

The PearlPAK® Clinical Prescribing Reference

Oral Estriol-Based Hormone Therapy for Menopause-Related Cognitive Symptoms — Evidence Summary & Dosing Guide

FDA UPDATE — NOVEMBER 2025 Black box warnings removed from all menopausal hormone therapy products. Initiation recommended before age 60 or within 10 years of menopause onset. Labels being revised with individualized benefit-risk language.

SYMPTOM PREVALENCE 70% OF MENOPAUSAL WOMEN EXPERIENCE COGNITIVE SYMPTOMS <i>Brain fog, word retrieval difficulty, and slowed processing speed are among the most reported — and most undertreated — symptoms of menopause.</i> <i>[1] Voskuhl RR. Today Show, NBC, 2024, New York Times, 2025</i>	CLINICAL EVIDENCE CONTEXT Estriol & the Brain PHASE 2 RCT <i>Oral estriol improved cognition vs placebo at 12 months. Women treated scored higher on cognitive tests than placebo at 12 months, with reduced regional brain atrophy on MRI.</i> <i>[2] Voskuhl RR et al. Lancet Neurology, 2016; 15(1):35-46; MacKenzie-Graham A et al, Brain & Behavior 2018; (8(9):e01086</i> Note: Trial population women with MS. Cognitive symptoms results in healthy menopausal women submitted for publication (Voskuhl, 2026)	TIMING OF MHT INITIATION Critical Window EARLY MHT INITIATION ASSOCIATED WITH REDUCED COGNITIVE DECLINE <i>Observational data support a "critical window" — initiating MHT within 10 years of menopause or before age 60 is associated with greater cognitive benefit than later initiation.</i> <i>[3] Shao H et al. Neurology, 2012; [4] Whitmer RA et al. Neurology, 2011</i> Note: Evidence is observational (MHT broadly, not estriol-specific). No RCT evidence yet for AD prevention with MHT.
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MECHANISM — WHY ESTRIOL IS DIFFERENT

ERβ-SELECTIVE BINDING Estriol binds preferentially to estrogen receptor beta (ERβ) in brain cells. Estradiol binds to Era strongly, the breast-associated receptor. Standard MHT using estradiol (WHI, KEEPS-Cog) showed no cognitive benefit.	No CONVERSION TO ESTRONE Unlike estradiol, estriol is not converted to estrone (E1) — the estrogen associated with increased clotting factor synthesis and elevated VTE risk with oral administration.
LOWER BREAST TISSUE PROLIFERATION ERβ selectivity reduces proliferative signaling in breast tissue. Estriol does not stimulate breast tissue in the same manner as estradiol.	NEUROPROTECTIVE ACTIVITY ERβ activation in the CNS reduces neuroinflammation, induces remyelination, and increases synaptic function — mechanisms underlying cognitive benefit seen in Voskuhl’s research at UCLA.

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DOSING — INDIVIDUALIZED PROTOCOL

PearlPAK® combines **oral estriol (1–8mg/day)** and **micronized progesterone**, compounded through a licensed US pharmacy using standardized protocol and packaging. Dosing is **highly individualized** based on patient symptom profile, history, and clinical response. Progesterone is required for patients with an intact uterus. Our clinical team determines and manages all dosing in coordination with the referring provider.

CleopatraRX's licensed clinicians handle all dosing decisions, titration, and ongoing management. Referring providers are not required to prescribe or manage the compounding protocol independently.

ESTRIOL VS. STANDARD MHT — KEY DIFFERENCES

	PEARLPAK® (ESTRIOL)	STANDARD MHT (ESTRADIOL)
Primary Receptor	✓ ERβ	ERα + ERβ
Breast tissue exposure	✓ Lower — ERβ selective	✓ Higher — ERα mediated
Converts to Estrone	✓ No	✓ Yes — higher clotting risk with oral; lower with transdermal
VTE Risk	✓ Lower (mechanism-based)	✓ Higher with oral E2; lower with transdermal
Cognitive / brain benefit	✓ Primary indication	Not brain-targeted
Vasomotor relief	✓ Moderate-Good	✓ Good-Excellent
US availability	✓ Compounded only – licensed pharmacy	✓ FDA-approved (patches in shortage 2026)
European safety data	✓ 40+ years (Germany, France, UK)	✓ Decades of use

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PATIENT SELECTION

IDEAL CANDIDATE — ANY ONE OF BELOW

- Cognitive symptoms: brain fog, word retrieval, memory
- Within 10 years of menopause or under age 60
- APOE4 carrier or Alzheimer's family history *
- Prior MHT with inadequate cognitive response
- Breast cancer concern
- Estradiol sensitivity

** No clinical evidence that PearlPAK® treats or prevents Alzheimer's disease. Standard MHT controversial effect on risk of later dementia; PearlPAK has not been studied for this indication specifically.*

STANDARD MHT CONTRAINDICATIONS

- Active or history of estrogen-receptor positive breast cancer
- Active thromboembolic disease or high VTE risk
- Undiagnosed abnormal uterine bleeding
- Active liver disease or impaired hepatic function
- Known hypersensitivity to estriol or excipients

EXPECTED CLINICAL TIMELINE



Individual results may vary

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REFER A PATIENT TO CLEOPATRARX

HOW IT WORKS

CleopatraRX offers individualized, clinician-managed estriol therapy at \$147/month, all-inclusive. Our licensed team handles the consultation, dosing, compounding coordination, and ongoing patient management — keeping your referring relationship informed throughout.

OPTION 01 — EMAIL

Refer Directly

Send patient referrals to:

physician@cleopatrarx.com

Include patient name, contact, and brief clinical context.

