Metagenics®

Clinically Tested

Estrovera®

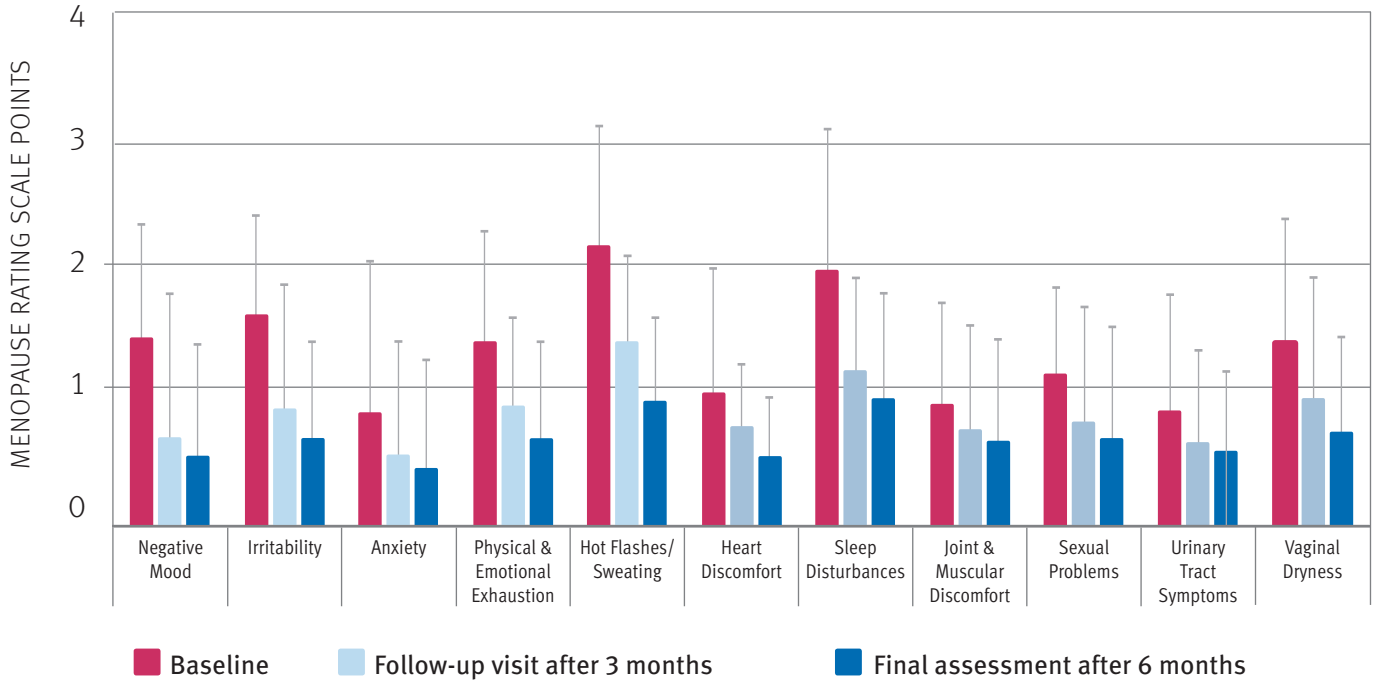
Featuring ERr 731®

Non-hormonal
menopausal symptom relief*

Significant reduction in menopausal symptom scores*†

- In a 2-year study with ERr 731®, up to 83% reduction of the total Menopause Rating Scale II (MRS II) total score was maintained from 60 weeks to 108 weeks*†[1]
- Significant improvements in MRS II total score and all 11 individual symptom scores reported over 12 weeks (compared to placebo)*[2]
- In a 6-month study, ERr 731® demonstrated progressive relief of multiple symptoms measured by the MRS II total score*[3]

– Open observational study of 252 peri- and postmenopausal women[3]
– MRS II total score at baseline, 3 months, and 6 months
– Significant decrease in MRS II total score, from an average of 14.5 points at baseline to 6.5 points ($p < 0.0001$) at 6 months*
– A notable improvement in health-related quality of life was also reported*



