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Synthetic Conjugated Estrogens, B

A new alternative for menopausal symptom relief

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Menopausal signs and symptoms remain a pervasive problem for many perimenopausal and postmenopausal women. The symptoms may have such a substantially adverse impact on the quality of life of these women that some type of intervention is needed or desired. Many estrogen-containing products are available for women who are candidates for hormone treatment. One of the newest, Enjuvia™ (synthetic conjugated estrogens, B [SCE-B]), is the only plant-derived SCE product that includes the component $\Delta^{8,9}$-dehydroestrone sulfate. SCE-B contains 10 primary estrogenic components in a formulation with modified-release characteristics that are designed to provide consistent plasma levels of the active estrogenic ingredients **(TABLE 1).**

Since the initial publication of the Women's Health Initiative (WHI) data on hormone therapy (HT; estrogen plus progestin) in 2002 and estrogen therapy (ET) in 2004, many health care professionals have been uncertain about the appropriate course of action regarding the treatment of moderate-to-severe menopausal signs and symptoms.[1,2] The WHI findings disputed a long-held assumption—that HT (for women with a uterus) or ET (for hysterectomized women) should be prescribed routinely to postmenopausal women to prevent certain diseases. At the same time, many organizations maintain that this treatment, especially at the lowest dosages possible, is still a viable approach for specific indications for women whose personal and family histories suggest

TABLE 1

Active constituents of conjugated synthetic estrogens, B*

Sodium 17β-estradiol sulfate
Sodium $\triangle^{8,9}$-dehydroestrone sulfate
Sodium estrone sulfate
Sodium equilenin sulfate
Sodium 17β-dihydroequilenin sulfate
Sodium equilin sulfate
Sodium 17β-dihydroequilin sulfate
Sodium 17α-dihydroequilenin sulfate
Sodium 17α-dihydroequilin sulfate
Sodium 17α-estradiol sulfate

*Listed in rank order of biologic potency.

that the benefits will likely outweigh the risks.[3-5] Risk assessment should be conducted on an individual basis, as benefits and risks identified in the WHI do not apply to all age ranges and all durations of therapy. For women younger than 50, or those at low risk for coronary heart disease, stroke, osteoporosis, breast cancer, or colon cancer, the absolute risk associated with ET or HT is likely to be lower than that reported in the WHI.[4]

This supplement reviews menopausal symptomatology; discusses how SCE-B fits into the oral ET armamentarium in 2006; presents pharmacokinetic data of the SCE-B constituents, including $\Delta^{8,9}$-dehydroestrone sulfate; and summarizes the findings of the pivotal clinical trial of SCE-B demonstrating the efficacy and safety of this new product.

Defining Menopausal Symptoms

By definition, women reach menopause after experiencing 12 months of amenorrhea without a pathologic cause.[6] Most menopausal women (75%-85%) develop clinical manifestations of estrogen deficiency that begin during the menopause transition and persist through and past menopause.

Vasomotor Symptoms. The most common menopause-related complaint is vasomotor symptoms, which include hot flashes, night sweats, and associated sleep disturbances.[7] The frequency, severity, and duration of these symptoms vary from woman to woman. In addition, women differ in their ability to tolerate the symptoms. Differing responses to vasomotor symptoms reflect social, cultural, psychological, and environmental factors that clinicians should consider in terms of educating, treating, advising, and reassuring each individual patient about menopause.[8] The National Institutes of Health (NIH) State-of-the-Science Panel ascribed vasomotor symptoms to ovarian aging, as opposed to general aging of the body, because these symptoms rarely occur before the menopause transition and become more severe in the later phases of the transition; occur with greater frequency and severity in younger women who undergo surgical or chemical menopause; and improve with estrogen treatment, as demonstrated in many high-quality interventional clinical trials.[9] These observations regarding vasomotor symptoms were supported by a 9-year-long, population-based study of 438 Australian women.[10]

Vulvovaginal Symptoms. Because the decline in estrogen levels is frequently accompanied by a drying of the vaginal epithelium, many menopausal women experience vulvovaginal itching, burning, dyspareunia, discharge, and infections.[11] Up to 40% of postmenopausal women have symptoms of atrophic vaginitis. Unlike vasomotor symptoms, which tend to resolve spontaneously over time, vaginal symptoms tend to worsen unless they are treated in a timely fashion.

