



October 1, 2024

VIA EMAIL

Samuel A.A. Levine, Director
Serena Viswanathan, Associate Director
Bureau of Consumer Protection
Federal Trade Commission
600 Pennsylvania Ave. N.W.
Washington, D.C. 20580
slevine1@ftc.gov
sviswanathan@ftc.gov

Ann Oxenham, Director, Office of Compliance
Cara Welch, Director, Office of Dietary
Supplement Programs
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5001 Campus Drive
College Park, MD 20740
ann.oxenham@fda.hhs.gov
cara.welch@fda.hhs.gov

Re: Unsubstantiated and Unapproved Marketing for Equelle

Dear Mr. Levine, Ms. Viswanathan, Ms. Oxenham, and Dr. Welch:

Each day, approximately 6,000 women in the United States reach menopause,¹ a transition period often marked by a variety of disruptive symptoms ranging from hot flashes and nights sweats to anxiety, pain and exhaustion. Pharmavite, LLC guarantees that its soy-based pill, Equelle, will provide menopause relief and claims the product is “clinically shown” to treat numerous symptoms, including, among many others, severe hot flashes and excessive night sweats.



Sponsored
Equelle
https://www.equelle.com › hot-flash › treatment
Severe Hot Flashes Treatment - 94% Patient Satisfaction Rate
Backed by 20 Years of clinical research, Equelle® offers proven hot flash treatment & more.
Subscribe & save. No commitment - cancel anytime, we email you 3 days before each...

Sponsored
Equelle
https://www.equelle.com
Excessive Night Sweats | Get Rid of Night Sweats
Equelle® is a new clinically proven hormone free plant based night sweat relief supplement.
Subscribe & save. No commitment - cancel...
How Equelle Works - Check Out Our Reviews
Deal: Up to 26% off Purchase

Pharmavite makes these treatment claims without the FDA’s approval, and without competent and reliable scientific substantiation – despite having received an FTC Notice of Penalty Offenses Concerning Substantiation of Product Claims just last year.² In short, the company is deceiving millions of consumers with its false and deceptive marketing campaign.

A. Background

Equelle, which first launched in Japan in 2014 before launching in the United States in 2019,³ is an over-the-counter oral daily supplement that contains one active ingredient: S-equol, a plant-based, non-hormonal compound that is produced through Equelle’s “patented soy germ fermentation process” and that purportedly mimics estrogen.⁴

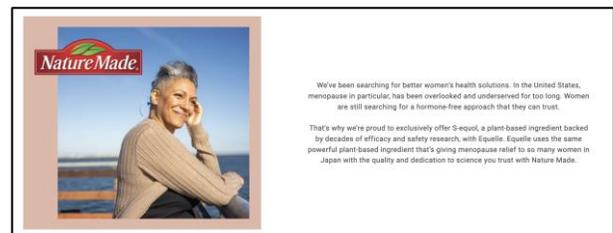
A one month’s supply of Equelle costs between \$37 and \$50, depending on whether a one-time purchase is made or whether a 30- or 90-day subscription plan is purchased.⁵ And according to the marketing, it takes 90 days to achieve optimal results and “feel like yourself again!”⁶ Since its introduction in the U.S., sales of Equelle have grown year after year.⁷

The Equelle brand is owned by Pharmavite, a California-based subsidiary of Otsuka Pharmaceutical Co. Ltd.,⁸ two companies that are no strangers to regulators and are well aware of their legal obligations to properly substantiate health claims. In addition to the FTC sending a Notice of Penalty Offenses Concerning Substantiation of Product Claims to both Pharmavite, as noted above, and Otsuka,⁹ both companies have been independently investigated for marketing products without sufficient substantiation. In 2009, the FTC investigated Pharmavite for advertising supplements as clinically proven to lower cholesterol without adequate substantiation.¹⁰ And in 2023, the FDA found that Otsuka was misleadingly advertising its drug Rexulti by overstating its ability to reduce depression without sufficient substantiation in violation of the Federal Food Drug & Cosmetic Act.¹¹

Of note, Pharmavite also owns the well-known supplement brand Nature Made®, a fact that Pharmavite includes in its marketing for Equelle presumably to build consumer trust.¹²



“From Nature Made®, America’s #1 Pharmacist Recommended Vitamin & Supplement Brand”



“Equelle uses the same powerful plant-based ingredient that’s giving menopause relief to so many women in Japan with the quality and dedication to science you trust with Nature Made.”

In addition to its website, Equelle is advertised in national television commercials, Google ads and on social media, among other places, and has been endorsed by actress Kate Walsh, famous for playing a doctor on Grey’s Anatomy,¹³ as well as others, including Chenoa Maxwell¹⁴ and Janine Delaney.¹⁵

B. Unsubstantiated and Unapproved Health and Disease-Treatment Claims

Throughout its marketing materials, Equelle is advertised as “clinically shown” to provide “menopause relief” and able to treat a variety of menopausal symptoms, including vasomotor symptoms (i.e., hot flashes, also called hot flushes, and night sweats), as well as insomnia and sleep disturbances, vaginal discomfort, anxiety, depression, and muscle and joint pain. The following are some examples.

Equelle Website¹⁶

The screenshot displays several sections of the Equelle website:

- Multi-symptom menopause relief. Guaranteed.** A dark green box with white text. Below the headline, it states: "Equelle is a revolutionary supplement, clinically shown to provide menopause support or your money back. †" and includes a "Get relief now →" button.
- Real results you can trust** A light green box with dark green text. It contains the text: "In randomized, clinical trials, women taking Equelle experienced significant improvements in menopausal symptom relief.^{3,4}" and a "Try Equelle" link.
- 2 tablets, once daily, for menopause relief in 90 days or less^{1-4,14}** A white box with a row of eight icons and their corresponding benefits: Fewer Hot Flashes, More Sleep, Alleviates Mood Swings, Reduces Vaginal Symptoms, Relieves Muscle Aches, Reduces Neck & Shoulder Stiffness, Supports Healthy Bones, and Supports Vascular Health[†].
- All-in-one SYMPTOM RELIEF** A dark green box with white text and icons. It lists: Fewer hot flashes, More sleep, Alleviates mood swings, Reduced vaginal symptoms, Relieves muscle aches, and Reduces neck & shoulder stiffness.
- Testimonial:** A light brown box with a quote: "I'm sleeping so much better and the hot flashes are so much less frequent. Mood swings are better too. I am so happy to have found something that works." attributed to "JESS, EQUELLE CUSTOMER" with a five-star rating.

Product Packaging



Google Ads

Sponsored
 Equelle
<https://www.equelle.com/hot-flash/treatment>
Severe Hot Flashes Treatment - 94% Patient Satisfaction Rate
 Backed by 20 Years of clinical research, Equelle® offers proven **hot flash treatment** & more.
 Subscribe & save. No commitment - cancel anytime, we email you 3 days before each...

