0.90), cyclic therapy was neutral (1.05), and estrogen-only (1.45) and tibolone (1.79, 1.43–2.25) increased it [49]. Progestogens differ in androgenic, glucocorticoid and mineralocorticoid activity and in hepatic effects, one basis for their different vascular and breast profiles [50]. For micronized progesterone, an expert review concluded that 200 mg daily for 12–14 days per month protects the endometrium for up to five years, that vaginal use is off-label and that transdermal progesterone does not protect [51]. The levonorgestrel-releasing intrauterine system (LNG-IUS) protects as well as systemic progestogens and better than sequential MPA, at the price of bleeding and spotting in the first months [52]. One further European restriction concerns two progestogens: after a 2022 referral, high-dose nomegestrol acetate (3.75–5 mg) and chlormadinone acetate (5–10 mg) are to be used at the lowest dose for the shortest time and only when other options are not appropriate, and products containing either, at any dose, must not be used by women with current or past meningioma [53].

Cognition, fracture, mortality and other endpoints

Dementia was the least generalizable element of the boxed warning: the WHI Memory Study randomized women aged 65–79, and its 23 additional cases of probable dementia per 10,000 women-years with CEE-MPA describe late initiation in old age [6,7]. Whether earlier initiation protects, harms or does nothing is not settled. A Danish nationwide nested case-control study found dementia associated with estrogen-progestogen therapy (HR 1.24, 1.17–1.33), rising with duration and present in women treated at 55 or younger; the authors themselves note that this may reflect predisposition in women who seek treatment rather than an effect of the drugs [24]. The randomized data in younger women are neutral: in ELITE, estradiol neither benefited nor harmed verbal memory, executive function or global cognition whether started within six or after ten years of menopause [54], and the KEEPS Continuation study found no long-term cognitive effect about ten years after four years of early therapy [55]. A 2025 systematic review and meta-analysis of ten studies with 1,016,055 participants found no association between MHT and mild cognitive impairment or dementia by timing, duration or type [25], and the 2025 ESE guideline recommends that MHT is not used to prevent or treat dementia [40]. The FDA has asked for the dementia warning to be removed from all labels, and approved the removal for the first products in February 2026, because the memory study enrolled a population much older than women starting MHT [35,56], a statement about applicability, not about benefit.

Fracture is the one prevention benefit that has never been in doubt. In the WHI, combined therapy reduced total fractures (HR 0.76, 0.69–0.83) and increased hip bone mineral density (BMD) by 3.7% over three years [30]; estrogen alone reduced hip (0.65, 0.45–0.94), clinical vertebral (0.64, 0.44–0.93) and total fractures (0.71, 0.64–0.80) [31]; the 2026 Cochrane estimates are RR 0.78 (0.71–0.86) for all clinical fractures with combined and 0.73 (0.65–0.80) with estrogen-only therapy [17]. The effect did not depend on baseline fracture risk in the combined trial [30] and was lost within a few years of stopping [8]. Incident diabetes fell by a fifth with CEE-MPA (HR 0.79, 0.67–0.93), with a measurable fall in insulin resistance in the first year [32]. Gallbladder disease and surgery increased with both oral regimens (HR 1.67 with CEE and 1.59 with CEE-MPA; 78 versus 47 and 55 versus 35 events per 10,000 women-years), a risk not tested by route [33]. All-cause mortality was unaffected at 18 years in the WHI as a whole [9]; in a Danish nationwide cohort of 876,805 women followed from age 45, hormone therapy was associated with an adjusted all-cause mortality HR of 0.96 (0.93–0.98), lowest after 3 to 10 years of use, with no unequivocal difference in cause-specific mortality; confounding by indication cannot be excluded, and the study shows an absence of excess mortality rather than a survival benefit [27]. Ovarian cancer is the one malignancy where estrogen alone fares worse: over 20 years of WHI follow-up, CEE alone increased ovarian cancer incidence (35 versus 17 cases; HR 2.04, 1.14–3.65) and ovarian cancer mortality, whereas CEE-MPA did not (HR 1.14, 0.82–1.59) and reduced endometrial cancer incidence (HR 0.72, 0.56–0.92) [26]; the absolute numbers are small, and EU product information carries an ovarian cancer statement for both regimens [43].

Tibolone, a synthetic steroid with estrogenic, progestogenic and androgenic metabolites, reduced vertebral and nonvertebral fractures and breast cancer in the Long-Term Intervention on Fractures with Tibolone trial in women with a mean age of 68, but doubled stroke (relative hazard 2.19, 1.14–4.23), which stopped the trial [57]; it increased endometrial cancer in the Million Women Study [49] and breast cancer in the Finnish registry [45]. Conjugated estrogens with the selective estrogen receptor modulator bazedoxifene protect the endometrium without a progestogen

(hyperplasia below 1% at 12 months), increase spine and hip BMD, and cause no more breast tenderness or bleeding than placebo, but long-term breast and cardiovascular outcomes are unknown [58].

Local vaginal estrogen and the genitourinary syndrome of menopause

The genitourinary syndrome of menopause (GSM), vulvovaginal atrophy with dryness, dyspareunia, urgency and recurrent urinary tract infection, affects about half of postmenopausal women, does not remit, and responds to low-dose vaginal estrogen with serum estradiol that remains within the postmenopausal range [59,60]. The Menopause Society and EMAS both recommend low-dose vaginal estrogen, vaginal prasterone (dehydroepiandrosterone) or oral ospemifene for symptoms not relieved by moisturizers and lubricants, without a progestogen and without a fixed limit of duration [38,59,60]. In the WHI Observational Study, vaginal estrogen was not associated with excess stroke, breast cancer, endometrial cancer or VTE, and users with an intact uterus had a lower global index of adverse events (HR 0.68, 0.55–0.86) [61]; in the 2019 individual-participant meta-analysis, vaginal estrogen was the only preparation without excess breast cancer risk [18]; and the 2020 PRAC review recorded that the evidence has not shown an increase in breast cancer with low-dose vaginal estrogen in women without prior breast cancer [46]. Intravaginal prasterone [62] and oral ospemifene 60 mg daily [63] were superior to placebo for dryness and dyspareunia in their pivotal trials.

After breast cancer the question changes. Systemic MHT increased new breast cancer events in the Hormonal Replacement Therapy After Breast Cancer: Is It Safe? (HABITS) trial (HR 2.4, 1.3–4.2; five-year cumulative incidence 22.2% versus 8.0%) [64], and tibolone increased recurrence in the LIBERATE trial (HR 1.40, 1.14–1.70) [65]; both remain contraindicated. Vaginal estrogen is a different matter. In a Danish cohort of 8,461 women with early estrogen receptor-positive breast cancer, vaginal estrogen was not associated with recurrence overall (RR 1.08, 0.89–1.32) or with mortality (HR 0.78, 0.71–0.87), but recurrence was increased in the subgroup taking adjuvant aromatase inhibitors (RR 1.39, 1.04–1.85) [28]; in Scottish and Welsh cohorts of 49,237 women, breast cancer-specific mortality was not increased in vaginal estrogen users (HR 0.77, 0.63–0.94) [29]. Because aromatase inhibition depends on near-zero estradiol, EMAS places non-hormonal preparations first in women on adjuvant endocrine therapy [60], the 2025 ESE guideline suggests low-dose vaginal estrogen after breast cancer only when non-hormonal therapies are ineffective [40], the Danish subgroup finding counsels particular caution with aromatase inhibitors [28], and EU product information still states that safety after breast cancer is not known [46].

The regulatory reversal of 2025–2026 and the European position

On 17 July 2025 the FDA convened an expert panel on menopause and hormone replacement therapy [66], followed by a public comment period. On 10 November 2025 the Department of Health and Human Services and the FDA announced that the agency was initiating removal of the class-wide boxed warnings, and the FDA wrote to all application holders with the changes it required [35,67]. The requested changes are the same for every product: the boxed warning loses its language on cardiovascular disease, breast cancer and probable dementia and its recommendation to use the lowest effective dose for the shortest time; the probable-dementia warning disappears from the label as a whole; systemic labels add consideration of starting therapy for moderate to severe VMS before age 60 or within 10 years of menopause and the WHI data for women aged 50–59, keep the boxed warning on endometrial cancer for estrogen-alone products, and keep the cardiovascular and breast cancer warnings outside the box; vaginal products carry only the safety information relevant to local use [35]. The stated basis was the agency's own literature review, utilization data, the panel and public input, set out by its leadership in JAMA [68]. On 12 February 2026 the FDA approved revised labeling for six products covering the four categories (systemic combination, systemic estrogen-alone, systemic progestogen-alone for women using estrogen, and vaginal estrogen), with submissions from 29 companies in review; implementation proceeds product by product [56]. On a revised label, the box carries only the endometrial-cancer warning for systemic estrogen-alone products [35,67].