Other Symptoms. Other menopause-related problems include changes in bone loss, emotional lability, changes in sleep patterns, and loss of libido.

Examining ET Treatment Options

Prescribing options are abundant when considering oral ET for management of vasomotor symptoms. All of the products in **TABLE 2** are indicated for the relief of moderate-to-severe vasomotor symptoms, and some have additional indications, including relief of vulvovaginal atrophy and related symptoms, prevention of postmenopausal osteoporosis, and treatment of hypoestrogenism caused by hypogonadism, oophorectomy, or primary ovarian

failure. They all have the same contraindications and FDA-required labeling of safety profiles, including increased risk of cardiovascular disorders, malignant neoplasms (eg, endometrial cancer, breast cancer), dementia, gallbladder disease, hypercalcemia, and visual abnormalities. Users of ET have an increased risk, albeit small, of developing hypertension, hyperlipoproteinemia (in those with preexisting hypertriglyceridemia), impaired liver function, hypothyroidism, fluid retention, and hypocalcemia. Finally, ET may precipitate exacerbations of endometriosis, asthma, diabetes mellitus, epilepsy, and migraine.[12]

Estrogen products share common pharmacologic effects. To date, no controlled trials have demonstrated the superiority of any single product. Therefore, safety data derived from clinical trials for one agent may be generalized to all agents within the same family.[4] Choice of ET relies on physician experience, patient preference, and product attributes. Use of ET should be consistent with treatment goals, benefits, and risks for the individual, taking into account symptoms that have an impact on quality of life.

TABLE 2

Treatment options for oral estrogen therapy

Active estrogen component	Brand	Available strengths (mg)
Synthetic conjugated estrogens, B (SCE-B)	Enjuvia™	0.3, 0.45, 0.625 0.9, 1.25
Conjugated estrogens, *USP* (conjugated equine estrogens [CEE])	Premarin®	0.3, 0.45, 0.625 0.9, 1.25
Synthetic conjugated estrogens, A (SCE-A)	Cenestin®	0.3, 0.45, 0.625 0.9, 1.25
Esterified estrogens (sodium estrone sulfate and sodium equilin sulfate)	Menest®	0.3, 0.625, 1.25, 2.5
Estropipate (piperazine estrone sulfate)	Ogen®, Ortho-Est®, various	0.625, 1.25, 2.5, 5
17β-estradiol, micronized	Estrace®, various	0.5, 1.0, 2.0
Estradiol acetate	Femtrace®	0.45, 0.9, 1.8

Adapted from: North American Menopause Society. Postmenopausal Hormone Therapy Primer. Jan. 1, 2006. Available at: http://www.menopause.org/edumaterials/htprimer2006.pdf Accessed January 1, 2006.

TABLE 3

Change from baseline in number of hot flashes (%)

Time period	Estrone sulfate 1.25 mg daily % change (*n*=5)	$\Delta^{8,9}$-dehydroestrone sulfate 0.125 mg daily % change (*n*=5)	Estrone sulfate + $\Delta^{8,9}$ % change (*n*=5)
8 wk	−88.06 ± 3.77	−95.00 ± 3.33	−100.00 ± 0.00
12 wk	−89.17 ± 6.12	−98.33 ± 1.67	−100.00 ± 0.00

*Listed in rank order of biologic potency.

Adapted from: Baracat E, et al. *J Clin Endocrinol Metab*. 1999;84:2020-2027.

