

Estrogen-alone drug products are approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Vasomotor symptoms associated with the menopause are, simply put, "hot flashes." A hot flush is a sudden feeling of heat, usually on the face, neck, shoulders, and chest. Hot flashes have been described as "recurrent, transient periods of flushing, sweating, and a sensation of heat, often accompanied by palpitation, feeling of anxiety, and sometimes followed by chills" (Ref. 14). When hot flashes occur at night, they are often called night sweats.

The indication for estrogen-androgen combination drug products is limited to that subset of women with "moderate to severe vasomotor symptoms associated with the menopause" that are "*not improved by estrogen alone*" (emphasis added). The precise wording of the indication quite narrowly defines the intended population. Thus, to be found effective for this narrow indication, there would need to be reliable evidence that estrogen-androgen combination products are effective in treating the population of menopausal women whose vasomotor symptoms are not relieved by estrogen alone.

FDA believes that substantial evidence is lacking that the addition of an androgen can improve the effectiveness of estrogen alone in the treatment of vasomotor symptoms (i.e., hot flashes). An early randomized, placebo-controlled, five-arm, two-period crossover clinical trial by Sherwin and Gelfand (Ref. 15) compared the effects on surgically menopausal women of immediate postoperative parenteral administration of estrogen alone (n=11), androgen alone (n=10), estrogen and androgen in combination (n=12), and placebo (n=10) to hysterectomy controls (n=10) and found that the androgen alone, estrogen-androgen combination, and control hysterectomy groups had lower (i.e., lower frequency and severity) menopausal somatic symptoms scores than the estrogen alone and placebo groups. The menopausal somatic symptoms score evaluated a constellation of symptoms including hot flashes, cold sweats, weight gain, rheumatic pains, cold hands and feet, breast pains, headaches, numbness and tingling, and skin crawls. A single-center, double-blind randomized, 6-month study by Hickok, Toomey, and Speroff (Ref. 2) compared the effects of treating surgically menopausal women with esterified estrogens alone (n=13) or in combination with methyltestosterone (n=13) on a similar constellation of menopausal symptoms, but found no statistically significant difference

between the two treatments. The 15 menopausal symptoms evaluated were hot flushes, cold sweats, vaginal dryness, cold hands and feet, breast pain or tenderness, numbness and tingling, skin crawls, edema, increased facial or body hair, voice deepening, acne, trouble sleeping, pounding of the heart, dizzy spells, and pressure or tightness in the head or body. A 2-year, multicenter, double-blind, randomized, parallel group study (Ref. 9) comparing the effects of 2 doses of conjugated equine estrogen and 2 doses of esterified estrogen plus methyltestosterone in a total of 311 surgically menopausal women found no differences among the groups in relief of hot flashes, sweats, and vaginal dryness.

Clinical studies that evaluated the effect of estrogen-androgen combination therapy specifically on hot flashes found that the combination does not reduce the frequency of vasomotor symptoms more than estrogen alone. Watts et al. (Ref. 1) compared treatment with esterified estrogens alone and treatment with esterified estrogens and methyltestosterone in a 2-year, multicenter, double-blind, randomized, parallel group study conducted in 66 surgically menopausal women. The authors found no significant difference in the mean reduction from baseline in the number of hot flashes between the two groups. Sarrel et al. (Ref. 17) found no meaningful differences in relief from hot flashes when 20 postmenopausal women were treated for 8 weeks with esterified estrogens or an esterified estrogens-androgen combination in a single-center, double-blind, randomized, parallel group study. Burger (Ref. 18) administered subcutaneous implants of estradiol and testosterone to 17 menopausal women who complained that symptoms persisted, particularly loss of libido, despite treatment with conjugated equine estrogens. There was no statistically significant change from baseline in hot flashes after treatment. Myers et al. (Ref. 19) conducted a 10-week, double-blind, placebo controlled, parallel group study in 40 naturally menopausal women comparing 4 treatments: Conjugated estrogens alone, conjugated estrogens and medroxyprogesterone, conjugated estrogens and androgen, and placebo. The study found that the estrogen and estrogen/medroxyprogesterone groups had significantly fewer hot flashes than the estrogen/androgen or placebo groups. The authors concluded: "This result is consistent with other studies showing no effect of androgen alone on hot flashes" (Ref. 19, p. 1129).

Other authors affirm the conclusion that estrogen-androgen combination drug products are not superior to estrogen in reducing vasomotor symptoms (Refs. 3, 20 through 23). Rosenberg summarized the evidence concerning the alleviation of vasomotor symptoms as follows: "Studies suggest that estrogen is primarily responsible for reductions in vasomotor symptoms and that the addition of androgen neither improves nor detracts from this beneficial effect" (Ref. 24, p. 400).

III. FDA's Conclusions Concerning the Safety and Effectiveness of Estrogen-Androgen Combination Drug Products

For the reasons discussed previously, FDA no longer regards combination drug products containing estrogen(s) and androgen(s) as having been shown to be effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone. The agency has closely examined the data and information that formed the basis for the 1976 finding that such combinations were effective for this indication, as well as the subsequent literature, and has determined that there is a lack of substantial evidence that this combination is effective for "moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone."

IV. References

The following references have been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Watts, N. B. et al., "Comparison of Oral Estrogens and Estrogens Plus Androgen on Bone Mineral Density, Menopausal Symptoms, and Lipid-Lipoprotein Profiles in Surgical Menopause," *Obstetrics & Gynecology*, 85:529-537, 1995.
2. Hickok, L. R., C. Toomey, and L. Speroff, "A Comparison of Esterified Estrogens With and Without Methyltestosterone: Effects on Endometrial Histology and Serum Lipoproteins in Postmenopausal Women," *Obstetrics & Gynecology*, 82:919-924, 1993.
3. Kaunitz, A. M., "The Role of Androgens in Menopausal Hormonal Replacement," *Endocrinology and Metabolism Clinics of North America*, 26(2):391-397, 1997.
4. ACOG Committee on Gynecologic Practice, "Committee Opinion: Androgen Treatment of Decreased Libido," *2002 Compendium of Selected Publications*, American College of Obstetricians and Gynecologists, Washington, DC, pp. 5-6, 2002.
5. Gelfand, M. M., and B. Wiita, "Androgen and Estrogen-Androgen Hormone