Two cautions apply. The announcement's claim that randomized trials show lower all-cause mortality in women who start within 10 years of menopause rests on subgroup and meta-analytic data that are consistent but not definitive [9,16,67]; and the removal of the lowest-dose, shortest-duration sentence creates no indication for prevention, since the FDA frames the change as correcting the applicability of the WHI to younger symptomatic women [35], conceding the long-standing criticism of a class-wide warning applied

to every dose, route and local product [36] without resolving the questions of long-term combined therapy and of MHT after 60.

Europe has made no equivalent move. EU product information for hormone replacement therapy follows a core summary of product characteristics maintained by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), into which the PRAC's May 2020 review of the 2019 Lancet meta-analysis added the persistence of breast cancer risk for 10 years or more after more than five years of use, recorded that low-dose vaginal estrogen has not been shown to increase breast cancer risk in women without prior breast cancer, and restated that treatment should be given at the lowest dose for the shortest time that works [46]. The core text has been revised twice since, in November 2024 for an interaction with hepatitis C antivirals and in December 2025 to warn against accidental transfer of estradiol gel or spray to children, without change to the class statements on breast cancer, VTE, stroke and dementia or to the contraindications [43]. Our search to 7 September 2026 found no EMA, PRAC or CMDh decision revisiting those statements and no equivalent MHRA action; the European position therefore remains the 2020 wording, which never contained a boxed warning in the American sense but does contain the lowest-dose, shortest-duration sentence the FDA has withdrawn. NICE guideline NG23, updated on 7 November 2024 and amended on 15 April 2026 on unscheduled bleeding, is individualized: discuss the benefits and risks of each option, use the lowest effective dosage, do not routinely offer selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) or clonidine first line for VMS alone, stop systemic therapy after a diagnosis of breast cancer, and treat genitourinary symptoms with vaginal estrogen; NICE's appraisal of 31 March 2026 recommends fezolinetant when hormone replacement therapy is unsuitable [69,70].

The societies converge on the framework the FDA has now adopted. The Menopause Society's 2022 position holds that for women younger than 60 or within 10 years of menopause without contraindications the benefit-risk balance is favorable for bothersome VMS and bone loss, worsens with later initiation, and calls for individualized duration with periodic reassessment rather than an arbitrary limit [38]; the EMAS care pathway of 2022 describes a stepwise, individualized approach from MHT to non-hormonal alternatives [39]; the International Menopause Society (IMS) recommendations of 2016 and its 2024 White Paper set out the five Ws of prescribing and its regulatory context [71,72]; and a European consortium has produced contraception-style eligibility criteria for MHT in women with medical conditions, built on 14 systematic reviews and 32 meta-analyses [73]. Two documents published after these set the current European reference. The 2025 ESE guideline, endorsed by EMAS and the British Menopause Society, recommends initiating MHT within 10 years of natural menopause or before 60, a targeted approach to continuation after 60, no use for prevention of cardiovascular disease, stroke or dementia, transdermal estrogen for women with previous VTE (when treatment is indicated after individual assessment), diabetes, hypertension or migraine with aura, no systemic MHT after breast cancer, and low-dose vaginal estrogen after breast cancer only when non-hormonal therapies fail [40]. The IMS issued new recommendations in December 2025, 342 graded recommendations and 40 key messages spanning midlife health, VMS, GSM, osteoporosis, cardiometabolic health, dementia, premature ovarian insufficiency (POI) and malignancies, with a correction published in April 2026 [74]. For POI, the 2024 international guideline led by the European Society of Human Reproduction and Embryology recommends hormone therapy, unless contraindicated, at least until the average age of natural menopause [75]. Table 2 gives the timeline.

Neurokinin receptor antagonists and other non-hormonal therapy

Hot flashes originate in hypothalamic KNDy (kisspeptin, neurokinin B, dynorphin) neurons. Estrogen restrains them; after menopause they hypertrophy and drive the thermoregulatory center of the preoptic area through neurokinin B acting at neurokinin 3 (NK3) receptors, narrowing the thermoneutral zone [89]. The first NK3 antagonist tested, MLE4901, cut weekly hot flashes by 45 percentage points more than placebo in a four-week crossover trial and produced transient alanine aminotransferase (ALT) rises of 4.5 to 5.9 times the upper limit of normal (ULN) in three of 37 women, an early signal of what was to come [90].

Fezolinetant, a selective NK3 antagonist, at 30 and 45 mg once daily reduced daily VMS frequency at week 12 by 2.39 and 2.55 episodes more than placebo in SKYLIGHT 1 and by 1.86 and 2.53 in SKYLIGHT 2, reduced severity, and kept its effect from week 1 to week 52, although the placebo comparison ended at week 12 [91,92]. In DAYLIGHT, a 24-week placebo-controlled trial in 453 women considered unsuitable for hormone therapy (contraindicated, cautioned, previous stoppers or averse), fezolinetant 45 mg reduced daily frequency by 1.93 episodes more than placebo (−2.64 to −1.22) and improved severity and sleep disturbance, with adverse events as frequent as

Table 2. Regulatory and guideline timeline, 2002–2026.

Date	Event	Reference
May–Jul 2002	WHI estrogen-plus-progestin trial stopped (May); results published (July)	3
2003	FDA class-wide boxed warning on estrogen and estrogen-progestogen products: cardiovascular disorders, invasive breast cancer, probable dementia; lowest dose for the shortest duration	35
May 2003	WHI Memory Study: probable dementia doubled with CEE-MPA in women ≥65	6
Feb–Apr 2004	WHI estrogen-alone trial stopped and published	4
2011	EMAS position statement on hormone therapy and VTE: transdermal estrogen preferred in women at risk	42
Oct 2012	DOPS: cardiovascular benefit of early, long-term therapy	13
Oct 2013	WHI cumulative 13-year follow-up	8
Mar 2015	Cochrane review: benefit in women starting within 10 years of menopause	16
Nov 2015	NICE guideline NG23 first published	69
2016	IMS recommendations on women's midlife health and MHT	71
Sep 2017	WHI 18-year mortality: no difference	9
Aug 2019	Collaborative Group meta-analysis of breast cancer risk	18
May 2020	PRAC updates EU hormone replacement therapy product information: risk persists ≥10 years after >5 years of use; low-dose vaginal estrogen not shown to raise breast cancer risk	46
Jul 2020	WHI 20-year breast cancer outcomes	10
Jul 2020	US National Academies report on compounded bioidentical hormones	76
2022	Menopause Society hormone therapy position statement; EMAS care pathway	38,39
Sep 2022	EMA measures on meningioma risk with nomegestrol- and chlormadinone-containing medicines (CHMP 1 Sep 2022)	53
12 May 2023	FDA approves fezolinetant	77
Jun 2023	Menopause Society nonhormone therapy position statement	78
7 Dec 2023	EU marketing authorization for fezolinetant	79
Aug 2024	WHI 20-year ovarian and endometrial cancer follow-up	26
12 Sep 2024	FDA adds liver injury warning to fezolinetant label	80
2024	IMS White Paper on the menopause	72

Continued on the next page.

with placebo (65.0% versus 61.1%) [81]. SKYLIGHT 4 randomized 1,830 women for 52 weeks of safety observation: adverse events were as frequent as with placebo, transaminase elevations above three times the ULN occurred in 6 of 583 women on placebo, 8 of 590 on 30 mg and 12 of 589 on 45 mg without a Hy's law case, and bone density did not change [93]. Fezolinetant was approved in the United States on 12 May 2023 [77] and in the EU on 7 December 2023 [79]. The EU summary of product characteristics gives 45 mg once daily, an effective half-life of 9.6 hours and metabolism mainly by cytochrome P450 (CYP) 1A2; moderate or strong CYP1A2 inhibitors, among which the label lists fluvoxamine and ethinylestradiol-containing contraceptives, are contraindicated [94], because fluvoxamine raises exposure more than ninefold, whereas smoking, a CYP1A2 inducer, lowers it [95].