Synthetic Conjugated Estrogens, B

SCE-B is the second synthetic conjugated estrogens product available in the United States. It is a blend of 10 plant-derived estrogenic substances that are the same 10 essential estrogens present in Premarin® (conjugated equine estrogens [CEE]) **(TABLE 1)**.[13] Indicated for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, SCE-B is available in dosage strengths ranging from 0.3 mg to 1.25 mg.[12]

SCE-B tablets are a cellulose-based polymer tablet core that is coated using Surelease® technology (aqueous ethylcellulose dispersion). This plasticized aqueous dispersion provides dependable, consistent delivery of conjugated estrogens into the gastrointestinal (GI) tract over time. Release of conjugated estrogens from SCE-B tablets occurs independently of gastric pH, with few fluctuations over the 24-hour dosing interval.[12] The conjugated estrogens in SCE-B tablets are soluble in water and are well absorbed from the GI tract after release from the drug formulation.[8,9]

$\Delta^{8,9}$–Dehydroestrone Sulfate

SCE-B is the first synthetic conjugated estrogens product to contain $\Delta^{8,9}$-dehydroestrone, a biologically active estrogen with a distinct pharmacologic profile

TABLE 4

Mean change in NUMBER of moderate-to-severe hot flashes per week*

SCE-B dose	0.3 mg (*N*=66)	0.625 mg (*N*=71)	1.25 mg (*N*=69)	Placebo (*N*=70)
Baseline				
Mean (SD)	104.3 (57.7)	97.3 (82.1)	86.8 (42.1)	96.4 (58.2)
Wk 4				
Mean (SD)	47.0 (52.9)	23.2 (26.9)	24.6 (47.0)	57.8 (47.5)
Mean change from baseline (SE)	–49.8 (5.2)	–72.8 (5.0)	–68.3 (5.1)	–37.2 (5.0)
P value vs placebo	0.005	<0.001	<0.001	—
Wk 8				
Mean (SD)	34.8 (50.8)	13.0 (17.8)	13.8 (27.3)	49.5 (47.9)
Mean change from baseline (SE)	–61.8 (4.6)	–83.0 (4.4)	–80.2 (4.5)	–45.9 (4.5)
Wk 12				
Mean (SD)	30.7 (47.7)	12.2 (18.7)	12.4(26.3)	47.5 (49.8)
Mean change from baseline (SE)	–66.3 (4.6)	–84.6 (4.4)	–82.6 (4.5)	–48.3 (4.5)
P value vs placebo	<0.001	<0.001	<0.001	—

*intent-to-treat population, last observation carried forward

SCE-B = synthetic conjugated estrogens, B; SD = Standard Deviation, SE = Standard Error

Adapted from Enjuvia (synthetic conjugated estrogens, B) Prescribing Information.Bala Cynwyd, PA:Duramed Pharmacueticals, Inc.; 2006.

that results in significant clinical activity in vasomotor, neuroendocrine (gonadotropin and prolactin), and bone preservation parameters.[14] Delta^{8,9}-dehydroestrone has efficacy similar to estrone sulfate but at a dose 10 times lower. When administered alone at a daily dose of 0.125 mg, it was shown to significantly reduce frequency and severity of vasomotor symptoms **(TABLE 3)**.[15] When administered alone, $\Delta^{8,9}$-dehydroestrone can significantly suppress urinary excretion of N-telopeptide, suggesting a potentially positive effect on bone.[15] It has also been shown to lack or have reduced activity in lipids and sex hormone binding globulin, suggesting limited or absent liver and vascular interactions.[14,15]

Pharmacokinetic Properties

In pharmacokinetics studies, SCE-B was well absorbed from the GI tract. Maximum plasma concentrations (C_{max}) of conjugated estrogens were attained at 8 hours and C_{max} of unconjugated estrogens were attained at about 9 hours after oral administration **(FIGURES 1A-1C)**.[16] The distribution, metabolism, and excretion of the exogenous estrogens contained in SCE-B are similar to those of endogenous estrogens.

Clinical Evidence of SCE-B Efficacy and Safety

To evaluate the efficacy and safety of SCE-B in the treatment of menopausal symptoms, 281 naturally or surgically postmenopausal women were randomized to a 12-week course of 1 of 4 daily treatments: SCE-B 0.3 mg, SCE-B 0.625 mg, SCE-B 1.25 mg, or placebo.[17] Subjects (mean age, 51.1 years; range 26-65) had been experiencing at least 7 moderate-to-

severe hot flashes per day or 50 moderate-to-severe hot flashes per week, and none had contraindications to ET. The majority (81%) of subjects were Caucasian (n=228) and 49 subjects (17.4%) were African American. At the end of the study, nonhysterectomized subjects received a 14-day course of medroxyprogesterone acetate 10 mg daily to protect them against endometrial hyperplasia associated with unopposed estrogen exposure.