Sponsored
 Equelle
<https://www.equelle.com>
Excessive Night Sweats | Get Rid of Night Sweats
 Equelle® is a new clinically proven hormone free plant based **night sweat relief** supplement.
 Subscribe & save. No commitment - cancel...
[How Equelle Works](#) · [Check Out Our Reviews](#)
Deal: Up to 26% off Purchase

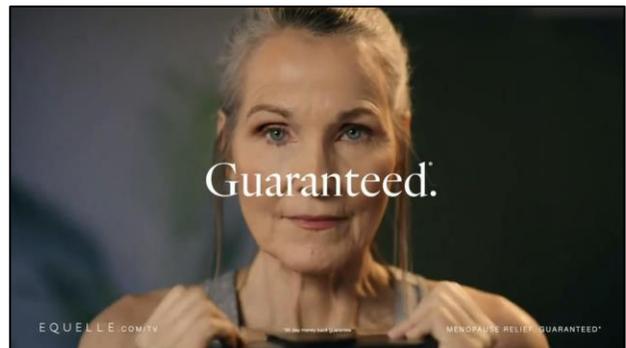
Sponsored
 Equelle
<https://www.equelle.com/menopause/relief>
Equelle® Official Site | Menopause Insomnia Relief
 Subscribe & save. No commitment - cancel anytime, we email you 3 days before each renewal.
 Equelle® offers a non-hormonal solution working for women just like you. See...

Sponsored
 Equelle
<https://www.equelle.com/vaginal/symptoms>
Menopausal Vaginal Relief
 94% Patient Satisfaction Rate — Subscribe & Save. No commitment - cancel anytime, we email you 3 days before each renewal.
[How Equelle Works](#) · [Check Out Our Reviews](#)
Deal: Up to 26% off Purchase

National Television Commercials¹⁷



Voiceover: *“At Equelle, we believe no symptom is too small”*
 Screen: *“Menopause relief for all.
 Menopause relief. Guaranteed.”*

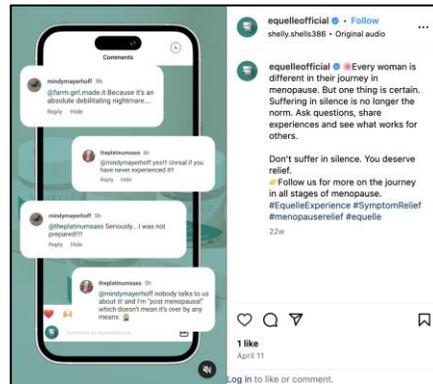


Voiceover: *“We’ve created clinically backed menopause relief that every woman deserves. ... Menopause Relief. Guaranteed.”*

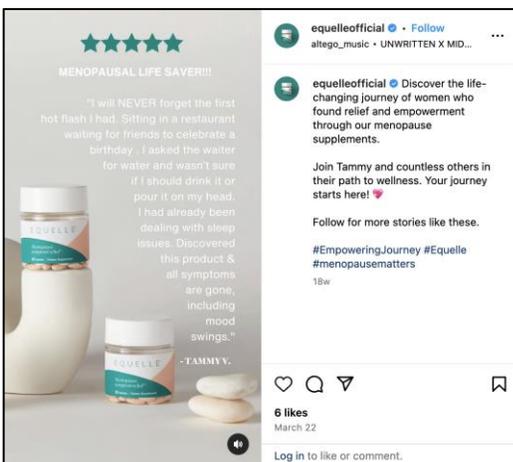
Equelle Social Media Platforms¹⁸



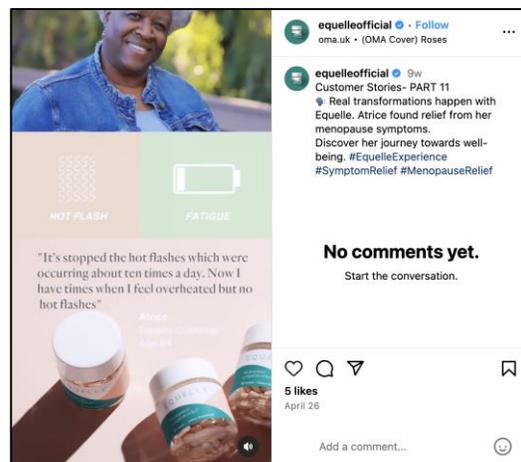
“This has been a life changing experience for me! I was a wreck a few months ago when I was taken off my HRT. I found this and have felt better ever since! Hot flashes are fading away...”



“Because it’s an absolute debilitating nightmare...Don’t suffer in silence. You deserve relief...#menopauserelief...”



“MENOPAUSAL LIFE SAVER!!! ‘I will NEVER forget the first hot flash I had. Sitting in a restaurant waiting for friends to celebrate a birthday. I asked the waiter for water and wasn’t sure if I should drink it or pour it on my head. I had already been dealing with sleep issues. Discovered this product & all symptoms are gone, including mood swings.’”



“It’s stopped the hot flashes which were occurring about ten times a day. Now I have times when I feel overheated but no hot flashes”

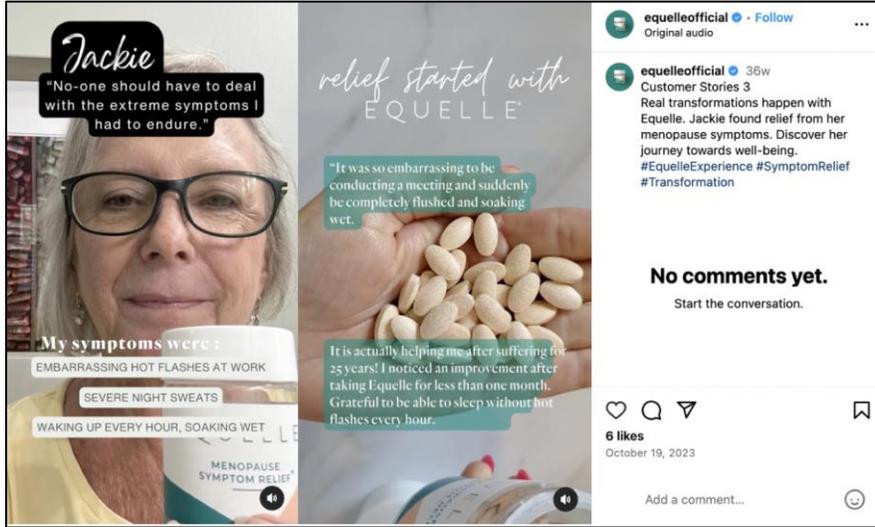


Image: “No-one should have to deal with the extreme symptoms I had to endure. ... My symptoms were: embarrassing hot flashes at work[,] severe night sweats[,] waking up every hour, soaking wet . . . It was so embarrassing to be conducting a meeting and suddenly be completely flushed and soaking wet. It is actually helping me after suffering for 25 years! I noticed an improvement after taking Equelle for less than one month. Grateful to be able to sleep without hot flashes every hour.”
 Caption: “Real transformations happen with Equelle.”



“...In a clinical study, women taking EQUELLE® for menopause symptom relief slept 50 minutes more on average per night vs. 16 minutes more on placebo...”