Liver injury became the defining safety issue. After a post-marketing case of serious liver injury, the FDA added a warning on 12 September 2024 and a boxed warning on 16 December 2024, with liver tests before treatment, monthly for three months and at months 6 and 9 [80]. In the EU, a review that identified three cases with hyperbilirubinemia and twelve with symptoms of liver injury led to a direct healthcare professional communication, agreed by the PRAC on 28 November 2024 and distributed in January 2025, that requires liver tests before treatment and monthly for three months, no initiation if ALT, aspartate aminotransferase (AST) or total bilirubin is at or above twice the ULN, and discontinuation at the thresholds given in Table 3 [82,83]. The MHRA published

Table 2 (continued). Regulatory and guideline timeline, 2002–2026.

Date	Event	Reference
7 Nov 2024	NICE NG23 updated	69
Nov 2024	CMDh revises the EU core SmPC for hormone replacement therapy (hepatitis C antiviral interaction)	43
Nov 2024	DAYLIGHT: fezolinetant in women unsuitable for hormone therapy	81
28 Nov 2024	PRAC agrees EU DHPC on fezolinetant liver injury (distributed 13 Jan 2025)	82
2024	International guideline on premature ovarian insufficiency	75
16 Dec 2024	FDA boxed warning for fezolinetant	80
10 Apr 2025	MHRA Drug Safety Update on fezolinetant	83
8 Jul 2025	MHRA approves elinzanetant (first approval worldwide)	84
17 Jul 2025	FDA expert panel on menopause and hormone replacement therapy	66
18 Sep 2025	CHMP positive opinion on elinzanetant	85
Oct 2025	ESE clinical practice guideline on menopause and perimenopause	40
24 Oct 2025	FDA approves elinzanetant	86
10 Nov 2025	FDA announces removal of class-wide boxed warnings from MHT products	35,67
17 Nov 2025	EU marketing authorization for elinzanetant	85
Dec 2025	IMS recommendations and key messages (correction Apr 2026)	74
Dec 2025	CMDh core SmPC revision: accidental transfer of estradiol gel or spray to children	43
Feb 2026	Danish nationwide cohort: no excess mortality with MHT	27
12 Feb 2026	FDA approves revised labeling for six MHT products covering the four categories; 29 companies' submissions in review	56
31 Mar 2026	NICE recommends fezolinetant (TA1143)	70
15 Apr 2026	NICE NG23 amended on unscheduled bleeding	69
Aug 2026	US and UK elinzanetant product information add a seizure warning	87,88
4 Sep 2026	Cochrane review of long-term hormone therapy updated (searches to 26 Sep 2024)	17

CEE, conjugated equine estrogens; CHMP, Committee for Medicinal Products for Human Use; CMDh, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human; DHPC, direct healthcare professional communication; DOPS, Danish Osteoporosis Prevention Study; EMA, European Medicines Agency; EMAS, European Menopause and Andropause Society; ESE, European Society of Endocrinology; EU, European Union; FDA, US Food and Drug Administration; IMS, International Menopause Society; MHRA, Medicines and Healthcare products Regulatory Agency; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; NICE, National Institute for Health and Care Excellence; PRAC, Pharmacovigilance Risk Assessment Committee; SmPC, summary of product characteristics; UK, United Kingdom; US, United States; VTE, venous thromboembolism; WHI, Women's Health Initiative.

the same advice on 10 April 2025, adding that fezolinetant should be avoided in known or suspected liver disease; the mechanism of the injury is unknown [83].

Elinzanetant is a dual antagonist of neurokinin 1 (NK1) and NK3 receptors. The dose is 120 mg at bedtime, the elimination half-life about 45 hours, and metabolism is by CYP3A4; the dose is halved with moderate inhibitors, and strong inhibitors are to be avoided under the US label, are not recommended under the EU summary of product characteristics and are contraindicated under the UK one [87,88,97]. In OASIS 1 and OASIS 2 (396 and 400 women), elinzanetant reduced daily moderate to severe VMS at week 12 by 3.2 episodes more than placebo in both trials, reduced severity, and improved sleep disturbance and menopause-specific quality of life [96]. OASIS 3 followed 628 women for 52 weeks; unlike OASIS 1 and 2 it set no minimum symptom frequency for entry, and the week-12 difference in daily frequency was −1.6 (−2.0 to −1.1), with numerical advantages persisting to week 50 and treatment-related adverse events more common with elinzanetant [98]. OASIS 4 addressed the population that needs non-hormonal treatment most: 474 women with VMS caused by endocrine therapy for breast cancer or risk reduction, randomized 2:1 for 12 weeks; from about 11.5

Table 3. Fezolinetant and elinzanetant compared, with the jurisdiction of each rule.

Characteristic	Fezolinetant	Elinzanetant
Target	Selective NK3 receptor antagonist [91]	Dual NK1 and NK3 receptor antagonist [96]
Dose	45 mg once daily in the EU; 30 and 45 mg studied [91,94]	120 mg once daily at bedtime; 60 mg with moderate CYP3A4 inhibitors [87,97]
Half-life	Effective half-life 9.6 h [94]	About 45 h [87]
Metabolism and interactions	CYP1A2 (minor CYP2C9, CYP2C19); moderate and strong CYP1A2 inhibitors (fluvoxamine, ethinylestradiol-containing contraceptives) contraindicated in the EU; fluvoxamine raises AUC to 939% of control; smoking lowers exposure [94,95]	CYP3A4; strong inhibitors and grapefruit to be avoided (US), not recommended (EU) or contraindicated (UK); moderate and strong inducers to be avoided (US) [87,88,97]
Efficacy, daily moderate-to-severe VMS vs placebo	SKYLIGHT 1 (week 12): −2.39 (30 mg), −2.55 (45 mg); SKYLIGHT 2: −1.86, −2.53; DAYLIGHT (week 24, women unsuitable for hormone therapy): −1.93 [81,91,92]	OASIS 1 and 2 (week 12): −3.2 each; OASIS 3 (52 weeks, no minimum frequency at entry): −1.6 at week 12; OASIS 4 (endocrine therapy for breast cancer): −3.4 at week 12 [96,98,99]
Other outcomes	Improved sleep disturbance in DAYLIGHT; no bone density or endometrial safety signal over 52 weeks [81,93]	Improved sleep disturbance and menopause-specific quality of life [96]
Liver signal in trials	ALT or AST >3× ULN: 6/583 placebo, 8/590 (30 mg), 12/589 (45 mg); no Hy's law case [93]	ALT or AST ≥3× ULN: 1.2% (120 mg) vs 1.0% placebo; no Hy's law case; 2/1,697 probably related, mild, reversible [100]
Post-marketing action	Serious liver injury reported; FDA warning 12 Sep 2024, boxed warning 16 Dec 2024; EU DHPC (PRAC 28 Nov 2024, distributed 13 Jan 2025); MHRA advice 10 Apr 2025 [80,82,83]	Seizures reported after marketing: US label (Aug 2026) and UK SmPC (Aug 2026) add a seizure warning; no liver action; independent liver safety board advised against routine monitoring [87,88,100]
Liver monitoring	Tests before treatment, monthly for 3 months, then at months 6 and 9 (FDA) or as clinically indicated (EU); do not start if ALT, AST or bilirubin ≥2× ULN; stop, in the EU wording, if transaminases >5× ULN, or ≥3× ULN with bilirubin >2× ULN or with symptoms [80,82]	US: tests before treatment and at 3 months; do not start if transaminases or bilirubin ≥2× ULN; stop at once for symptoms of liver injury, or if transaminases >5× ULN, or >3× ULN with bilirubin >2× ULN. UK: tests before treatment and if symptoms occur. EU: no requirement [87,88,97]

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episodes per day, the difference was −3.5 (−4.4 to −2.6) at week 4 and −3.4 (−4.2 to −2.5) at week 12, with headache, fatigue and somnolence the common adverse events and serious adverse events in 2.5% versus 0.6% [99]. Across the phase 1–3 program, ALT or AST at or above three times the ULN occurred in 1.2% of women on 120 mg and 1.0% on placebo, with no Hy's law case and two probably related, mild and reversible cases among 1,697 treated women; the independent liver safety board considered routine monitoring unnecessary [100]. The regulators diverge. The US label, which carries no boxed warning, requires baseline liver tests, no initiation at transaminases or bilirubin at or above twice the ULN, a repeat at three months, immediate discontinuation if symptoms of liver injury appear, and discontinuation at transaminases above five times the ULN or above three times the ULN with bilirubin above twice the ULN; the UK summary of product characteristics recommends liver tests before treatment and if symptoms occur; the EU summary of product characteristics requires none [87,88,97]. Seizures have been reported in treated women since marketing: the US label revised in August 2026 and the UK text of the same month advise patients of the risk and counsel caution with a history of seizures or conditions that lower the seizure threshold, and the US label adds that somnolence, fatigue, dizziness and related nervous system effects occurred in 11.9% of women versus 3.5% on placebo across the OASIS trials, with a warning about driving; the EU text carried neither warning at the time of writing [87,88,97]. Pregnancy is a contraindication in all three [87,88,97]. Elinzanetant was approved by the MHRA on 8 July 2025 [84,103] and by the FDA on 24 October 2025 [86], and authorized in the EU on 17 November 2025 with an indication that, unlike the US one, includes VMS caused by adjuvant endocrine therapy for breast cancer [85]. Table 3 compares the two drugs.