During a 2-week baseline period, and then over the course of the 12-week study, daily diaries were maintained. Study particpants recorded the occurrence and severity of each hot flash, as follows: 1 = mild (sensation of heat without perspiration); 2 = moderate (sensation of heat with perspiration but able to continue activity); and 3 = severe (sensation of heat with sweating that caused the subject to stop activity). Physical examinations were performed and diaries collected at weeks 4, 8, and 12. At week 12, subjects were asked to rank the overall effectiveness of the study drug (1 = excellent; 2 = good; 3 = fair; and 4 = poor). Adverse events were collected throughout the study and subjects were asked to rank and record the severity of adverse reactions (1 = mild; 2 = moderate; or 3 = severe).

FIGURE 1A

Free estrone mean plasma concentration over time*

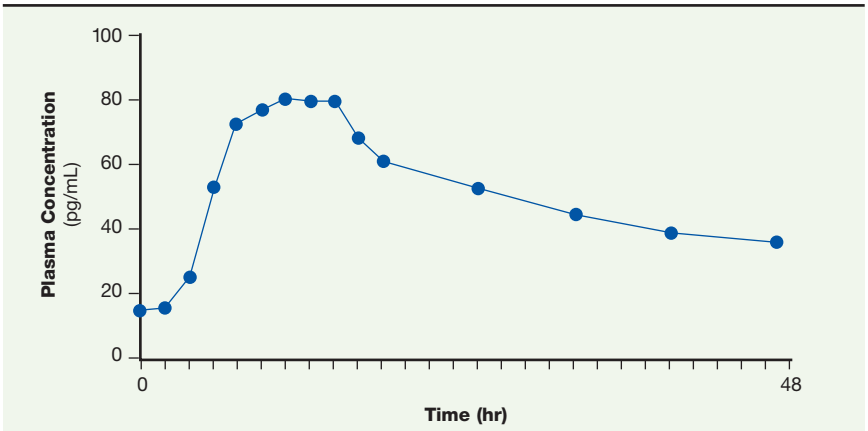


FIGURE 1B

Free equilin mean plasma concentration over time*

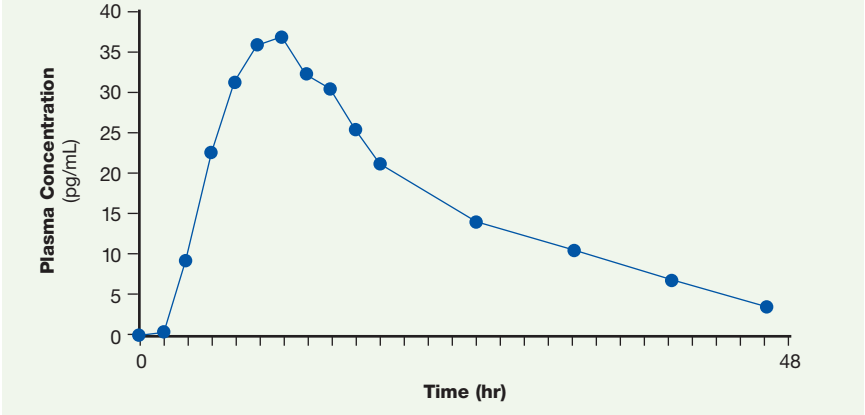
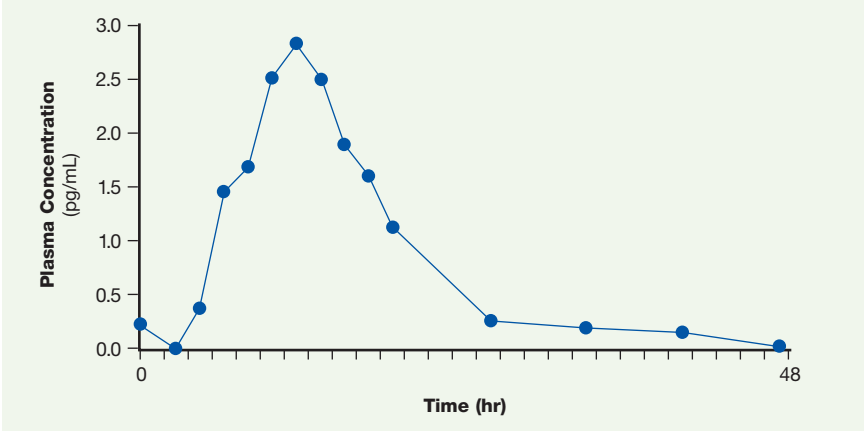