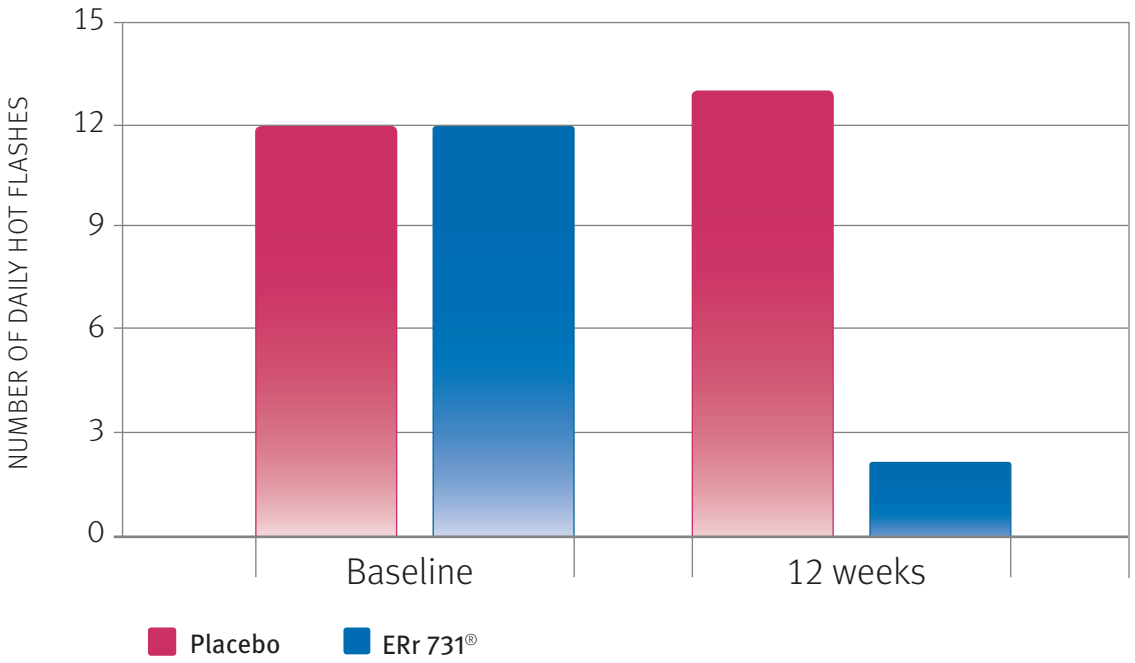
~75% Decrease in Median Daily Hot Flashes*††

Effective relief similar to average decrease with low-dose hormone therapies*

- In a 12-week study, ERr 731® reduced median number of daily hot flashes from 12 to 2*[4]
- Similar to average 75% decrease with low-dose hormone therapies*[5]
- Significant reduction in the number and severity of hot flashes in just 28 days (compared to placebo)*[4]
- Notably more effective than other plant-based products*[6]

– 12-week study of 112 perimenopausal women[4]

– ERr 731® subjects reported a significant decrease in the median number of daily hot flashes compared to subjects taking placebo*



†This estimated ratio is not included in the publication of cumulative results of a 12-week study followed by 2 48-week observational studies (OS). It is calculated from the mean change of the MRS II total score of 5.7 at the end of the first 48-week OS divided by the baseline score of 34. There was no change in total score from the end of the first OS to the end of the second OS. These results are from the ERr 731® subgroup only, which was administered ERr 731® daily for a total of 108 weeks. This calculation does not take into account some changes in study population over time.

††This estimated ratio is not included in the publication of a 12-week, multicenter, randomized, placebo-controlled clinical study of 112 postmenopausal women. It is calculated from the median change of 9 daily hot flashes divided by the median baseline value of 12 daily hot flashes.