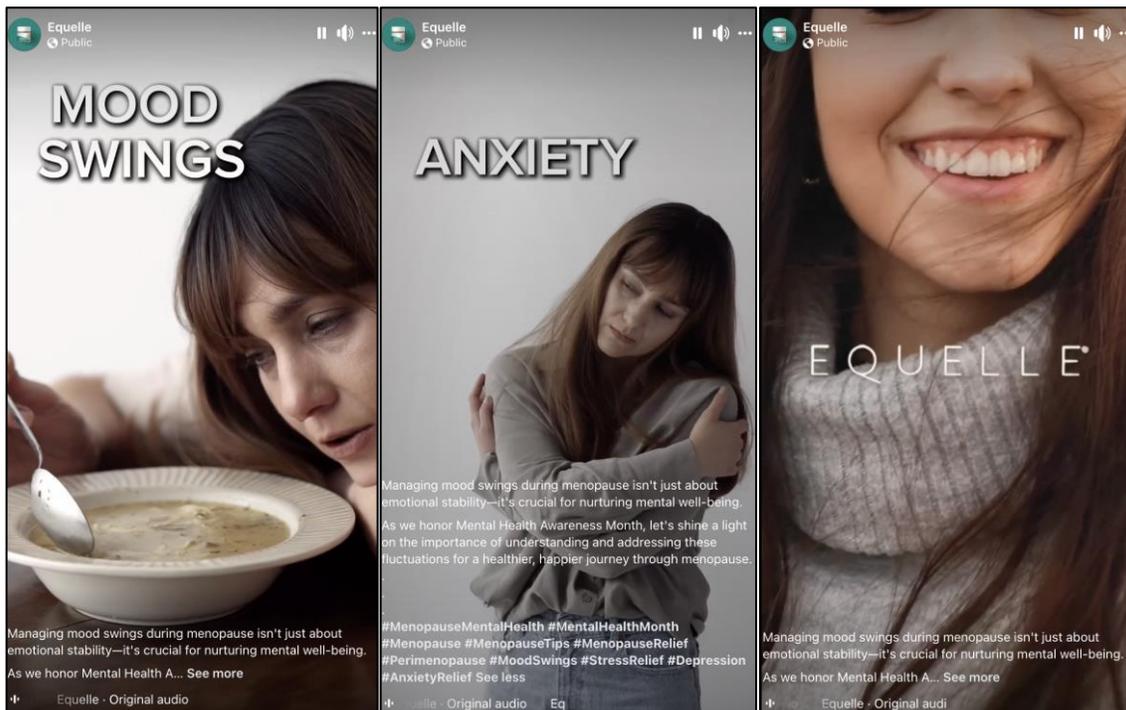
“Muscle aches can get in the way of a good night’s sleep. We’ve got relief ready. Enjoy Equelle everyday to help provide relief to the muscle aches and joint pain that comes along with menopause...”



“...Vaginal soreness and irritation are symptoms that can make some forms of intimacy unusually painful. #TryEQUELLE to help reduce vaginal irritation, soreness, and itching, and enjoy what should be one of the most sexually liberating periods of your life.”



“How are you feeling? Mood swings can become more frequent as you experience menopause. #TryEQUELLE to help manage symptoms like decreased moods...”



“Managing mood swings during menopause isn’t just about emotional stability – it’s crucial for nurturing mental well-being. As we honor Mental Health Awareness Month, let’s shine a light on the importance of understanding and addressing these fluctuations for a healthier, happier journey through menopause. ...#MenopauseRelief ... #StressRelief #Depression #AnxietyRelief”



“I went into early menopause because of the hysterectomy...My symptoms were: HOT FLASHES[,] WEIGHT GAIN[,] DEPRESSED...Found (Equelle) through an internet search after my doctor wanted to put me on Paxil...No more hot flashes, weight gain under control, feeling myself again”

Influencer Marketing¹⁹



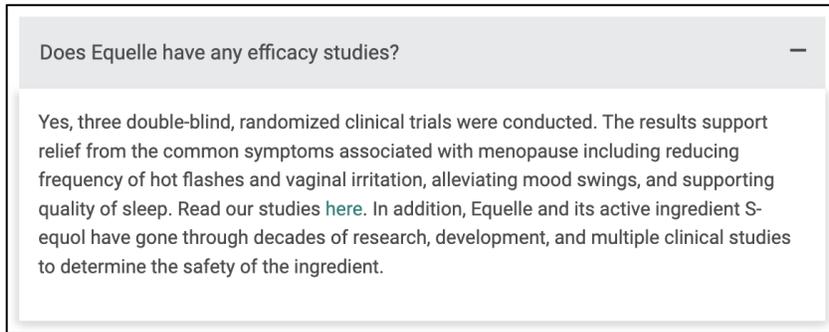
“...EQUELLE has helped me with my hot flashes and mood swings; I use to have them frequently throughout the day and night, but I’m starting to notice that they don’t happen as often...”

There are two primary problems with all of these health and disease-treatment claims, as well as the more than 800 examples TINA.org has catalogued and made available at www.truthinadvertising.org/evidence/equelle-menopause-claims/: (1) Equelle has not been approved by the FDA, and (2) the claims are not properly substantiated by competent and reliable scientific evidence.

With respect to FDA approval, the agency has made clear in numerous warning letters, as well as drug approvals, that claims that a product can treat menopause²⁰ and many of its symptoms, including, for example, moderate to severe hot flashes and night sweats,²¹ moderate to severe vaginal pain during intercourse and dryness,²² depression, anxiety and

insomnia,²³ and joint and muscle pain,²⁴ are drug claims requiring FDA approval, which Equelle does not have.

Moreover, the substantiation Pharmavite relies on for its treatment claims – three clinical trials referenced in its marketing materials²⁵ – do not amount to competent or reliable scientific evidence sufficient to substantiate Pharmavite’s health and disease-treatment claims.



For starters, all three trials were funded by Otsuka/Pharmavite and conducted by its employees. Further, one of the trials was a pilot study and thus only reached preliminary findings, among other issues. And the other two trials failed to substantiate Equelle’s claims about the product because of issues such as inadequate samplings, the formulation studied and deficient results.

These material limitations, as well as others, are discussed in more detail below.

2012 Hot Flash Pilot Study

The first trial provided on the Equelle website is a pilot study cited as the support for the claim that Equelle reduces hot flashes.²⁶

-5
fewer hot flashes per day ¹

1. Equelle is associated with a reduction in hot flashes.

In a double-blind, active comparator trial in postmenopausal women (N=102), Equelle provided clinically meaningful reductions in daily hot flash frequency as early as week 4^b

- Reductions in hot flash frequency was clinically meaningful at Week 4 (P=0.063), with continued reduction through Week 8
- Patients receiving Equelle experienced approximately 5 fewer hot flashes per day at Week 8 in comparison to 10.4 hot flashes per day at baseline

This eight-week pilot study contains numerous flaws that prevent it from properly substantiating Equelle’s unqualified marketing claims, including but not limited to the following:

- **Preliminary findings:** Because this was a pilot study, the findings were merely preliminary in nature. As the researchers stated, “[t]hese results must be considered preliminary and will require confirmation in a larger trial. ... Findings from this study warrant further investigation in a larger placebo-controlled, statistically powered study.”²⁷
- **Inadequate sampling:** Only 88 participants, the majority of whom were non-Hispanic/Latino white, completed the trial. Further, the study did not include a placebo group. As the researchers stated, “[s]tudy limitations include the absence of an inert placebo arm and the small sample size. ... As this study was designed to be an active comparator pilot study with a relatively small sample size, the statistical power was not strong enough to adjust for multiple comparisons or to demonstrate statistical significance of trends apparent in the intermediate time points.”²⁸
- **Different dose and formulation:** Study participants who were given an S-equol supplement were given one of three different doses (10 mg, 20 mg or 40 mg), each one also containing isoflavones (daidzein, genistein, and glycitein). Participants were instructed to consume the intervention twice per day.²⁹ Equelle’s current formulation consists of 10 mg S-equol and 240 mg of calcium and consumers are instructed to consume it once per day.³⁰
- **Inadequate duration:** The study was only eight weeks long. As the researchers stated, “[i]t is acknowledged that clinicians desire a length of ≥ 12 weeks to demonstrate the treatment’s efficacy on vasomotor symptoms.”³¹
- **Study results based on self-reported symptoms:** To evaluate Equelle’s effect on menopausal symptoms, the study relied on two subjective self-assessments: participants’ daily diary entries regarding the frequency and severity of their hot flashes, and participants’ responses to the Greene Climacteric Scale, a self-reporting questionnaire that asks the degree to which participants experience 21 symptoms of menopause on a 4-point scale (0 = Not at all, 1 = A little, 2 = Quite a bit, 3 = Extremely).³² Self-reporting introduces several biases (e.g., social desirability bias, recall bias, measurement error bias) that can pose major problems in medical research if not properly accounted for.³³ None of these biases were addressed in the study. Further, as researchers in other studies have noted, “a number of publications have highlighted that the simple measure of frequency and severity of vasomotor symptoms may not provide an overarching assessment of the overall efficacy of an intervention since the frequency/severity of vasomotor symptoms do not necessarily correlate with the degree of bother and quality of life of symptomatic menopausal women.”³⁴
- **Biased researchers and company funding:** The study was funded by Otsuka Pharmaceutical Co., Ltd. and was conducted by company employees.

2012 Muscle & Joint Pain Study

The second trial is cited as support for Equelle's claims that it can alleviate hot flashes, as well as improve muscle and joint aches and pains, in postmenopausal women.³⁵

<p>As published in the Journal of Women's Health</p> <p>A Natural S-equol Supplement Alleviates Hot Flashes and Other Menopausal Symptoms in Equol Nonproducing Postmenopausal Women</p> <p>Read the Article</p>	<p>2. Equelle improves muscle and joint aches and pains.</p> <p>In a multicenter, double-blind placebo-controlled trial (N=160) with 12 weeks of intervention (placebo or S-equol), Equelle provided statistically significant reductions in:</p> <ul style="list-style-type: none">• Neck or shoulder muscle stiffness as early as week 12 (P=0.004 vs baseline)
---	--

This 12-week study also contains numerous flaws that prevent it from properly substantiating Equelle's unqualified marketing claims, including but not limited to the following:

- **Inadequate sampling:** The study sampling was relatively small (just 126 participants completed the study) and homogenous (all were postmenopausal, equol nonproducing³⁶ Japanese women with stable menopause symptoms). The study also excluded those with "severe menopausal symptoms requiring treatment."³⁷ In addition, the study included women who had as few as one hot flush per day, with the average hot flush frequency among participants being three per day. According to the researchers, these numbers are "lower than the inclusion criteria of 7/day recommended by the U.S. Food and Drug Administration."³⁸
- **Different formulation:** The formulation provided to participants in the study consisted of 10 mg S-equol, as well as 11.4 mg isoflavones (daidzein, genistein, and glycitein). Equelle's current formulation consists of 10 mg S-equol and 240 mg of calcium.³⁹
- **Study results based on self-reported symptoms:** Like the 2012 Hot Flash Pilot Study, this study used subjective self-assessments to evaluate participants' menopause symptoms.
- **Inadequate results:** The study did not find any statistically significant improvements in daytime or nighttime sweating, or irritability. Further, while the study found that the treatment group showed a greater decrease in hot flush frequency than the placebo group, this decrease occurred only in women with at least three hot flushes per day (and a mean of 4.9 hot flushes per day). Finally, during the 6-week postintervention period, hot flush frequency and neck/shoulder muscle stiffness *increased* in the treatment group but not in the placebo group.⁴⁰
- **Biased researchers and company funding:** The study was funded by Otsuka Pharmaceutical Co., Ltd. and was conducted by company employees.

2009 Mood Study

The third trial is cited as support for Equelle’s claims that it can relieve menopausal symptoms.⁴¹



Like the first two trials, this 12-week study contains numerous flaws that prevent it from properly substantiating Equelle’s unqualified marketing claims, including but not limited to the following:

- **Inadequate sampling:** The study sampling was small (only 39 premenopausal, 25 perimenopausal and 70 postmenopausal women participated in the study) and homogenous (all were Japanese women). As the researchers noted, “Japanese menopausal women with high soy intake have fewer vasomotor symptoms than their North American counterparts do.”⁴²
- **Different formulation:** The formulation provided to participants in the study – either once per day or three times per day, depending on which treatment group they were in – consisted of 10 mg S-equol, 0.8 mg daidzein, 2.0 mg genistein and 4.5 mg glycitein.⁴³ Equelle’s current formulation consists of 10 mg S-equol and 240 mg of calcium taken once per day.
- **Study results based on self-reported symptoms:** Like both of the 2012 studies, this study used subjective self-assessments to evaluate participants’ menopause symptoms.
- **Inadequate results:** The study found significant improvements in mood-related symptoms of menopause, but only in those who were given the treatment three times per day *and* were equol nonproducers⁴⁴ (a total of 29 participants). As the study noted, the lack of significant differences between the treatment group that received 10mg of equol per day and the placebo groups “suggest that a one-time dose of 10 mg equol supplement is insufficient. Given the rapid pharmacokinetic elimination of the equol supplement, it is likely that administration several times daily is required for effectiveness.”⁴⁵ Notably, the company tells consumers to take just one serving of Equelle (i.e., 10mg S-equol) per day.⁴⁶
- **Company funding:** The study was funded by Otsuka Pharmaceutical Co., Ltd.

The rest of the “clinical research” listed on the Equelle website is either (1) not published,⁴⁷ (2) did not study the effects of S-equol or Equelle on menopausal symptoms,⁴⁸ or (3) not a clinical trial.⁴⁹

In short, Equelle does not have the necessary substantiation for any of its health and disease-treatment claims, a fact that is supported by numerous experts in the field, including The Menopause Society.⁵⁰

It is also troubling that the company, while featuring women of various races and ethnic backgrounds in its marketing campaign, as shown in the examples above, only studied Japanese women in both of its clinical trials. The exclusion of all other races and ethnicities is of concern not only because the company’s unqualified marketing for its “clinically shown”⁵¹ and “clinically validated”⁵² supplements is directed at women of all races and ethnicities, but because women of different races experience menopause differently.⁵³ For example, some studies have found that Japanese women are less likely to experience hot flashes than Western women.⁵⁴ And other studies have found that Japanese women reach menopause later than white, Black, Hispanic and Chinese women do.⁵⁵ Even among Asian women, there are more than 30 different sub-ethnic groups that have variations in the menopausal symptom experience.⁵⁶

C. Conclusion

Approximately two million women enter menopause each year in the United States, the vast majority of whom experience symptoms of varying type and severity.⁵⁷ It is, therefore, not surprising that the menopause supplement industry is a multibillion-dollar industry that is expected to grow to more than \$22 billion by 2028.⁵⁸ Pharmavite is targeting this susceptible population of consumers to exploit their vulnerabilities with a deceptively marketed supplement. As an established company that is well aware of its legal responsibility to ensure it has appropriate substantiation and approval in order to make drug claims, there is simply no excuse for Pharmavite’s multiple violations of law. TINA.org urges the FTC and FDA to open investigations into the Equelle brand and take appropriate enforcement action.