FIGURE 1C

Free $\Delta^{8,9}$ dehydroestrone sulfate mean plasma concentration over time*



Source: Duramed Research, Bala Cynwyd, Pa. Data on file.
*Single dose, fasting study, 2x0.625 mg

TABLE 5

Mean change in SEVERITY of moderate-to-severe hot flashes per week*

SCE-B dose	0.3 mg (*N*=66)	0.625 mg (*N*=71)	1.25 mg (*n*=69)	Placebo (*n*=70)
Baseline				
Mean (SD)	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)	2.5 (0.3)
Wk 4				
Mean (SD)	2.1 (0.8)	1.9 (1.0)	1.5 (1.1)	2.2 (0.8)
Mean change from baseline (SE)	–0.5 (0.1)	–0.6 (0.1)	–1.0 (0.1)	–0.3 (0.1)
P value vs placebo	0.036	0.002	<0.001	—
Wk 8				
Mean (SD)	1.7 (1.1)	1.5 (1.1)	1.0 (1.1)	2.0 (0.9)
Mean change from baseline (SE)	–0.8 (0.1)	–1.0 (0.1)	–1.5 (0.1)	–0.5 (0.1)
Wk 12				
Mean (SD)	1.5 (1.2)	1.1 (1.2)	1.0 (1.1)	1.9 (1.1)
Mean change from baseline (SE)	–1.0 (0.1)	–1.4 (0.1)	–1.5 (0.1)	–0.6 (0.1)
P value vs placebo	0.023	<0.001	<0.001	—

*intent-to-treat population, last observation carried forward

SCE-B = synthethic conjugated estrogens,B; SD= standard deviation; SE = standard error

Adapted from: Enjuvia (synthetic conjugated estrogens, B) Prescribing Information. Bala Cynwyd, PA:Duramed Pharmaceuticals, Inc; 2006.

TABLE 6

Mean change from baseline in vasomotor symptoms in hysterectomized women randomized to SCE-B 0.3 mg

	SCE-B (*n*=32)		Placebo (*n*=31)	
Study visit	**Severity**	**Frequency**	**Severity**	**Frequency**
Wk 4	–0.43	–78.52	–0.10	–53.17
Wk 8	–0.56	–86.64	–0.33	–61.73
Wk 12	–0.96	–90.76	–0.53	–59.80

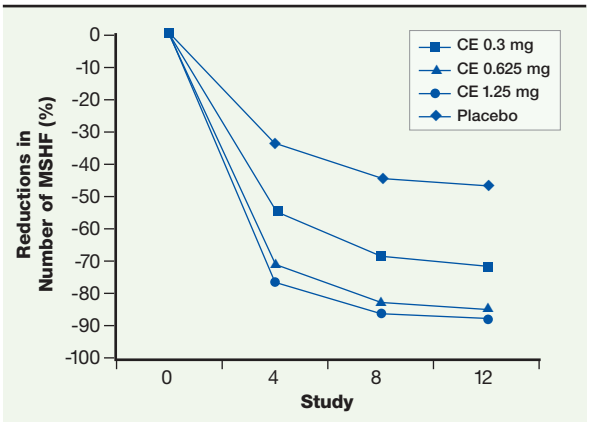
Adapted from: Reape KZ, Baker GS. Low 0.3 mg dose of synthetic conjugated estrogens, B (SCE-B) is effective in reducing the frequency and severity of vasomotor symptoms in surgically menopausal women. Presented at the North American Menopause Society Annual Meeting, September 28-October 1, 2005;San Diego, Calif. Abstract LB-14. Available at: http://www.menopause.org/medkit_latebreaking.pdf. Accessed February 27, 2006.