The older options are the yardstick, and their effects are modest: paroxetine 7.5 mg at night reduced VMS frequency and severity in two tri-

Table 3 (continued). Fezolinetant and elinzanetant compared, with the jurisdiction of each rule.

Characteristic	Fezolinetant	Elinzanetant
Other precautions	Not recommended during ongoing oncologic treatment, endocrine therapy included, and a case-by-case decision after completion (EU); concomitant systemic estrogen not recommended (EU); avoid in known liver disease or at higher risk of it (MHRA) [83,94]	Caution with a history of seizures or a lowered seizure threshold (US, UK); CNS effects (somnolence, fatigue, dizziness) 11.9% vs 3.5% in the OASIS trials, with a driving caution (US); pregnancy contraindicated (US, EU, UK); concomitant systemic estrogen not recommended (EU); moderate or severe hepatic impairment not recommended (US), severe impairment contraindicated (UK) [87,88,97]
Regulatory status	FDA 12 May 2023 [77]; EU 7 Dec 2023 [79]; NICE TA1143 31 Mar 2026, when hormone replacement therapy is unsuitable [70]	MHRA 8 Jul 2025 [84]; CHMP positive opinion 18 Sep 2025 and EU authorization 17 Nov 2025, indication including VMS caused by adjuvant endocrine therapy for breast cancer [85,97]; FDA 24 Oct 2025 [86]
Position in network meta-analysis (indirect)	Superior to paroxetine, desvenlafaxine and gabapentin; not significantly different from 27 hormone regimens; below tibolone and CE-bazedoxifene for 75% response [101]	Superior to paroxetine, desvenlafaxine and gabapentin for frequency; comparable to fezolinetant for frequency and severity; better for sleep [102]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; CE, conjugated estrogens; CHMP, Committee for Medicinal Products for Human Use; CNS, central nervous system; CYP, cytochrome P450; DHPC, direct healthcare professional communication; EU, European Union; FDA, US Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; NK, neurokinin; PRAC, Pharmacovigilance Risk Assessment Committee; SmPC, summary of product characteristics; UK, United Kingdom; ULN, upper limit of normal; US, United States; VMS, vasomotor symptoms.

als [104]; venlafaxine 75 mg reduced daily VMS by 1.8 episodes more than placebo, against 2.3 for oral estradiol 0.5 mg [105]; escitalopram 10–20 mg by 1.4 episodes, with 55% versus 36% of women achieving at least a 50% reduction [106]; gabapentin 900 mg by 45% versus 29% with placebo, with adverse events in 50% versus 28% [107]; and oxybutynin 2.5 or 5 mg twice daily reduced hot flash scores in women with and without breast cancer, at the cost of anticholinergic effects [108]. Indirect comparisons in network meta-analyses, with the usual limits of transitivity, put the neurokinin antagonists ahead of the non-hormonal comparators they included: fezolinetant 45 mg reduced daily frequency by 1.1 to 2.2 episodes more than paroxetine 7.5 mg, desvenlafaxine and gabapentin, did not differ significantly from 27 hormone regimens, which is not equivalence, and was less effective than tibolone and conjugated estrogens with bazedoxifene for a 75% response [101]; elinzanetant was superior to paroxetine, desvenlafaxine and gabapentin for frequency, comparable to fezolinetant for frequency and severity, and better than fezolinetant for sleep disturbance [102]. Venlafaxine, escitalopram and oxybutynin were not in these networks, and no head-to-head trial against hormone therapy exists. The Menopause Society's 2023 statement recommends cognitive behavioral therapy, clinical hypnosis, SSRIs and SNRIs, gabapentin and fezolinetant at the highest level of evidence and oxybutynin at levels I–II, and recommends against clonidine, pregabalin, supplements and most complementary approaches [78]. Hormone therapy remains the most effective treatment for VMS; the neurokinin antagonists are for women who cannot or will not take it [78,101].

A prescribing framework for 2026

The following framework follows the EMAS, ESE, IMS, NICE and Menopause Society positions; where it departs from EU product information, it says so; it takes the American label change as confirmation, not as new evidence [38-40,69,74].

Systemic MHT is for symptoms: moderate to severe VMS, and the sleep and mood disturbance that track with them, in women younger than 60 or within 10 years of menopause who have no contraindication, and for prevention of bone loss in such women when other agents are unsuitable [38,39]. It is not for prevention of cardiovascular disease or dementia [16,25]. The contraindications in EU product information apply to systemic estrogen of any route: known, past or suspected breast cancer or other estrogen-dependent malignancy, undiagnosed genital bleeding, untreated endometrial hyperplasia, previous or current VTE, known thrombophilic disorders, active or recent arterial thromboembolic disease, and acute liver disease or liver disease with liver function tests not

returned to normal [43]; the consortium eligibility criteria give a condition-by-condition grid for the situations the label does not settle [73].

The regimen decides most of the risk. Estradiol rather than CEE; transdermal rather than oral in any woman with obesity, hypertension, diabetes, migraine with aura, smoking, hypertriglyceridemia, gallbladder disease or a family history of VTE, at 50 µg daily or less unless symptoms require more, with oral estradiol 1 mg acceptable in a healthy woman without vascular risk factors [21,23,41,42]. In a woman with a uterus, micronized progesterone 200 mg for 12–14 days a month while cyclical bleeding is acceptable, or a continuous combined regimen with a licensed daily progestogen dose once it is not, with endometrial protection reassessed whenever the estrogen dose is raised; dydrogesterone is the alternative on the observational breast and venous data; the 52 mg LNG-IUS, within its licensed interval for endometrial protection, serves when contraception or bleeding control is also needed; MPA, norethisterone and the norpregnanes are second choices on the same observational grounds, not excluded options [19,20,41,51,52]. A hysterectomized woman needs no progestogen unless she has a previous diagnosis of endometriosis, the one case in which EU product information allows one to be added [43]. The dose is the lowest that controls symptoms, reviewed at three months; there is no evidence-based maximum duration, so treatment continues while symptoms warrant and the balance holds, with reassessment at least yearly, and neither tapering nor abrupt cessation changes the longer-term course of symptoms [35,38,69]. Monitoring is clinical: blood pressure and body mass index at baseline, breast screening by the national program, and assessment of bleeding beyond the first six months of systemic therapy or beyond three months of a change in dose or preparation [69]. Routine hormone measurements have no place in symptom-guided MHT; laboratory testing follows comorbidity and co-medication, the neurokinin antagonists have their own label-specific liver rules [82,87,88], and testosterone therapy requires its own biochemical monitoring [109].

Three situations need specific rules. A woman with a history of VTE or a known thrombophilia should receive no oral estrogen, and a non-hormonal agent is the first alternative; where treatment is still indicated after individual assessment, ideally with hematology advice, low-dose transdermal estradiol with micronized progesterone or dydrogesterone is what EMAS and the ESE guideline support, with the departure from the product license, which contraindicates systemic estrogen of any route, documented [40-43]. A woman after breast cancer should receive no systemic MHT and no tibolone [40,64,65]. For VMS during adjuvant endocrine therapy, elinzanetant holds an EU indication for exactly this situation [85,99], whereas fezolinetant is not recommended under its EU summary of product characteristics during ongoing oncologic treatment, endocrine therapy included, and becomes a case-by-case decision once treatment is complete [94]; gabapentin, oxybutynin and an SSRI or SNRI are alternatives, with potent CYP2D6 inhibitors such as paroxetine and fluoxetine avoided in women taking tamoxifen. For GSM, moisturizers and lubricants first, then low-dose vaginal estrogen agreed with the oncologist, which the ESE guideline reserves for failure of non-hormonal measures, with particular caution during aromatase inhibitor treatment [28,29,40,60]. A woman with POI (loss of ovarian function before 40) or early menopause (40–44), spontaneous or surgical, needs hormone replacement rather than symptom treatment, unless contraindicated, until at least the average age of natural menopause, with disease-specific advice after cancer; the WHI risk estimates were obtained in older women and should not be transferred to her, and MHT is not contraception [40,75].