Sincerely,



Laura Smith, Esq.
Legal Director
Truth in Advertising, Inc.



Bonnie Patten, Esq.
Executive Director
Truth in Advertising, Inc.

Cc via email: Christine Burdick-Bell, General Counsel, Pharmavite

¹ Society for Women’s Health Research, Menopause, https://swhr.org/health_focus_area/menopause/; Pausing to Learn More About Menopause, Mayo Clinic Health System (Nov. 30, 2021), <https://www.mayoclinichealthsystem.org/hometown-health/speaking-of-health/too-embarrassed-to-ask-part-3>; Press Release, Equelle, Kate Walsh Partners With Women’s Dietary Supplement Brand EQUELLE® to Modernize Menopause Conversation (Sept. 19, 2019), <https://www.prnewswire.com/news-releases/kate-walsh-partners-with-womens-dietary-supplement-brand-equelle-to-modernize-menopause-conversation-300921434.html>.

While TINA.org understands and appreciates that individuals who do not identify as women may also experience menopause, the term women is used to reflect the marketing at issue.

² List of April 2023 Recipients of the FTC’s Notice of Penalty Offenses Concerning Substantiation of Product Claims, https://www.ftc.gov/system/files/ftc_gov/pdf/Published-list-Recipients.pdf.

³ Equelle: About Us, <https://equelle.com/pages/about-us>; Press Release, Equelle, Introducing EQUELLE®: A New Non-Hormonal Supplement for Menopause Symptom Relief (Apr. 11, 2019), <https://www.prnewswire.com/news-releases/introducing-equelle-a-new-non-hormonal-supplement-for-menopause-symptom-relief-300830024.html>.

⁴ Equelle Menopause Multi-Symptom Relief, <https://equelle.com/products/equelle>; How Does Equelle Work?, <https://equelle.com/pages/how-it-works>; Equelle Frequently Asked Questions, <https://equelle.com/a/faqs>.

⁵ Equelle Menopause Multi-Symptom Relief, <https://equelle.com/products/equelle>.

⁶ *Id.*

⁷ Otsuka Integrated Report 2022, at 37, https://www.otsuka.com/en/ir/library/pdf/annual/2022_all_a4.pdf.

⁸ Equelle: About Us, <https://equelle.com/pages/about-us>; Equelle Product Story, <https://www.otsuka.co.jp/en/two-core-businesses/stories/equelle/>; Pharmavite: What We Make - Equelle, <https://www.pharmavite.com/what-we-make/equelle/>; Pharmavite Who We Are, <https://www.pharmavite.com/who-we-are/>; Otsuka: Pharmavite, <https://www.otsuka-america.com/company/pharmavite.html>; Otsuka Companies, <https://www.otsuka-america.com/company/>; Press Release, Otsuka Pharmaceutical, EQUELLE: Dietary Supplement to Support Women’s Health Expansion of US Business Through Launch of Sales Via D-to-C Channel (Apr. 12, 2019), https://www.otsuka.co.jp/en/company/newsreleases/2019/20190412_1.html; Press Release, Otsuka Pharmaceutical, US Launch of EQUELLE, a Dietary Supplement to Support Women’s Health (Oct. 31, 2017), https://www.otsuka.co.jp/en/company/newsreleases/2017/20171031_1.html.

⁹ List of April 2023 Recipients of the FTC’s Notice of Penalty Offenses Concerning Substantiation of Product Claims, https://www.ftc.gov/system/files/ftc_gov/pdf/Published-list-Recipients.pdf.

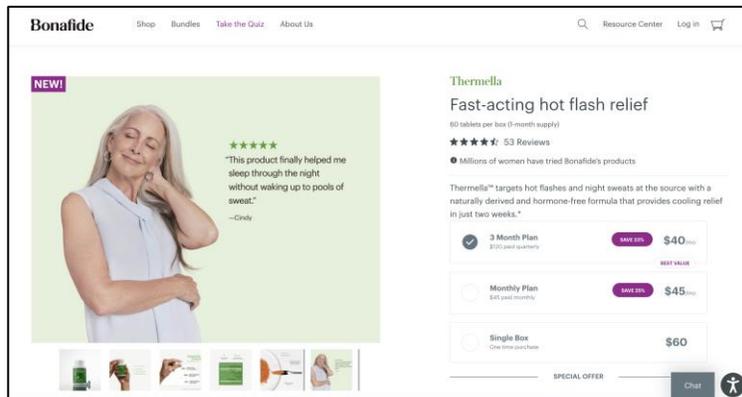
¹⁰ Closing Letter from FTC to Pharmavite Re: Advertising for NatureMade CholestOff, Matter No. 0723233 (Apr. 16, 2009), https://www.ftc.gov/sites/default/files/documents/closing_letters/pharmavite-llc/090416cholestoffclosingletter.pdf.

¹¹ Letter from FDA to Otsuka Pharm. Re: NDA 205422, REXULTI® (brexpiprazole) tablets, for oral use, MA 772, 791 (Oct. 31, 2023), <https://www.fda.gov/media/173730/download?attachment>; Letter from FDA to Otsuka Pharm. Re: NDA 205422, REXULTI® (brexpiprazole) tablets, for oral use, MA 772, 791 (Dec. 20, 2023), <https://www.fda.gov/media/175161/download?attachment>.

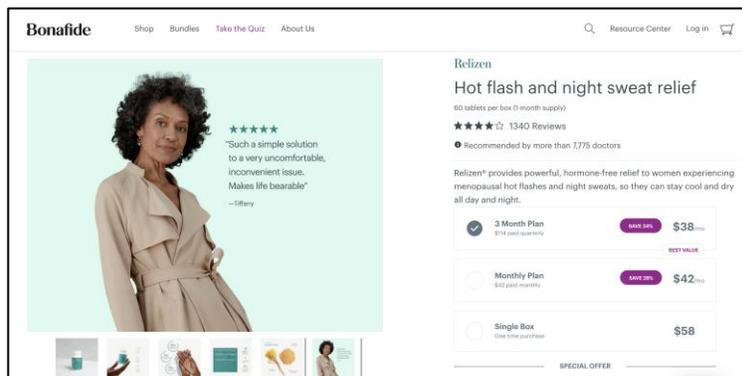
In 2008, 13 states and the District of Columbia sued Otsuka for, among other things, promoting the drug Abilify for pediatric use when the product was not approved for use in children, resulting in a \$4+ million settlement. Press Release, Dept. of Just., Otsuka to Pay More Than \$4 Million to Resolve Off-Label

Marketing Allegations Involving Ability (Mar. 27, 2008), https://www.justice.gov/archive/opa/pr/2008/March/08_civ_244.html#:~:text=Today's%20settlement%20resolves%20government%20allegations,to%20treat%20dementia%2Drelated%20psychosis.

