NEWSLETTER JUNI 2026

FIRST TO KNOW

ESTETROL (E4) FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Schweizerische Gesellschaft für Gynäkologische Endokrinologie, Kontrazeption und Menopause

Simoncini T et al.

Estetrol (E4) for the treatment of moderate to severe vasomotor symptoms in postmenopausal women - Efficacy and safety results from the phase 3 E4COMFORT I multicenter, placebo-controlled study

Maturitas. 2026

BACKGROUND

Estetrol (E4), sold under the brand name Fylrevy®, was approved in the EU in 2026. On January 30, 2026, the EMA/CHMP issued a positive recommendation, and on March 27, 2026, the European Commission granted approval for its use as hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.

STUDY SUMMARY

The Phase 3 E4COMFORT I study evaluated the efficacy and safety of 15 and 20 mg doses of Estetrol (E4) versus a placebo over 12 weeks in 640 postmenopausal women aged 40–65 years who experienced at least seven moderate or severe hot flashes (VMS) daily or at least 50 per week. The study was multicenter, randomized, double-blind, placebo-controlled, and parallel-group with 1:1:1 randomization. The primary endpoints were changes in the frequency and severity of moderate-to-severe VMS after four and 12 weeks. Participants kept daily diaries to document the number of hot flashes, symptom severity, and medication use. Severity was defined as follows: 1 = mild, 2 = moderate, and 3 = severe. Weekly symptom severity was calculated as the mean of the daily scores. A mixed model for repeated measures (MMRM) with Dunnett's correction was used for statistical analysis. Reported least squares mean differences correspond to model-adjusted mean differences compared to placebo, accounting for repeated measurements and covariates.

Efficacy – Frequency: Both E4 doses significantly reduced weekly VMS frequency compared with placebo. After four weeks, the least squares (LS) mean difference versus placebo was −9.63 episodes per week for E4 15 mg ($p = 0.038$) and −14.94 episodes per week for E4 20 mg ($p < 0.001$). After 12 weeks, the figures were −16.41 ($p < 0.001$) and −22.49 ($p < 0.0001$), respectively.

Efficacy – Severity: Symptom severity decreased significantly. After four weeks: E4 15 mg: −0.27 versus placebo ($p = 0.0109$); E4 20 mg: −0.29 ($p = 0.0051$). After 12 weeks: −0.54 and −0.66, both $p < 0.0001$.

Responders: After 12 weeks, 82.5% of patients on E4 15 mg and 87.0% of patients on E4 20 mg achieved a ≥50% reduction in VMS frequency compared to 60.5% of patients on placebo (both $p < 0.001$).

≥75% reduction: 63.3% and 74.5%, respectively, versus 39.5%; $p < 0.001$ in both cases. Complete freedom from symptoms was observed in 32.5% of patients on E4 15 mg and 38.5% of patients on E4 20 mg, compared with 17.4% of patients on placebo ($p = 0.0014$ and $p < 0.001$, respectively).

Safety: Treatment-emergent adverse events (TEAEs) occurred more frequently in the E4 groups than in the placebo group overall. The most common treatment-associated TEAEs were endometrial events, particularly in women who had not undergone a hysterectomy and were receiving unopposed E4. Vaginal bleeding or spotting occurred in 47.6% of patients on E4 15 mg and 59.2% of patients on E4 20 mg, versus 10.6% of patients on placebo. Other common non-endometrial TEAEs included breast pain (8.0% and 10.8%, respectively), breast tenderness (4.2% and 5.6%), headache (6.6% and 4.7%), and nausea (2.3%-3.8% in both groups). Nipple pain and vaginal discharge were also reported. No venous thromboembolisms or cardiovascular events were reported in the E4 groups.

CONCLUSION

In conclusion, estetrol (E4) at 15 and 20 mg demonstrated a clinically and statistically significant reduction in moderate-to-severe vasomotor symptoms (VMS) as early as four weeks, with further improvement by week 12. The limitations of the E4COMFORT-I study include its comparatively short duration of 12 weeks and the lack of long-term data on cardiovascular and oncological safety. Additionally, no direct statistical comparison was performed between the 15-mg and 20-mg doses. In women who had not undergone a hysterectomy, Estetrol was administered unopposed. As expected, this led to an increased incidence of endometrium-related side effects and bleeding. However, this does not reflect routine clinical practice, in which Estetrol is combined with a progestin. Furthermore, the study population was predominantly white (89.2%), which may limit the generalizability of the findings to other ethnic groups. Overall, the data support Estetrol as an HRT option.