Testosterone has one indication: the global consensus endorsed by EMAS and the IMS supports transdermal testosterone at doses approximating premenopausal concentrations only for postmenopausal women with hypoactive sexual desire disorder, with no evidence of benefit for cognition, bone, mood or cardiovascular disease [109]. Compounded bioidentical products have no place: the US National Academies concluded in 2020 that evidence of their safety and effectiveness is insufficient and that their use should be restricted to documented allergy to an approved product or to a dose or form that is not available; regulated estradiol and micronized progesterone are themselves body-identical [76].

Much remains unresolved. Whether transdermal estradiol with micronized progesterone changes coronary events, stroke or breast cancer mortality has never been tested in a randomized trial; every European preference rests on cohorts [19,21,41]. Whether MHT started early changes dementia risk is unknown; the randomized data are short, the cohorts conflict, and the meta-analytic answer is null [24,25,55]. The breast cancer excess with combined therapy, and its dependence on progestogen and duration, is established in observational data, the Lancet meta-analysis estimating about one additional case over 20 years per 50 women who use daily combined therapy for five years from age 50, per 70 with intermittent progestogen and per 200 with estrogen alone, with unknown consequences for mortality [18]. For the neurokinin antagonists, the questions are the true incidence and mechanism of fezolinetant hepatotoxicity, whether the milder

liver signal of elinzanetant holds in post-marketing use, cardiovascular and bone outcomes beyond 52 weeks, and comparative effectiveness against low-dose transdermal estradiol in head-to-head trials that have not been done [93,100-102].

Conclusion

The WHI was right about what it tested and was applied to what it had not tested. Twenty-four years on, the evidence supports a narrower statement than either the 2003 warning or the enthusiasm that preceded it: for a symptomatic woman younger than 60 or within 10 years of menopause without contraindications, systemic MHT is the most effective treatment for VMS, prevents fractures, has shown no increase in coronary events or mortality, carries risks of VTE and stroke that observational data place with oral rather than low-dose transdermal estradiol, and carries a risk of breast cancer that depends on the progestogen and rises with duration. The revised American labels say this; EU product information keeps its 2020 class wording, and the European societies have said it for a decade. Low-dose vaginal estrogen has reassuring safety data in women without breast cancer and, after breast cancer, is a shared decision with the oncologist. Fezolinetant and elinzanetant add mechanism-targeted non-hormonal options that outperform the older drugs in indirect comparison, at the cost, for fezolinetant, of liver monitoring. The prescribing decision has not become simpler; it has become individual, and it depends on route, progestogen, dose, timing and the woman's own history in ways that a class warning could never express.

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V.N.V.: conceptualization, methodology, investigation, validation, writing – original draft, writing – review and editing. The author read and approved the final version and agrees to be accountable for all aspects of the work.

Ethics statement

No ethical approval was required. No human or animal data were collected.

Data availability

No new data were generated; all data discussed are in the cited publications and regulatory documents.

References

1. Manson JE, Crandall CJ, Rossouw JE, Chlebowski RT, Anderson GL, Stefanick ML, et al. The Women's Health Initiative Randomized Trials and Clinical Practice: A Review. JAMA. 2024 May 28;331(20):1748-1760. doi: 10.1001/jama.2024.6542. PMID: 38691368.
2. Sprague BL, Trentham-Dietz A, Cronin KA. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. Obstet Gynecol. 2012 Sep;120(3):595-603. doi: 10.1097/AOG.0b013e318265df42. PMID: 22914469; PMCID: PMC3607288.
3. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al.; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002 Jul 17;288(3):321-33. doi: 10.1001/jama.288.3.321. PMID: 12117397.
4. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al.; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA. 2004 Apr 14;291(14):1701-12. doi: 10.1001/jama.291.14.1701. PMID: 15082697.
5. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al.; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004 Oct 6;292(13):1573-80. doi: 10.1001/jama.292.13.1573. PMID: 15467059.
6. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al.; WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. JAMA. 2003 May 28;289(20):2651-62. doi: 10.1001/jama.289.20.2651. PMID: 12771112.
7. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al.; Women's Health Initiative Memory Study. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA. 2004 Jun 23;291(24):2947-58. doi: 10.1001/jama.291.24.2947. PMID: 15213206.
8. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013 Oct 2;310(13):1353-68. doi: 10.1001/jama.2013.278040. PMID: 24084921; PMCID: PMC3963523.
9. Manson JE, Aragaki AK, Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, et al.; WHI Investigators. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Ran-

domized Trials. JAMA. 2017 Sep 12;318(10):927-938. doi: 10.1001/jama.2017.11217. PMID: 28898378; PMCID: PMC5728370.
10. Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, et al. Association of Menopausal Hormone Therapy With Breast Cancer Incidence and Mortality During Long-term Follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA. 2020 Jul 28;324(4):369-380. doi: 10.1001/jama.2020.9482. PMID: 32721007; PMCID: PMC7388026.
11. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007 Apr 4;297(13):1465-77. doi: 10.1001/jama.297.13.1465. PMID: 17405972.
12. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998 Aug 19;280(7):605-13. doi: 10.1001/jama.280.7.605. PMID: 9718051.
13. Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. BMJ. 2012 Oct 9;345:e6409. doi: 10.1136/bmj.e6409. Epub 2012 Oct 9. PMID: 23048011.
14. Harman SM, Black DM, Naftolin F, Brinton EA, Budoff MJ, Cedars MI, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women: a randomized trial. Ann Intern Med. 2014 Aug 19;161(4):249-60. doi: 10.7326/M14-0353. PMID: 25069991.
15. Hodis HN, Mack WJ, Henderson VW, Shoupe D, Budoff MJ, Hwang-Levine J, et al.; ELITE Research Group. Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. N Engl J Med. 2016 Mar 31;374(13):1221-31. doi: 10.1056/NEJMoa1505241. PMID: 27028912; PMCID: PMC4921205.
16. Boardman HM, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women. Cochrane Database Syst Rev. 2015 Mar 10;2015(3):CD002229. doi: 10.1002/14651858.CD002229.pub4. Epub 2015 Mar 10. PMID: 25754617; PMCID: PMC10183715.
17. Bofill Rodriguez M, Yong LN, Mirkov S, Bekos C, Lethaby A, Farquhar C. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2026 Sep 4;9(9):CD004143. doi: 10.1002/14651858.CD004143.pub7. Epub 2026 Sep 4. PMID: 42695385; PMCID: PMC13543657.
18. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet. 2019 Sep 28;394(10204):1159-1168. doi: 10.1016/S0140-6736(19)31709-X. Epub 2019 Aug 29. PMID: 31474332; PMCID: PMC6891893.
19. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2008 Jan;107(1):103-11. doi: 10.1007/s10549-007-9523-x. Epub 2007 Feb 27. PMID: 17333341; PMCID: PMC2211383.
20. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ. 2020 Oct 28;371:m3873. doi: 10.1136/bmj.m3873. Epub 2020 Oct 28. PMID: 33115755; PMCID: PMC7592147.
21. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ. 2019 Jan 9;364:k4810. doi: 10.1136/bmj.k4810. Epub 2019 Jan 9. PMID: 30626577; PMCID: PMC6326068.
22. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al.; Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007 Feb 20;115(7):840-5. doi: 10.1161/CIRCULATIONAHA.106.642280. PMID: 17309934.
23. Renoux C, Dell'aniello S, Garbe E, Suissa S. Transdermal and oral hormone replacement therapy and the risk of stroke: a nested case-control study. BMJ. 2010 Jun 3;340:c2519. doi: 10.1136/bmj.c2519. Epub 2010 Jun 3. PMID: 20525678.
24. Pourhadi N, Mørch LS, Holm EA, Torp-Pedersen C, Meaidi A. Menopausal hormone therapy and dementia: nationwide, nested case-control study. BMJ. 2023 Jun 28;381:e072770. doi: 10.1136/bmj-2022-072770. Epub 2023 Jun 28. PMID: 37380194; PMCID: PMC10302215.
25. Melville M, He L, Desai R, Nyamayaro P, Fox C, Kothari KU, et al. Menopause hormone therapy and risk of mild cognitive impairment or dementia: a systematic review and meta-analysis. Lancet Healthy Longev. 2025 Dec;6(12):100803. doi: 10.1016/j.lanhl.2025.100803. Epub 2025 Dec 22. PMID: 41448220.
26. Chlebowski RT, Aragaki AK, Pan K, Haque R, Rohan TE, Song M, et al. Menopausal Hormone Therapy and Ovarian and Endometrial Cancers: Long-Term Follow-Up of the Women's Health Initiative Randomized Trials. J Clin Oncol. 2024 Oct 20;42(30):3537-3549. doi: 10.1200/JCO.23.01918. Epub 2024 Aug 22. PMID: 39173088.
27. Mikkelsen AP, Bergholt T, Lidegaard Ø, Scheller NM. Menopausal hormone therapy and long term mortality: nationwide, register based cohort study. BMJ. 2026 Feb 18;392:e085998. doi: 10.1136/bmj-2025-085998. Epub 2026 Feb 18. PMID: 41708152; PMCID: PMC12915068.
28. Cold S, Cold F, Jensen MB, Cronin-Fenton D, Christiansen P, Ejlertsen B. Systemic or Vaginal Hormone Therapy After Early Breast Cancer: A Danish Observational Cohort Study. J Natl Cancer Inst. 2022 Oct 6;114(10):1347-1354. doi: 10.1093/jnci/djac112. PMID: 35854422; PMCID: PMC9552278.
29. McVicker L, Labeit AM, Coupland CAC, Hicks B, Hughes C, McMenamin Ú, et al. Vaginal Estrogen Therapy Use and Survival in Females With Breast Cancer. JAMA Oncol. 2024 Jan 1;10(1):103-108. doi: 10.1001/jamaoncol.2023.4508. PMID: 37917089; PMCID: PMC10623297.
30. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al.; Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA. 2003 Oct 1;290(13):1729-38. doi: 10.1001/jama.290.13.1729. PMID: 14519707.
31. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, et al.; Women's Health Initiative Investigators. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J Bone Miner Res. 2006 Jun;21(6):817-28. doi: 10.1359/jbmr.060312. PMID: 16753012.
32. Margolis KL, Bonds DE, Rodabough RJ, Tinker L, Phillips LS, Allen C, et al.; Women's Health Initiative Investigators. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. Diabetologia. 2004 Jul;47(7):1175-1187. doi: 10.1007/s00125-004-1448-x. Epub 2004 Jul 14. PMID: 15252707.
33. Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, et al. Effect of estrogen therapy on gallbladder disease. JAMA. 2005 Jan 19;293(3):330-9. doi: 10.1001/jama.293.3.330. PMID: 15657326.
34. Anderson GL, Judd HL, Kaunitz AM, Barad DH, Beresford SA, Pettinger M, et al.; Women's Health Initiative