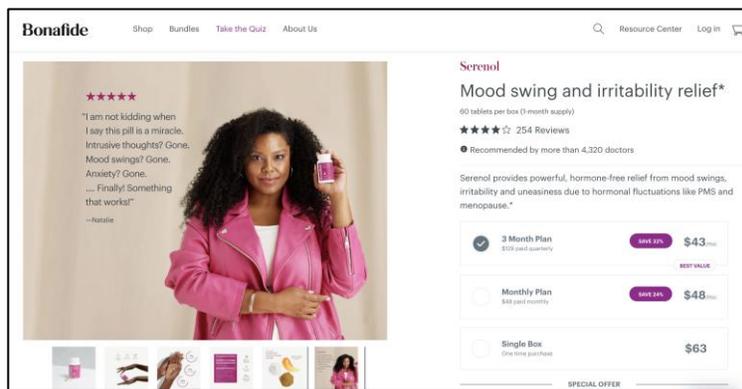
¹² Equelle: About Us, <https://equelle.com/pages/about-us>. Pharmavite also owns another menopause supplement brand, Bonafide, which it also markets as, among other things, able to relieve hot flashes, night sweats, and anxiety. See Pharmavite, Bonafide, <https://www.pharmavite.com/what-we-make/bonafide/>; Hello Bonafide, <https://hellobonafide.com/>; Bonafide Thermella, Fast-acting hot flash relief, <https://hellobonafide.com/products/thermella>; Bonafide Relizen, Hot flash and night sweat relief, <https://hellobonafide.com/products/relizen>; Bonafide Serenol, Mood swing and irritability relief*, <https://hellobonafide.com/products/serenol>.



“Thermella targets hot flashes and night sweats at the source with a naturally derived and hormone-free formula that provides cooling relief in just two weeks... ‘This product finally helped me sleep through the night without waking up to pools of sweat.’”



“Relizen provides powerful, hormone-free relief to women experiencing menopausal hot flashes and night sweats, so they can stay cool and dry all day and night. ... ‘Such a simple solution to a very uncomfortable, inconvenient issue. Makes life bearable.’”



“Serenol provides powerful, hormone-free relief from mood swings, irritability and uneasiness due to hormonal fluctuations like PMS and menopause... ‘I am not kidding when I say this pill is a miracle. Intrusive thoughts? Gone. Mood swings? Gone. Anxiety? Gone. ... Finally! Something that works!’”

As such, an investigation into Pharmavite’s marketing directed at menopausal women should also include an investigation into its Bonafide brand.

¹³ CoveyClub, @coveyclub, Instagram (June 7, 2021), <https://www.instagram.com/p/CP1w-h7Icl5/>; Equelle (@equelleofficial), Instagram (Nov. 15, 2019), <https://www.instagram.com/p/B45Pr2vDiC2/>; Kate Walsh (@katewalsh), Instagram (Oct. 28, 2019), https://www.instagram.com/p/B4LGdULHXOs/?utm_source=ig_web_copy_link&igsh=MzRIODBiNWF1ZA==; Press Release, Pharmavite, Kate Walsh Partners With Women’s Dietary Supplement Brand Equelle® to Modernize Menopause Conversation (Sept. 19, 2019), <https://www.pharmavite.com/perspectives/news/kate-walsh-partners-with-womens-dietary-supplement-brand-equelle-to-modernize-menopause-conversation/>.

¹⁴ Equelle (@equelleofficial), Instagram (Oct. 15, 2021), <https://www.instagram.com/p/CVELetTvESu/>.

¹⁵ Janine Delaney (@janine_delaney), Instagram, https://www.instagram.com/Janine_delaney/; Equelle (@equelleofficial), Instagram (Oct. 25, 2019), <https://www.instagram.com/p/B4DATTDjd73/>.

¹⁶ Equelle, <https://equelle.com/>; Equelle Menopause Multi-Symptom Relief, <https://equelle.com/products/equelle>.

¹⁷ Equelle TV Spot, ‘Hot Flashes,’ <https://www.ispot.tv/ad/548z/equelle-hot-flashes>; Equelle TV Spot, ‘Yeah, Right,’ <https://www.ispot.tv/ad/5U6m/equelle-yeah-right>.

¹⁸ Equelle (@equelleofficial), Instagram (Apr. 19, 2024), https://www.instagram.com/reel/C59FJmeOrM_/?utm_source=ig_web_copy_link&igsh=MzRIODBiNWF1ZA%3D%3D; Equelle (@equelleofficial), Instagram (Apr. 11, 2024), https://www.instagram.com/reel/C5pFm8cL0O5/?utm_source=ig_web_copy_link&igsh=MzRIODBiNWF1ZA%3D%3D; Equelle (@equelleofficial), Instagram (Mar. 22, 2024), <https://www.instagram.com/p/C41B818u6TY/>; Equelle (@equelleofficial), Instagram (Apr. 26, 2024), https://www.instagram.com/reel/C6Pwdy1LPY2/?utm_source=ig_web_copy_link&igsh=MzRIODBiNWF1ZA%3D%3D; Equelle (@equelleofficial), Instagram (Oct. 19, 2023), https://www.instagram.com/reel/CymK1zwgF_l/?igsh=MTh6eG9mNGtuZ2plZA%3D%3D; Equelle (@equelleofficial), Instagram (Aug. 15, 2021), <https://www.instagram.com/p/CSm6y5kBhny/>; Equelle (@equelleofficial), Instagram (Apr. 17, 2020), https://www.instagram.com/p/B_FnVdqj1U2/; Equelle, Facebook (Jan. 20, 2022), <https://www.facebook.com/photo/?fbid=1090636368439505&set=pb.100063741153214.-2207520000>; Equelle® (@EQUELLEofficial), Twitter (Oct. 26, 2022, 12:00 PM), <https://x.com/EQUELLEofficial/status/1585300222317678593>; Equelle, Facebook Reel,

<https://www.facebook.com/reel/3575064369382896>; Equelle (@equelleofficial), Instagram (Oct. 5, 2023), <https://www.instagram.com/p/CyCBLcFgUfP/>.

Of note, Pharmavite also encourages Equelle users to deceptively market for the brand on social media. See, e.g., Equelle (@equelleofficial), Instagram (Jan. 11, 2022), <https://www.instagram.com/p/CYm46chAa-A/>.

¹⁹ @fabnfitbycarla, Instagram (Oct. 28, 2021), <https://www.instagram.com/p/CVILUG1v2HP/>.

²⁰ See, e.g., FDA Warning Letter to Bonagens (Nov. 17, 2020), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/bonagens-609905-11172020> (“Examples of some of the website claims that provide evidence that your products are intended for use as drugs include:… ‘alleviate the effects of menopausal syndrome … menopausal and sleeping disorders’”).

²¹ See Veozah Highlights of Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216578s000lbl.pdf (“VEOZAH is a neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause.”); Brisdelle Highlights of Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204516s000lbl.pdf (“BRISDELLE is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.”).

Moderate vasomotor symptoms are generally defined as the sensation of heat with sweating but able to continue activities. Severe vasomotor symptoms are generally defined as the sensation of heat with sweating causing cessation of activities. FDA, Draft Guidance for Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms (Jan. 2003), <https://www.fda.gov/media/71359/download>; Ramandeep Bansai & Neelam Aggarwal, *Menopause Hot Flashes: A Concise Review*, 10 J. Mid-Life Health 6 (2019), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6459071/>; Lora Todorova et al., *Prevalence and Impact of Vasomotor Symptoms Due to Menopause Among Women in Brazil, Canada, Mexico, and Nordic Europe: A Cross-Sectional Survey*, 30 Menopause 1179 (2023), https://journals.lww.com/menopausejournal/fulltext/2023/12000/prevalence_and_impact_of_vasomotor_symptoms_due_to.3.aspx#:~:text=VMS%20were%20categorized%20as%20mild,Food%20and%20Drug%20Administration%20definitions.&text=Mild%20VMS%20were%20defined%20as,causing%20cessation%20of%20an%20activity.