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

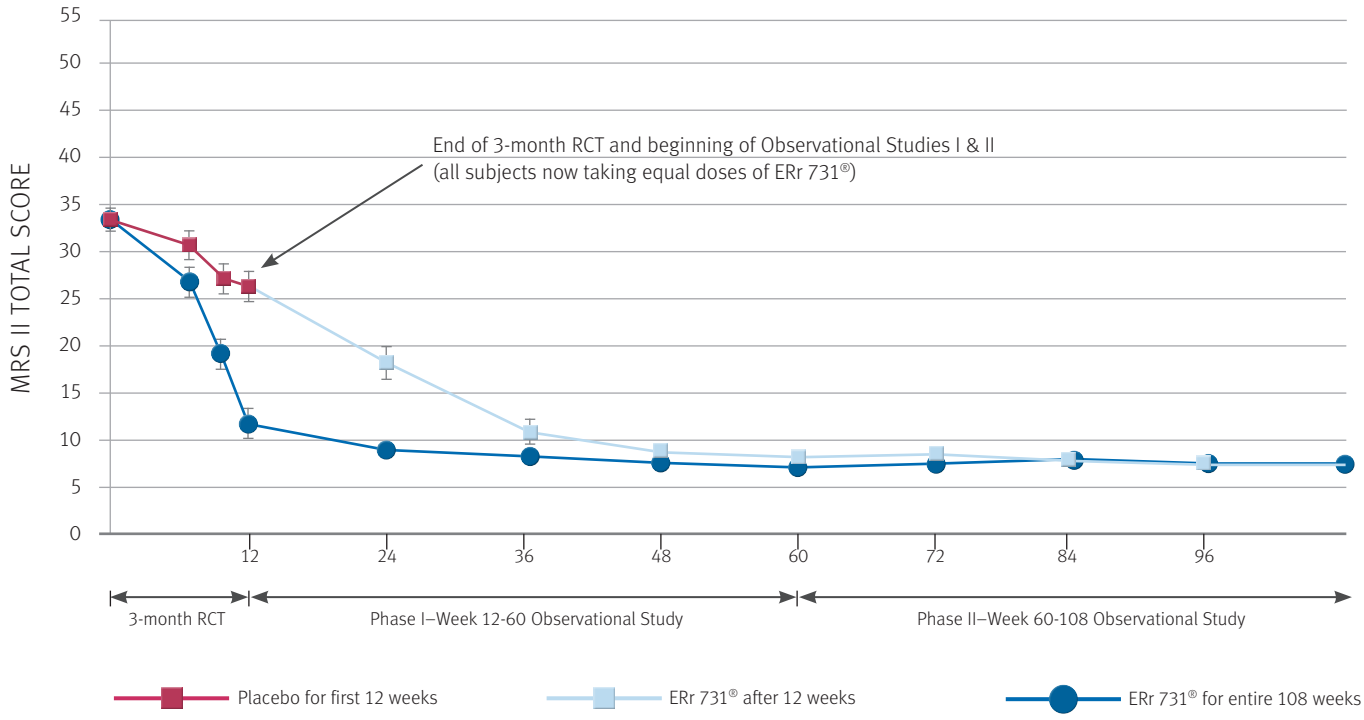
Extensive Scientific Validation

JAMA recently published a systematic review and meta-analysis that investigated the association between plant-based therapies and the reduction of the frequency of hot flashes and vaginal dryness.
The *JAMA* study included the assessment ERr 731®, an extract of Siberian rhubarb (*Rheum rhaponticum* L.) found to be associated with the reduction of hot flashes. ERr 731® is the key ingredient in Estrovera.[7]

Multiple Well-Designed Clinical Studies

- 2 multicenter, prospective, randomized, double-blind, placebo-controlled Phase III clinical trials (12 weeks)[2,4,8]
- 1- and 2-year open observational studies to demonstrate long-term efficacy and safety*[1]
- 6-month prospective, post-marketing surveillance study in 70 gynecological centers[3]
- Estrovera provides a clinically effective dose of ERr 731® in just 1 tablet daily*

– 12-week randomized, controlled trial followed by 96-week observational study of 109 perimenopausal women with hot flashes[1]
– ERr 731® arm showed a dramatic and statistically significant improvement in MRS II total scores compared to placebo*