Investigators. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures: the Women's Health Initiative randomized trial. JAMA. 2003 Oct 1;290(13):1739-48. doi: 10.1001/jama.290.13.1739. PMID: 14519708.
35. U.S. Food and Drug Administration. FDA requests labeling changes related to safety information to clarify the benefit/risk considerations for menopausal hormone therapies. Silver Spring (MD): FDA; 2025 (updated 12 February 2026). https://www.fda.gov/drugs/drug-alerts-and-statements/fda-requests-labeling-changes-related-safety-information-clarify-benefitrisk-considerations (accessed 7 September 2026).
36. Sriprasert I, Hodis HN, Mack WJ, Rosser M, Evans ML, Xu X, et al. Elimination of the Black Box Warning on Menopausal Hormone Therapy. Obstet Gynecol. 2026 May 1;147(5):642-646. doi: 10.1097/AOG.0000000000006226. Epub 2026 Feb 13. PMID: 41687116.
37. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA. 2004 Jan 7;291(1):47-53. doi: 10.1001/jama.291.1.47. PMID: 14709575.
38. "The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-794. doi: 10.1097/GME.0000000000002028. PMID: 35797481.
39. Lambrinoudaki I, Armeni E, Goulis D, Bretz S, Ceausu I, Durmusoglu F, et al. Menopause, wellbeing and health: A care pathway from the European Menopause and Andropause Society. Maturitas. 2022 Sep;163:1-14. doi: 10.1016/j.maturitas.2022.04.008. Epub 2022 May 12. PMID: 35569270.
40. Lumsden MA, Dekkers OM, Faubion SS, Lindén Hirschberg A, Jayasena CN, Lambrinoudaki I, et al. European society of endocrinology clinical practice guideline for evaluation and management of menopause and the perimenopause. Eur J Endocrinol. 2025 Sep 30;193(4):G49-G81. doi: 10.1093/ejendo/lvaf206. PMID: 41082911.
41. Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. Climacteric. 2018 Aug;21(4):341-345. doi: 10.1080/13697137.2018.1446931. Epub 2018 Mar 23. PMID: 29570359.
42. Tremollieres F, Brincat M, Erel CT, Gambacciani M, Lambrinoudaki I, Moen MH, et al.; European Menopause and Andropause Society. EMAS position statement: Managing menopausal women with a personal or family history of VTE. Maturitas. 2011 Jun;69(2):195-8. doi: 10.1016/j.maturitas.2011.03.011. Epub 2011 Apr 12. PMID: 21489728.
43. Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). Core SmPC for hormone replacement therapy products. CMDh/131/2003, Rev. 11, December 2025. Amsterdam: Heads of Medicines Agencies; 2025. https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Product_Information/Core_SPC_PL/Core_SPCs/CMDh_131-2003_Rev11_2025_12_clean_-_Core_SmPC_HRT.pdf (accessed 7 September 2026).
44. Canonico M, Carcaillon L, Plu-Bureau G, Oger E, Singh-Manoux A, Tubert-Bitter P, et al. Postmenopausal Hormone Therapy and Risk of Stroke: Impact of the Route of Estrogen Administration and Type of Progestogen. Stroke. 2016 Jul;47(7):1734-41. doi: 10.1161/STROKEAHA.116.013052. Epub 2016 Jun 2. PMID: 27256671; PMCID: PMC4927222.
45. Siitonen H, Joensuu J, Savolainen-Peltonen H, Gissler M, Ylikorkala O, Mikkola TS. Update of the impact of menopausal hormone therapy on breast cancer risk. Eur J Cancer. 2025 May 2;220:115340. doi: 10.1016/j.ejca.2025.115340. Epub 2025 Mar 11. PMID: 40107092.
46. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 11-14 May 2020. Amsterdam: EMA; 2020. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-11-14-may-2020 (accessed 7 September 2026).
47. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1996 Feb 7;275(5):370-5. doi: 10.1001/jama.1996.03530290040035. PMID: 8569016.
48. Grady D, Gebretsadik T, Kerlikowske K, Ernster V, Petitti D. Hormone replacement therapy and endometrial cancer risk: a meta-analysis. Obstet Gynecol. 1995 Feb;85(2):304-13. doi: 10.1016/0029-7844(94)00383-O. PMID: 7824251.
49. Beral V, Bull D, Reeves G; Million Women Study Collaborators. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2005 Apr 30-May 6;365(9470):1543-51. doi: 10.1016/S0140-6736(05)66455-0. PMID: 15866308.
50. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. Endocr Rev. 2013 Apr;34(2):171-208. doi: 10.1210/er.2012-1008. Epub 2012 Dec 13. PMID: 23238854; PMCID: PMC3610676.
51. Stute P, Neulen J, Wildt L. The impact of micronized progesterone on the endometrium: a systematic review. Climacteric. 2016 Aug;19(4):316-28. doi: 10.1080/13697137.2016.1187123. Epub 2016 Jun 9. PMID: 27277331.
52. Somboonporn W, Panna S, Temtanakitpaisan T, Kaewrudee S, Soontrapa S. Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women: systematic review and meta-analysis. Menopause. 2011 Oct;18(10):1060-6. doi: 10.1097/gme.0b013e31821606c5. PMID: 21720280.
53. European Medicines Agency. New measures to minimise risk of meningioma with medicines containing nomegestrol or chlormadinone (EMA/874908/2022). Amsterdam: EMA; 28 November 2022. https://www.ema.europa.eu/en/documents/referral/new-measures-minimise-risk-meningioma-medicines-containing-nomegestrol-or-chlormadinone_en.pdf (accessed 7 September 2026).
54. Henderson VW, St John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, et al. Cognitive effects of estradiol after menopause: A randomized trial of the timing hypothesis. Neurology. 2016 Aug 16;87(7):699-708. doi: 10.1212/WNL.0000000000002980. Epub 2016 Jul 15. PMID: 27421538; PMCID: PMC4999165.
55. Gleason CE, Dowling NM, Kara F, James TT, Salazar H, Ferrer Simo CA, et al. Long-term cognitive effects of menopausal hormone therapy: Findings from the KEEPS Continuation Study. PLoS Med. 2024 Nov;21(11):e1004435. doi: 10.1371/journal.pmed.1004435. Epub 2024 Nov 21. PMID: 39570992; PMCID: PMC11581397.
56. U.S. Food and Drug Administration. FDA approves labeling changes to menopausal hormone therapy products [press release]. Silver Spring (MD): FDA; 12 February 2026. https://www.fda.gov/news-events/press-announcements/fda-approves-labeling-changes-menopausal-hormone-therapy-products (accessed 7 September 2026).
57. Cummings SR, Ettinger B, Delmas PD, Kenemans P, Stathopoulos V, Verweij P, et al.; LIFT Trial Investigators. The effects of tibolone in older postmenopausal women. N Engl J Med. 2008 Aug 14;359(7):697-708. doi: 10.1056/NEJMoa0800743. PMID: 18703472; PMCID: PMC3684062.
58. Pinkerton JV, Harvey JA, Lindsay R, Pan K, Chines AA, Mirkin S, et al.; SMART-5 Investigators. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab. 2014 Feb;99(2):E189-98. doi: 10.1210/jc.2013-1707. Epub 2014