²² OSPHENA Highlights of Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203505s015lbl.pdf (“INDICATIONS AND USAGE... The treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause[;] The treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause.”).

²³ See, e.g., FDA Warning Letter to Enlifta, LLC (Feb. 18, 2021), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/enlifta-llc-612253-02182021> (“Examples of some of the website claims that provide evidence that your “Enlifta Mood Elevator” and “Enlifta Anxiety” are intended for use as drugs include: ... ‘The Only Doctor Designed Depression Pill, Enlifta Depression Supplement – Best Natural Antidepressant.’ ... ‘ENLIFTA: OUR #1 BEST-SELLING DEPRESSION SUPPLEMENT’ ... ‘A new natural supplement is providing relief to people across America suffering with severe anxiety and stress!’ ... ‘Unlike other supplements and prescription medications, Enlifta Anxiety helps to manage stress and associated anxiety without causing excess fatigue...’ ... ‘... for the treatment of insomnia and anxiety’”).

²⁴ See, e.g., FDA Warning Letter to The Truth Company, LLC (Nov. 14, 2022), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/truth-company-llc-611501-11142022> (“Examples of some of the website claims that provide evidence that your products are intended for use as drugs include: ... ‘zuRelief: Reduce Pain...’ ... ‘I am an MD and there is no product on the conventional over the counter market that approaches the combination

of safety and effectiveness of zuRelief for my own joint and muscle aches.’ ... ‘Pain Support – *Can Turmeric Relieve Arthritis, Joint Pain & Inflammation?*’); FDA Warning Letter to ActiveHerb Tech., Inc. (May 15, 2019), <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/activeherb-technology-inc-574615-05152019> (“Examples of some of the labeling claims that provide evidence that your products are intended for use as drugs include: ... JointsJoy... ‘shown to inhibit inflammation reactions and to inhibit pain’... ‘relieves pain’... ‘relieve muscle aches’”).

²⁵ Equelle Frequently Asked Questions, <https://equelle.com/a/faqs>; Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; Equelle® (@EQUELLEofficial), Twitter (Apr. 6, 2022, 8:56 AM), <https://x.com/EQUELLEofficial/status/1511689176818896900>.

²⁶ Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; Belinda H. Jenks et al., *A Pilot Study on the Effects of S-equol Compared to Soy Isoflavones on Menopausal Hot Flash Frequency*, 21 *J. Women’s Health* 674 (2012), <https://pubmed.ncbi.nlm.nih.gov/22409590/>. See also Equelle Clinical Data, [https://ce.mayo.edu/sites/default/files/media/2024-05/Equelle_HCP_Web_Clinical%20Data%20\(2\)_0.pdf](https://ce.mayo.edu/sites/default/files/media/2024-05/Equelle_HCP_Web_Clinical%20Data%20(2)_0.pdf).

²⁷ Jenks, *supra* note 26. See also J. Haxby Abbott, *The Distinction Between Randomized Clinical Trials (RCT) and Preliminary Feasibility and Pilot Studies: What They Are and Are Not*, 44 *J. Orthopaedic & Sports Physical Therapy* 555 (2014), <https://www.jospt.org/doi/pdf/10.2519/jospt.2014.0110#:~:text=Feasibility%20and%20pilot%20studies%20play,a%20planned%20full%20size%20RCT>.

²⁸ Jenks, *supra* note 26.

²⁹ *Id.*

³⁰ *Id.*

³¹ *Id.*

³² Greene Climacteric Scale, https://www.jeanhailes.org.au/uploads/Health-professionals/Menopause_symptom_scale_Greene_Climacteric.pdf; State Trait Anxiety Inventory, <https://www.advancedassessments.co.uk/resources/Mental-Health-Test.pdf>.

³³ Alaa Althubaiti, *Information Bias in Health Research: Definition, Pitfalls, and Adjustment Methods*, 9 *J. Multidisciplinary Healthcare* 211, 212-4 (2016), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4862344/pdf/jmdh-9-211.pdf>; Pauline M. Maki & Rebecca C. Thurston, *Menopause and Brain Health: Hormonal Changes Are Only Part of the Story*, 11 *Frontiers in Neurology* 1, 3 (2020), <https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2020.562275/full>.

³⁴ Viktor E. Radzinsky et al., *Succinate-Based Dietary Supplement for Menopausal Symptoms: A Pooled Analysis of Two Identical Randomized, Double-Blind, Placebo-Controlled Clinical Trials*, 2019 *Obstetrics and Gynecology Int’l* 1, 7 (2019), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6875258/pdf/OGI2019-1572196.pdf>.

³⁵ Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; Takeshi Aso et al., *A Natural S-equol Supplement Alleviates Hot Flushes and Other Menopausal Symptoms in Equol Nonproducing Postmenopausal Japanese Women*, 21 *J. Women’s Health* 92 (2012), <https://pubmed.ncbi.nlm.nih.gov/21992596/>.

³⁶ As the study explains, equol nonproducers are women who are unable to metabolize S-equol from daidzein (a soy isoflavone found in soybeans and other legumes). By contrast, equol producers are women who can naturally convert daidzein into S-equol.

Approximately 50 percent of Asian women and 25 percent of non-Asian women are equol producers. Researchers have found that these women experience milder menopause symptoms than equol nonproducers, and this distinction can have an impact on the efficacy of various treatment options.

Id. See also Jenks, *supra* note 26; Naoko Ishiwata et al., *New Equol Supplement for Relieving Menopausal Symptoms: Randomized, Placebo-Controlled Trial of Japanese Women*, 16 *Menopause* 141 (2009), <https://pubmed.ncbi.nlm.nih.gov/19131846/>; Equelle Frequently Asked Questions, <https://equelle.com/a/faqs>; Mohammed M. Alshehri et al., *Therapeutic Potential of Isoflavones with an Emphasis on Daidzein*, 2021 *Oxidative Med. and Cellular Longevity* 1 (2021), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8448605/pdf/OMCL2021-6331630.pdf>; Cecilia Ortiz & Bruno Manta, *Advances in Equol Production: Sustainable Strategies for Unlocking Soy Isoflavone Benefits*, 7 *Results in Chemistry* 101288 (2024), <https://www.sciencedirect.com/science/article/pii/S2211715623005271>; Wulf H. Utian et al., *S-equol: A Potential Nonhormonal Agent For Menopause-Related Symptom Relief*, 24 *J. Women's Health* 200 (2015), <https://pubmed.ncbi.nlm.nih.gov/25692726/>.

³⁷ *Id.*

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; Naoko Ishiwata et al., *New Equol Supplement for Relieving Menopausal Symptoms: Randomized, Placebo-Controlled Trial of Japanese Women*, 16 *Menopause* 141 (2009), <https://pubmed.ncbi.nlm.nih.gov/19131846/>.

⁴² *Id.*

⁴³ *Id.*

⁴⁴ See *supra* note 36.

⁴⁵ *Id.*

⁴⁶ Equelle Frequently Asked Questions, <https://equelle.com/a/faqs>.