Nonhysterectomized women were asked to record the incidence and severity of any uterine bleeding.

Over the course of the study, progressive reduction in the mean number and mean severity of moderate-to-severe hot flashes occurred with all 3 dose strengths of SCE-B at all time points **(TABLES 4 AND 5; FIGURE 2).** The placebo response was similar to that reported in other vasomotor studies.[18,19] Reductions in both the number and severity of hot flashes in the actively treated women for all dose strengths was significant at all time points **(FIGURE 2).** A subset analysis showed that even at the lowest dose of SCE-B

FIGURE 2

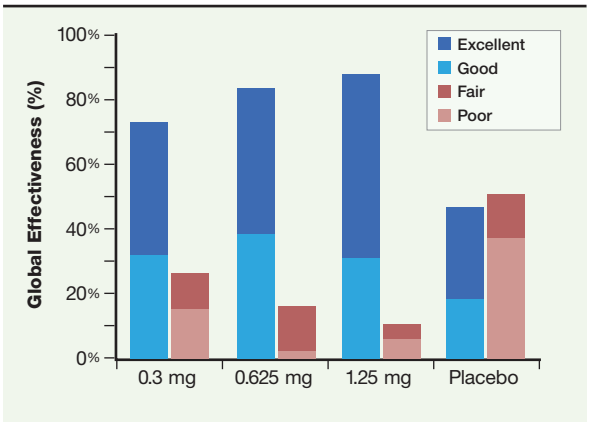
Reductions in number of moderate-to-severe hot flashes (%)



*Percent change from baseline at wk 4, 8, and 12 significantly different from placebo for all active treatment groups (*P*<.05)
Adapted from: Utian WH, et al. *Obstet Gynecol*. 2004;103:245-253.
MSHF = moderate-to-severe hot flashes

FIGURE 3

Patient assessment of overall effectiveness at week 12 (%)



P<.001 active treatment vs placebo for "good" plus "excellent" pairwise comparison
Adapted from: Utian WH, et al. *Obstet Gynecol*. 2004;103:245-253.

evaluated, significant decreases in both frequency and severity of vasomotor symptoms was noted at 4 weeks in surgically menopausal women, a group of patients that is often less responsive to therapy **(TABLE 6)**.[20-22] The overall effectiveness of SCE-B in diminishing menopausal symptoms was judged to be good or excellent by 74% of the 0.3-mg group, 85% of the 0.625-mg group, 90% of the 1.25-mg group, and 48% of the placebo group **(FIGURE 3).**

All 3 SCE-B dose strengths were found to be well tolerated and safe over the 12-week trial. Treatment-related adverse events tended to be mild or moderate in severity. They were reported by 21%, 42%, 44%, and 35% of the SCE-B 0.3 mg, 0.625 mg, 1.25 mg, and placebo treatment groups, respectively. The type of adverse events reported by actively treated women was consistent with those reported by estrogen users. Notably, there were no reports of breast pain by the SCE-B 0.3-mg treatment group. In nonhysterectomized women who experienced uterine bleeding/spotting during the trial, the average severity was less among those who received SCE-B than among those who received placebo.

In Summary

SCE-B 0.3 mg, 0.625 mg, and 1.25 mg significantly reduced the frequency and severity of vasomotor symptoms in a group of highly symptomatic women over the course of a 12-week trial, with significant clinical improvement apparent at the 4-week checkpoint. The efficacy of the lowest dose formulation may be attributed, at least in part, to the presence of the $\Delta^{8,9}$-dehydroestrone sulfate component, which has been shown to have unique estrogenic properties and high potency. It is also notable that no study participant assigned to receive the 0.3-mg dose strength experienced breast pain, a common estrogenic effect.

Findings from the pivotal clinical trial of SCE-B demonstrate that women experiencing menopausal symptoms have a new alternative—an oral ET product that is safe, effective, and well tolerated. With significant activity reported at the lowest daily dose of 0.3 mg, this 10-component, plant-derived estrogen product offers the major benefit of a low effective dose for management of vasomotor symptoms among postmenopausal women.

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