1. Hasper I, Ventskovskiy BM, Rettenberger R, et al. Long-term efficacy and safety of the special extract ERr 731 of *Rheum rhaponticum* in perimenopausal women with menopausal symptoms. *Menopause*. 2009; 16(1):117-131.
2. Heger M, Ventskovskiy BM, Borzenko I, et al. Efficacy and safety of a special extract of *Rheu rhaponticum* (ERr 731) in perimenopausal women with climacteric complaints: a 12-week randomized, double-blind, placebo-controlled trial. *Menopause*. 2006; 13(5):744-759.
3. Kaszkin-Bettag M, Beck S, Richardson A, Heger PW, Beer AM. Efficacy of the special extract ERr 731 from rhapontic rhubarb for menopausal complaints: a 6-month open observational study. *Altern Ther Health Med*. 2008; 14(6):32-38.
4. Kaszkin-Bettag M, Ventskovsky BM, Solskyy S, et al. Confirmation of the efficacy of ERr 731® in perimenopausal women with menopausal symptoms. *Altern Ther Health Med*. 2009; 15(1):24-34.
5. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev*. 2004; (4):CD002978.
6. Albertazzi P. Menopause: alternatives to estrogen to manage hot flushes. *Gynecol Endocrinol*. 2005; 20(1):13-21.
7. Franco OH, Chowdbury R, Troup J et al. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. JAMA. 2016; 315: 2554-2563.
8. Kaszkin-Bettag M, Ventskovsky BM, Kravchenko A, et al. The special extract ERr 731 of the roots of Rheum rhaponticum decreases anxiety and improves health state and general wellbeing in perimenopausal women. *Menopause*. 2007; 14(2):270-283.
9. Chang JL, Montalto MB, Heger PW et al. Rheum rhaponticum Extract (ERr 731): Postmarketing Data on Safety Surveillance and Consumer Complaints. *Integr Med (Encinitas)*. 2016; 15: 34-39.

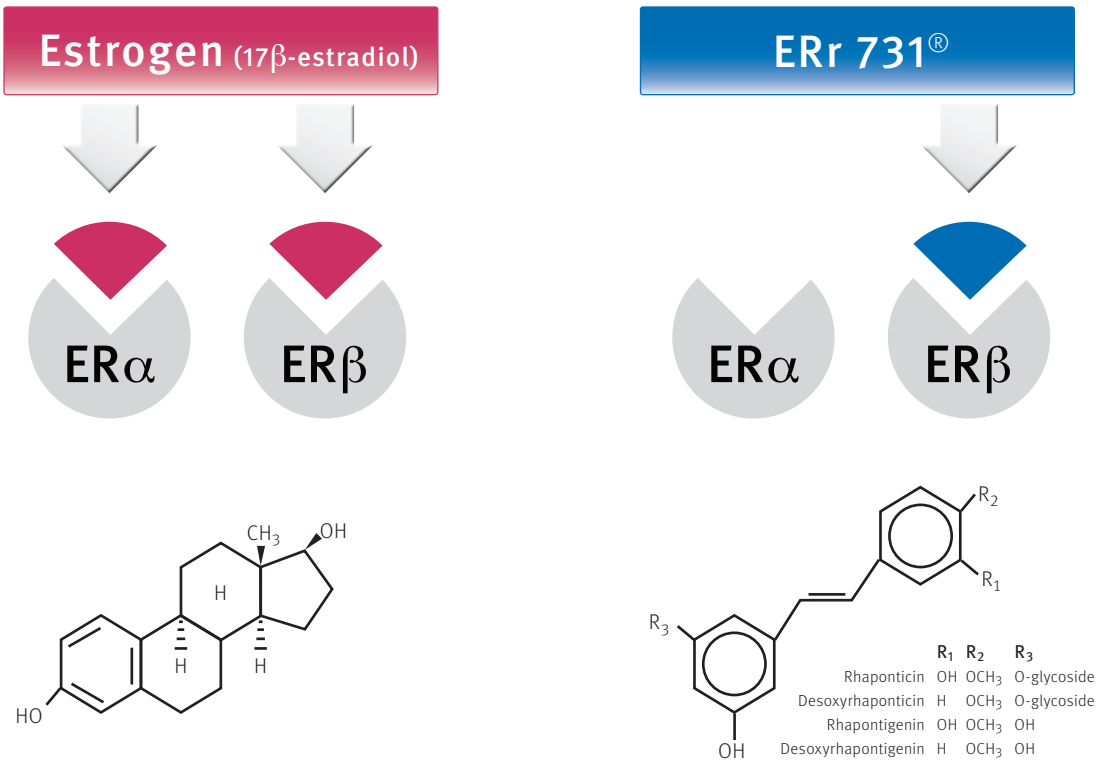
Exceptional Safety Profile*

Integrative Medicine: A Clinician's Journal (*IMCJ*) published results from a comprehensive post-marketing and customer complaints survey, which confirm the safety of ERr 731® as a non-hormonal therapy for the relief of common symptoms of menopause.*[9]

ERr 731® is a key ingredient in Estrovera. ERr 731® has been recommended by healthcare professionals in Europe since 1993.