What time of day should I take Equelle? —

What time of day you take Equelle is not as important as ensuring you are getting 10 mg of S-Equol (that's 2 tablets) daily. This said, you may prefer to take Equelle to align with when you experience the most symptoms (ie: take in the PM before bed if you experience the majority of symptoms at night).

⁴⁷ Pharmavite cites to “Data on file. 1811 Study Report. Pharmavite LLC” on the Equelle website as support for the claims that Equelle improves sleep, reduces vaginal symptoms and improves mood. Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; see also Equelle Clinical Data, [https://ce.mayo.edu/sites/default/files/media/2024-05/Equelle_HCP_Web_Clinical%20Data%20\(2\)_0.pdf](https://ce.mayo.edu/sites/default/files/media/2024-05/Equelle_HCP_Web_Clinical%20Data%20(2)_0.pdf).

Not only is the study sponsored by Pharmavite, but it does not appear to be published or peer-reviewed. See A Nutritional Supplement on Vasomotor Symptoms in Women, <https://ctv.veeva.com/study/a-nutritional-supplement-on-vasomotor-symptoms-in-women>.

As the FTC has stated, “[a] rigorous, unbiased peer review process, like that required by established and reputable scientific journals, provides some level of assurance that the research meets accepted norms in the relevant field.” (Of course, “[t]he mere fact that a study is published, however, isn’t a guarantee of quality or proof that the product is effective for the advertised benefit.”) FTC’s Health Products Compliance Guidance, https://www.ftc.gov/system/files/ftc_gov/pdf/Health-Guidance-508.pdf.

⁴⁸ Equelle also lists another pilot study on its website as general support for Equelle’s marketing claims.



Equelle Clinical Research, <https://equelle.com/pages/clinical-research>; Yuko Tousen et al., *Natural S-equol Decreases Bone Resorption in Postmenopausal, non-equol-producing Japanese Women: A Pilot Randomized, Placebo-Controlled Trial*, 18 *Menopause* 563 (2011), <https://pubmed.ncbi.nlm.nih.gov/21252728/>.

In addition to being a pilot study and thus only arriving at preliminary results, the study also used a different dose and formulation than Equelle; examined a small (just 93 participants) and homogenous (all were Japanese women) sampling; arrived at inadequate results (as noted by the researchers, “[t]hese findings suggest that 10 mg/day of natural S-equol supplementation contributes to bone health in non-equol producing postmenopausal women without adverse effects”); was funded by Otsuka Pharmaceutical Co., Ltd.; and was conducted by company employees.

⁴⁹ Equelle also lists several other publications on its Clinical Research page. However, none of them are clinical trials examining the impact of Equelle or S-equol on menopausal symptoms. See Equelle Clinical Research, <https://equelle.com/pages/clinical-research>.

⁵⁰ The evidence Equelle relies on to substantiate its marketing claims is so lacking that The Menopause Society (formerly named The North American Menopause Society, or NAMS), the country’s leading nonprofit organization comprised of nearly 3,000 members across different disciplines dedicated to promoting the health of menopausal women, does not recommend S-equol as a treatment for vasomotor symptoms associated with menopause. According to The Menopause Society,

Soy metabolite equol ... Few studies have considered whether study participants can metabolize soy, which is critical for soy’s potential estrogenic effects. Only 35% of North American women can metabolize the soy isoflavone daidzein to equol. Women who are able to metabolize soy into equol would be expected to experience relief from VMS with soy products or equol. Women who cannot produce equol after ingesting soy do not benefit from soy but would be expected to benefit from equol. Tests to ascertain whether women are equol producers are not commercially available to the public or healthcare professionals. A 2019 systematic review and meta-analysis found positive effects of equol supplementation over placebo for reducing VMS frequency in three of five trials. Null findings in the remaining two trials were hypothesized to have been because of large differences in VMS at baseline in one trial and inclusion of only equol-producing women in the largest trial. A limitation in most studies (4 of the 6) was inclusion of fewer than 50 participants per group. There is currently mixed evidence for soy foods, soy extracts, and the soy metabolite equol from widely diverse studies, with some significant limitations. (Level II; not recommended)

Chrisandra L. Shufelt et al., *The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society*, 30 *Menopause: J. North Am. Menopause Soc'y* 573-590, <https://www.menopause.org/docs/default-source/professional/2023-nonhormone-therapy-position-statement.pdf>; see also Menopausal Symptoms: In Depth. NIH National Center for Complementary and Integrative Health, <https://www.nccih.nih.gov/health/menopausal-symptoms-in-depth> (“Phytoestrogens, herbs, and other dietary supplements haven’t been clearly shown to relieve menopause symptoms. . . . Dietary supplements may have side effects or interact with drugs, and little is known about their long-term safety.”); Hot Flashes: What Can I Do?, NIH National Institute on Aging, <https://www.nia.nih.gov/health/menopause/hot-flashes-what-can-i-do> (“Buyer beware: Unproven, nonscientific ‘treatments’ for hot flashes . . . You may have heard about black cohosh, DHEA, or soy isoflavones to treat hot flashes. These products are not proven to be effective...”).

⁵¹ See, e.g., Equelle, <https://equelle.com/>.

⁵² See, e.g., Equelle (@equelleofficial), Instagram (Nov. 16, 2021), https://www.instagram.com/p/CWWqueRpk3L/?img_index=2.

⁵³ See, e.g., Alisha Haridasani Gupta, *How Menopause Affects Women of Color*, N.Y. Times, Aug. 23, 2023 (updated Sept. 4, 2023), <https://www.nytimes.com/2023/08/23/well/live/menopause-symptoms-women-of-color.html#:~:text=But%20researchers%20have%20found%20that,and%20anxiety%20than%20hot%20flashes>.

⁵⁴ Eun-Ok Im et al., *Sub-Ethnic Differences in the Menopausal Symptom Experience: Asian American Midlife Women*, 21 *J. Transcultural Nursing* 123 (2010), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2838208/pdf/nihms113346.pdf>.

⁵⁵ Ellen B. Gold et al., *Factors Associated with Age at Natural Menopause in a Multiethnic Sample of Midlife Women*, 153 *Am. J. Epidemiology* 865 (2001), <https://academic.oup.com/aje/article/153/9/865/124589?login=false>.

⁵⁶ Eun-Ok Im, *supra* note 54.

⁵⁷ Mark D. Grant et al., *Menopausal Symptoms: Comparative Effectiveness of Therapies Review No. 47* 1(2015), https://www.ncbi.nlm.nih.gov/books/NBK285463/pdf/Bookshelf_NBK285463.pdf.

⁵⁸ Kate Hardcastle, *Menopause Supplement Industry to Grow to \$22.7 Billion by 2028 As Women Seek Out Alternative Treatments*, *Forbes*, Oct. 7, 2022, <https://www.forbes.com/sites/katehardcastle/2022/10/07/menopause-supplement-industry-to-grow-to-227-billion-by-2028-as-women-seek-out-alternative-treatments/>; Jennifer Sauer et al., *The Economic Impact of Menopause: A Survey of Women 35+ and Employers*, AARP Research (Jan. 2024), <https://www.aarp.org/pri/topics/work-finances-retirement/employers-workforce/menopause-workplace/>; Menopause Market Size, Share & Trends Analysis Report By Treatment (Dietary Supplements, OTC Pharma Products), By Region (North America, Europe, Latin America), and Segment Forecasts, 2024-2030, <https://www.grandviewresearch.com/industry-analysis/menopause-market>.