Jan 17. PMID: 24438370.
59. The NAMS 2020 GSM Position Statement Editorial Panel. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. Menopause. 2020 Sep;27(9):976-992. doi: 10.1097/GME.0000000000001609. PMID: 32852449.
60. Hirschberg AL, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, et al. Topical estrogens and non-hormonal preparations for postmenopausal vulvovaginal atrophy: An EMAS clinical guide. Maturitas. 2021 Jun;148:55-61. doi: 10.1016/j.maturitas.2021.04.005. Epub 2021 Apr 14. PMID: 33896654.
61. Crandall CJ, Hovey KM, Andrews CA, Chlebowski RT, Stefanick ML, Lane DS, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. Menopause. 2018 Jan;25(1):11-20. doi: 10.1097/GME.0000000000000956. PMID: 28816933; PMCID: PMC5734988.
62. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al.; VVA Prasterone Research Group. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. Menopause. 2016 Mar;23(3):243-56. doi: 10.1097/GME.0000000000000571. PMID: 26731686.
63. Bachmann GA, Komi JO; Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480-6. doi: 10.1097/gme.0b013e3181c1ac01. PMID: 20032798.
64. Holmberg L, Iversen OE, Rudenstam CM, Hammar M, Kumpulainen E, Jaskiewicz J, et al.; HABITS Study Group. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. J Natl Cancer Inst. 2008 Apr 2;100(7):475-82. doi: 10.1093/jnci/djn058. Epub 2008 Mar 25. PMID: 18364505.
65. Kenemans P, Bundred NJ, Foidart JM, Kubista E, von Schoultz B, Sismondi P, et al.; LIBERATE Study Group. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. Lancet Oncol. 2009 Feb;10(2):135-46. doi: 10.1016/S1470-2045(08)70341-3. Epub 2009 Jan 23. PMID: 19167925.
66. U.S. Food and Drug Administration. FDA Expert Panel on Menopause and Hormone Replacement Therapy for Women - 07/17/2025. Silver Spring (MD): FDA; 2025. https://www.fda.gov/patients/fda-expert-panels/fda-expert-panel-menopause-and-hormone-replacement-therapy-women-07172025 (accessed 7 September 2026).
67. U.S. Food and Drug Administration. HHS advances women's health, removes misleading FDA warnings on hormone replacement therapy [press release]. Silver Spring (MD): FDA; 10 November 2025. https://www.fda.gov/news-events/press-announcements/hhs-advances-womens-health-removes-misleading-fda-warnings-hormone-replacement-therapy (accessed 7 September 2026).
68. Makary MA, Nguyen CP, Høeg TB, Tidmarsh GF. Updated Labeling for Menopausal Hormone Therapy. JAMA. 2026 Jan 13;335(2):117-118. doi: 10.1001/jama.2025.22259. PMID: 41212720.
69. National Institute for Health and Care Excellence. Menopause: identification and management. NICE guideline NG23. London: NICE; 2015 (updated 7 November 2024 and 15 April 2026). https://www.nice.org.uk/guidance/ng23 (accessed 7 September 2026).
70. National Institute for Health and Care Excellence. Fezolinetant for treating moderate to severe vasomotor symptoms associated with menopause. Technology appraisal guidance TA1143. London: NICE; 31 March 2026. https://www.nice.org.uk/guidance/ta1143 (accessed 7 September 2026).
71. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016 Apr;19(2):109-50. doi: 10.3109/13697137.2015.1129166. Epub 2016 Feb 12. PMID: 26872610.
72. Panay N, Ang SB, Cheshire R, Goldstein SR, Maki P, Nappi RE; International Menopause Society Board. Menopause and MHT in 2024: addressing the key controversies - an International Menopause Society White Paper. Climacteric. 2024 Oct;27(5):441-457. doi: 10.1080/13697137.2024.2394950. Epub 2024 Sep 13. PMID: 39268862.
73. Mendoza N, Ramírez I, de la Viuda E, Coronado P, Baquedano L, Llaneza P, et al. Eligibility criteria for Menopausal Hormone Therapy (MHT): a position statement from a consortium of scientific societies for the use of MHT in women with medical conditions. MHT Eligibility Criteria Group. Maturitas. 2022 Dec;166:65-85. doi: 10.1016/j.maturitas.2022.08.008. Epub 2022 Aug 30. PMID: 36081216.
74. Panay N, Fenton A, Hamoda H, Hillard T, Islam R, Pedder H, et al.; IMS Recommendations Writing Group. International Menopause Society (IMS) recommendations and key messages on women's midlife health and menopause. Climacteric. 2025 Dec;28(6):634-656. doi: 10.1080/13697137.2025.2585487. Epub 2025 Dec 23. PMID: 41433054.
75. Panay N, Anderson RA, Bennie A, Cedars M, Davies M, Ee C, et al.; ESHRE, ASRM, CREWHIRL, and IMS Guideline Group on POI. Evidence-based guideline: premature ovarian insufficiency. Hum Reprod Open. 2024;2024(4):hoae065. doi: 10.1093/hropen/hoae065. Epub 2024 Dec 9. PMID: 39660328; PMCID: PMC11631070.
76. National Academies of Sciences, Engineering, and Medicine. The clinical utility of compounded bioidentical hormone therapy: a review of safety, effectiveness, and use. Washington (DC): The National Academies Press; 2020. doi: 10.17226/25791. https://nap.nationalacademies.org/catalog/25791 (accessed 7 September 2026).
77. Lee A. Fezolinetant: First Approval. Drugs. 2023 Aug;83(12):1137-1141. doi: 10.1007/s40265-023-01917-1. PMID: 37462862.
78. "The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause. 2023 Jun 1;30(6):573-590. doi: 10.1097/GME.0000000000002200. PMID: 37252752.
79. European Medicines Agency. Veoza (fezolinetant): EPAR - medicine overview. Amsterdam: EMA; 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/veoza (accessed 7 September 2026).
80. U.S. Food and Drug Administration. FDA adds warning about rare occurrence of serious liver injury with use of Veozah (fezolinetant) for hot flashes due to menopause [drug safety communication]. Silver Spring (MD): FDA; 12 September 2024 (updated 16 December 2024). https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-warning-about-rare-occurrence-serious-liver-injury-use-veozah-fezolinetant-hot-flashes-due (accessed 7 September 2026).
81. Schaudig K, Wang X, Bouchard C, Hirschberg AL, Cano A, Shapiro C M M, et al. Efficacy and safety of fezolinetant for moderate-severe vasomotor symptoms associated with menopause in individuals unsuitable for hormone therapy: phase 3b randomised controlled trial. BMJ. 2024 Nov 18;387:e079525. doi: 10.1136/bmj-2024-079525. Epub 2024 Nov 18. PMID: 39557487; PMCID: PMC11571049.
82. European Medicines Agency. Direct healthcare professional communication: Veoza (fezolinetant): risk of drug-induced liver injury and new recommendations on monitoring of liver function before and during treatment. Amsterdam: EMA; 2025 (agreed by PRAC 28 November