- Multiple well-documented in vitro and in vivo studies for toxicology and metabolism demonstrate a high degree of safety*[10-14]
- No clinically relevant changes in safety parameters—including gynecological findings, vital parameters, and laboratory safety parameters associated with treatment after 108 weeks of clinical observation*[1]
- The clinical benefits of ERr 731® appear to be related to binding of ERβ as demonstrated in laboratory studies*[12,13]

– ERr 731®, the main ingredient in Estrovera, demonstrates selective affinity for ERβ in endometrial tissue.* [12,13]



10. Papke A, Kretzschmar G, Zierau O, Kaszkin-Bettag M, Vollmer G. Effects of the special extract ERr 731from *Rheum rhaponticum* on estrogen-regulated targets in the uterotrophy model of ovariectomized rats. *J Steroid Biochem Mol Biol.* 2009; 17(4-5):176-184.
11. Kaszkin-Bettag M, Richardson A, Rettenberger R, Heger PW. Long-term toxicity studies in dogs support the safety of the special extract ERr 731 from the roots of *Rheum rhaponticum*. *Food Chem Toxicol.* 2008; 46(5):1608-1618.
12. Wober J, Möller F, Richter T, et al. Activation of estrogen receptor-beta by a special extract of *Rheum rhaponticum* (ERr 731), its aglycones and structurally related compounds. *J Steroid Biochem Mol Biol.* 2007; 107(3-5):191-201.
13. Möller F, Zierau O, Jandausch A, Rettenberger R, Kaszkin-Bettag M, Vollmer G. Subtype-specific activation of estrogen receptors by a special extract of *Rheum rhaponticum* (ERr 731), its aglycones and structurally related compounds in U2OS human osteosarcoma cells. *Phytomedicine.* 2007; 11:716-726.
14. Keiler AM, Papke A, Kretzschmar G, Zierau O, Vollmer G. Long-term effects of the rhapontic rhubarb extract ERr 731 on estrogen-regulated targets in the uterus and on the bone in ovariectomized rats. *J Steroid Biochem Mol Biol.* 2012; 128(1-2):62-68.

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

Clinically Tested

Estrovera®

Featuring ERr 731®

Non-hormonal menopausal symptom relief*

Highly Efficacious

Up to 83% reduction in menopausal symptoms*†

Exceptional Safety Profile

ERr 731® recommended by healthcare professionals in Europe since 1993

Extensively Studied

Multiple well-designed, randomized, double-blind, placebo-controlled studies*

Simple Dosing

Well-tolerated, once-daily tablet*

†This estimated ratio is not included in the publication of cumulative results of a 12-week study followed by 2 48-week observational studies (OS). It is calculated from the mean change of the MRS II total score of 5.7 at the end of the first 48-week OS divided by the baseline score of 34. There was no change in total score from the end of the first OS to the end of the second OS. These results are from the ERr 731® subgroup only, which was administered ERr 731® daily for a total of 108 weeks. This calculation does not take into account some changes in study population over time.

Serving size: 1 Tablet

Rhapontic Rhubarb (*Rheum rhaponticum* L.) Root† Extract (ERr 731®) [providing 2.2 mg rhaponticin and 1 mg desoxyrhaponticin]	4 mg

Other Ingredients: Microcrystalline cellulose, stearic acid (vegetable), croscarmellose sodium, silica, and enteric coating (ethyl cellulose, ammonium hydroxide, hydroxypropylmethylcellulose, hydroxypropylcellulose, medium chain triglycerides, sodium alginate, oleic acid, and stearic acid).

Directions: Take one tablet with food and a glass of water once daily at the same time of day or as directed by your healthcare practitioner.

Form: 30 Tablets, 90 Tablets

Caution: Do not use if pregnant or nursing. This product is contraindicated for individuals with any known or suspected estrogen-dependent cancer. If taking medication, consult your healthcare practitioner before use.

This product is non-GMO, gluten free, and vegetarian.

†Also known as Siberian rhubarb root.

*** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.**

For more information, contact your Metagenics representative or call: **800.692.9400**

www.WhyEstrovera.com