OPTION 02 — PRESCRIPTION FORM

Submit a Prescription

Download and complete our prescription form: [Prescription Form Download](#)

INCLUDED IN \$147/MONTH

Initial Consultation

Individualized dosing

Compounding & dispensing

Monthly delivery

Ongoing clinical management

Patient support

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ESTRIOL — VOSKUHL RESEARCH & MECHANISM

- 1 Voskuhl RR. "Menopause and Hormonal Effects." NBC Today Show feature on PearlPAK® and menopausal cognitive symptoms, 2024. CleopatraRX.com press release, May 2024. New York Times Feature *Sex Hormones are Brain Hormones*, 2025.
- 2 Voskuhl RR, Wang H, Wu TC, Sicotte NL, Nakamura K, Kurth F, et al. Estriol combined with glatiramer acetate for women with relapsing-remitting multiple sclerosis: a randomized, placebo-controlled, phase 2 trial. *Lancet Neurol*. 2016 Jan;15(1):35– 46. doi: 10.1016/S1474-4422(15)00322-1.

Phase 2 RCT · n=158 women with RRMS · Cognitive improvement and reduced cerebral cortex brain atrophy at 12 months in estriol treated vs. placebo treated

- 3 Itoh N, Itoh Y, Meyer CE, et al. Neuroprotection in Cerebral Cortex Induced by the Pregnancy Hormone Estriol. Preprint / submitted for publication. Voskuhl RR, UCLA. Early findings show 12-month oral estriol treatment improves cognitive symptoms in otherwise healthy menopausal women.

Healthy menopausal women cognitive results, submitted for publication as of April 2026

- 4 Itoh N, Itoh Y, Meyer CE, Suen TT, et al. (Voskuhl RR). Estrogen receptor beta in astrocytes modulates cognitive function in mid-age female mice. *Nat Commun*. 2023 Sep 28;14(1):6044. doi: 10.1038/s41467-023-41820-5.

Identifies ERβ in astrocytes as key mechanistic target for estriol's neuroprotective effect

- 5 MacKenzie-Graham A, Brook J, Kurth F, Itoh Y, et al. (Voskuhl RR). Estriol-mediated neuroprotection in multiple sclerosis localized by voxel-based morphometry. *Brain Behav*. 2018 Sep;8(9):e01086. doi: 10.1002/brb3.1086.

Phase 2 RCT · n=111 women with MS · Reduced regional brain atrophy at 12 months in estriol treated vs. placebo treated

- 6 Voskuhl RR, Kuhle J, Siddarth P, Itoh N, Patel K, MacKenzie-Graham A. Decreased neurofilament light chain levels in estriol-treated multiple sclerosis. *Ann Clin Transl Neurol* 2022 Vol. 9 Issue 8 Pages 1316-1320. doi: 10.1002/acn3.51622.

Phase 2 RCT · n=111 women with MS · Lower blood biomarker of neurodegeneration at 12 months in estriol treated vs. placebo treated

MHT TIMING, COGNITION & ALZHEIMER'S RISK — OBSERVATIONAL DATA

- 7 Shao H, Breitner JCS, Whitmer RA, Wang J, Hayden K, et al. Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology*. 2012;79(18):1846–1852. doi: 10.1212/WNL.0b013e318271f823.
- 8 Whitmer RA, Quesenberry CP, Zhou J, Yaffe K. Timing of hormone therapy and dementia: the critical window theory revisited. *Ann Neurol*. 2011;69(1):163–169. doi: 10.1002/ana.22239.

Observational cohort · Kaiser Permanente · Supports critical window hypothesis for MHT initiation near menopause

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- 9 Gleason C. E. , Dowling N. M. , Wharton W., Manson J. E., Miller V. M., Atwood C. S., et al. Effects of Hormone Therapy on Cognition and Mood in Recently Postmenopausal Women: Findings from the Randomized, Controlled KEEPS-Cognitive and Affective Study. PLoS Med 2015 Vol. 12 Issue 6 Pages e1001833; discussion e1001833. doi: 10.1371/journal.pmed.1001833.

ESTRIOL SAFETY — EUROPEAN CLINICAL USE

- 10 Voskuhl R. All women with multiple sclerosis should start hormone replacement therapy at menopause unless contraindicated: Yes. Mult Scler. 2024 Aug;30(9):1107–1109. doi: 10.1177/13524585241246211.
Review safety and efficacy of estriol in health and disease
- 11 Kim S, Liva SM, Dalal MA, Verity MA, Voskuhl RR. Estriol ameliorates autoimmune demyelinating disease: implications for multiple sclerosis. Neurology. 1999 Apr 12;52(6):1230–1238. doi: 10.1212/wnl.52.6.1230.
Foundational preclinical study establishing estriol's neuroprotective mechanism

FDA POLICY UPDATE

- 12 U.S. Food & Drug Administration. FDA Drug Safety Communication: FDA removes boxed warning for all menopause hormone therapy products. FDA.gov. November 2025. [Pending final label revision as of Q1 2026.]
Confirms removal of black box warnings; recommends initiation before age 60 or within 10 years of menopause onset

Important Limitations Notice: References [7] and [8] are observational studies examining MHT broadly (primarily estradiol-based formulations) and are subject to healthy-user bias and confounding. They do not establish causation and are not specific to estriol or PearlPAK®. Reference [2] is a Phase 2 RCT in an MS population; findings are supportive but not directly generalizable to otherwise healthy menopausal women. The menopause-specific estriol trial (Reference [3]) is submitted for publication and has not yet undergone peer review. No randomized controlled trial has demonstrated that any MHT formulation prevents Alzheimer's disease. PearlPAK® is a compounded medication and is not FDA-approved as a standalone product. All prescribing decisions should reflect individualized clinical judgment.

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