2024, disseminated 13 January 2025). https://www.ema.europa.eu/en/documents/dhpc/direct-healthcare-professional-communication-dhpc-veoza-fezolinetant-risk-drug-induced-liver-injury-new-recommendations-monitoring-liver-function-during-treatment_en.pdf (accessed 7 September 2026).
83. Medicines and Healthcare products Regulatory Agency. Fezolinetant (Veoza): risk of liver injury; new recommendations to minimise risk. Drug Safety Update. London: MHRA; 10 April 2025. https://www.gov.uk/drug-safety-update/fezolinetantv-veoza-risk-of-liver-injury-new-recommendations-to-minimise-risk (accessed 7 September 2026).
84. Medicines and Healthcare products Regulatory Agency. MHRA approves elinzanetant to treat moderate to severe vasomotor symptoms (hot flushes) caused by menopause [press release]. London: MHRA; 8 July 2025. https://www.gov.uk/government/news/mhra-approves-elinzanetant-to-treat-moderate-to-severe-vasomotor-symptoms-hot-flushes-caused-by-menopause (accessed 7 September 2026).
85. European Medicines Agency. Lynkuet (elinzanetant): EPAR - medicine overview. Amsterdam: EMA; 2025. https://www.ema.europa.eu/en/medicines/human/EPAR/lynkuet (accessed 7 September 2026).
86. U.S. Food and Drug Administration. Drugs@FDA: NDA 219469, Lynkuet (elinzanetant), approval action of 24 October 2025. Silver Spring (MD): FDA; 2025. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=219469 (accessed 7 September 2026).
87. U.S. Food and Drug Administration. Lynkuet (elinzanetant) capsules: prescribing information, revised August 2026 (DailyMed SPL version 10, published 4 August 2026). Silver Spring (MD): FDA; 2026. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f42884ff-7dff-419c-8a0c-affe2ed73818 (accessed 7 September 2026).
88. Bayer plc. Lynkuet 60 mg soft capsules: summary of product characteristics (date of revision of the text 3 August 2026; emc last updated 12 August 2026). Leatherhead: Datapharm, electronic medicines compendium; 2026. https://www.medicines.org.uk/emc/product/101980/smpc (accessed 7 September 2026).
89. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. Front Neuroendocrinol. 2013 Aug;34(3):211-27. doi: 10.1016/j.yfrne.2013.07.003. Epub 2013 Jul 17. PMID: 23872331; PMCID: PMC3833827.
90. Prague JK, Roberts RE, Comninos AN, Clarke S, Jayasena CN, Nash Z, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2017 May 6;389(10081):1809-1820. doi: 10.1016/S0140-6736(17)30823-1. Epub 2017 Apr 3. PMID: 28385352; PMCID: PMC5439024.
91. Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. Lancet. 2023 Apr 1;401(10382):1091-1102. doi: 10.1016/S0140-6736(23)00085-5. Epub 2023 Mar 13. PMID: 36924778.
92. Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, et al. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT. J Clin Endocrinol Metab. 2023 Jul 14;108(8):1981-1997. doi: 10.1210/clinem/dgad058. PMID: 36734148; PMCID: PMC10348473.
93. Neal-Perry G, Cano A, Lederman S, Nappi RE, Santoro N, Wolfman W, et al. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. Obstet Gynecol. 2023 Apr 1;141(4):737-747. doi: 10.1097/AOG.0000000000005114. Epub 2023 Mar 9. PMID: 36897180; PMCID: PMC10026946.
94. European Medicines Agency. Veoza: EPAR - product information (summary of product characteristics). Amsterdam: EMA; 2023 (revised 2025). https://www.ema.europa.eu/en/documents/product-information/veoza-epar-product-information_en.pdf (accessed 7 September 2026).
95. Iwai M, Nielsen J, Miyagawa M, Patton M, Bonate PL, Wang X, et al. In Vitro Evaluation of CYP-Mediated Metabolism of Fezolinetant and Pharmacokinetic Interaction Between Fezolinetant and Fluvoxamine in Healthy Postmenopausal Smokers and Nonsmokers. J Clin Pharmacol. 2025 Apr;65(4):508-519. doi: 10.1002/jcph.6157. Epub 2024 Nov 19. PMID: 39558800; PMCID: PMC11937985.
96. Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. JAMA. 2024 Aug 22;332(16):1343-54. doi: 10.1001/jama.2024.14618. Epub 2024 Aug 22. PMID: 39172446; PMCID: PMC11342219.
97. European Medicines Agency. Lynkuet (elinzanetant): EPAR - product information (summary of product characteristics). Amsterdam: EMA; 2025 (date of first authorisation 17 November 2025). https://www.ema.europa.eu/en/documents/product-information/lynkuet-epar-product-information_en.pdf (accessed 7 September 2026).
98. Panay N, Joffe H, Maki PM, Nappi RE, Pinkerton JV, Simon JA, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: A Phase 3 Randomized Clinical Trial. JAMA Intern Med. 2025 Nov 1;185(11):1319-1327. doi: 10.1001/jamainternmed.2025.4421. PMID: 40920404; PMCID: PMC12418220.
99. Cardoso F, Parke S, Brennan DJ, Briggs P, Donders G, Panay N, et al. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. N Engl J Med. 2025 Aug 21;393(8):753-763. doi: 10.1056/NEJMoa2415566. Epub 2025 Jun 2. PMID: 40454634.
100. Lewis JH, Andrade RJ, Larrey D, Horsmans Y, Anderson RA, Trajanovic M, et al. Liver Safety of the Dual Neurokinin-1/-3 Receptor Antagonist Elinzanetant. Drug Saf. 2026 Aug;49(8):985-1002. doi: 10.1007/s40264-026-01663-9. Epub 2026 Mar 18. PMID: 41849128; PMCID: PMC13354706.
101. Morga A, Ajmera M, Gao E, Patterson-Lomba O, Zhao A, Mancuso S, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. Menopause. 2024 Jan 1;31(1):68-76. doi: 10.1097/GME.0000000000002281. Epub 2023 Nov 27. PMID: 38016166; PMCID: PMC11812669.
102. Wojciechowski P, Kolonko K, Giannopoulou A, Smela B, Olewinska E, Bolling KR, et al. Comparative Efficacy of Elinzanetant Versus Other Non-Hormonal Pharmaceutical Therapies for the Treatment of Moderate-to-Severe Vasomotor Symptoms Associated With Menopause: A Network Meta-Analysis. BJOG. 2026 Mar 15. doi: 10.1111/1471-0528.70213. Epub 2026 Mar 15. PMID: 41834312.
103. Lee A. Elinzanetant: First Approval. Drugs. 2026 Jan;86(1):121-125. doi: 10.1007/s40265-025-02244-3. Epub 2025 Nov 12. PMID: 41222830; PMCID: PMC12799696.
104. Simon JA, Portman DJ, Kaunitz AM, Mekonnen H, Kazempour K, Bhaskar S, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. Menopause. 2013 Oct;20(10):1027-35. doi: 10.1097/GME.0b013e3182a66aa7. PMID: 24045678.
105. Joffe H, Guthrie KA, LaCroix AZ, Reed SD, Ensrud KE, Manson JE, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. JAMA Intern Med. 2014 Jul;174(7):1058-66. doi: 10.1001/jamainternmed.2014.1891. PMID: 24861828; PMCID: PMC4179877.
106. Freeman EW, Guthrie KA, Caan B, Sternfeld B, Co-

hen LS, Joffe H, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. JAMA. 2011 Jan 19;305(3):267-74. doi: 10.1001/jama.2010.2016. PMID: 21245182; PMCID: PMC3129746.
107. Guttuso T, Kurlan R, McDermott MP, Kieburtz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol. 2003 Feb;101(2):337-45. doi: 10.1016/s0029-7844(02)02712-6. PMID: 12576259.
108. Leon-Ferre RA, Novotny PJ, Wolfe EG, Faubion SS, Ruddy KJ, Flora D, et al. Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603). JNCI Cancer Spectr. 2020 Feb;4(1):pkz088. doi: 10.1093/jncics/pkz088. Epub 2019 Oct 21. PMID: 32337497; PMCID: PMC7050158.
109. Davis SR, Baber R, Panay N, Bitzer J, Perez SC, Islam RM, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. J Clin Endocrinol Metab. 2019 Oct 1;104(10):4660-4666. doi: 10.1210/jc.2019-01603. PMID: 31498871; PMCID: PMC6821450.