



**NATIONAL
WOMEN'S
HEALTH
NETWORK**

A VOICE FOR WOMEN, A NETWORK FOR CHANGE

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August 21, 2006

Andrew Von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Citizen petition urging FDA to stop Solvay Pharmaceuticals and Breckenridge Pharmaceuticals from marketing esterified estrogens & methyltestosterone combination products for vasomotor symptoms associated with menopause that don't respond to treatment with exogenous estrogen alone; these products include Estratest and Estratest H.S., (Solvay Pharmaceuticals) and Syntest D.S. and Syntest H.S. (Breckenridge Pharmaceuticals).

Dear Dr. Von Eschenbach:

The National Women's Health Network, a public interest group with a nationwide membership, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21, U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30 to immediately bar Solvay Pharmaceuticals (hereafter referred to as 'Solvay') from marketing Estratest & Estratest H.S., (hereafter referred to as 'Estratest') and Breckenridge Pharmaceuticals (hereafter referred to as 'Breckenridge') from marketing Syntest D.S. and Syntest H.S. (a product formerly known as Menogen and hereafter referred to as 'Syntest'), for indications of vasomotor symptoms associated with menopause. Both Estratest and Syntest are esterified estrogens & methyltestosterone combination products (hereafter referred to as 'estrogen/testosterone products').

2006P-0346

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We are filing this petition because: 1) neither Estratest nor Syntest has been approved by the FDA for the labeled indications for which they are marketed: moderate to severe vasomotor symptoms that don't respond to treatment with exogenous estrogen alone; 2) in 2003, the FDA concluded that there is no substantial evidence of efficacy of estrogen/testosterone products for the treatment of vasomotor symptoms that don't respond to treatment with exogenous estrogen alone; 3) according to reviews conducted by FDA's own medical staff and the findings of its scientific advisors, there are significant known risks associated with estrogen/testosterone products as well as significant outstanding safety questions associated with testosterone products that have not yet been adequately studied.^{1,2}

Estratest came on the U.S. market around 1964, although the exact date is unclear. It was not the first estrogen/testosterone product to be sold in the United States, and the products that preceded it had been on the market since before the FDA's current drug approval requirements for demonstrating safety and efficacy for labeled indications were in place. As a result, none of the estrogen/testosterone products had been evaluated by the FDA for safety and efficacy as would be required today prior to marketing. Estratest was made available based on the argument that it was equivalent to the estrogen/testosterone products already available. In 1981, after prompting from the FDA, Reid-Provident (which is now Solvay) sought to formalize that approval and filed Abbreviated New Drug Applications (ANDA): ANDA 87-212 for Estratest H.S. and ANDA 87-597 requesting FDA approval for Estratest.

As of August 2006, 25 years after the ANDAs for Estratest were filed, the FDA still has not ruled on the applications. In the meantime, Solvay continues to market Estratest for the management of moderate to severe vasomotor symptoms that do not respond to estrogen therapy, despite the fact that it does not have FDA approval and scientific evidence does not support these claims.

In 1997, Breckenridge brought Syntest (originally labeled Menogen) onto the market as a generic version of Estratest, thereby circumventing current requirements for independently demonstrating that the product is safe and effective. Neither Solvay nor Breckenridge has provided the FDA with the evidence of safety and efficacy necessary to support FDA approval of their respective products.

I. Action Requested

As of August 2006, Solvay and Breckenridge continue to market Estratest and Syntest, respectively, for the relief of moderate to severe vasomotor symptoms associated with menopause that don't respond to treatment with exogenous estrogen alone, even though the FDA stated – three years ago - that this indication is not supported by scientific evidence. FDA should act immediately to halt this marketing of estrogen/testosterone products for an unapproved, unproven indication.

II. Statement of Grounds

1. FDA review has concluded that estrogen/testosterone products have not been shown to be effective for relief of vasomotor symptoms that don't respond to treatment with exogenous estrogen alone.

In a notice published in the Federal Register on April 14, 2003 (Federal Register DOCID: fr14ap03-60) the FDA submitted a proposed amendment to an earlier finding that had allowed combination estrogen/androgen products (which include estrogen/testosterone products) to remain on the market with a labeled indication for relief of moderate to severe vasomotor symptoms associated with menopause that don't respond to treatment with exogenous estrogen alone. The FDA concluded that the addition of testosterone to estrogen products did not provide any greater relief for vasomotor symptoms associated with menopause. The FDA specifically stated, "...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."³ Yet Estratest and Syntest remain on the market for these exact indications.

2. Without Benefits, There are Only Risks: Overview of Safety Issues

In evaluating the safety of estrogen/testosterone products, the known risks of estrogen and testosterone when used independently are compounded by the unanswered safety questions about long-term use of the

combination product. Couple these risks with a lack of evidence of benefit and the risk-benefit calculation clearly weighs towards risk. Consequently, women taking these products are exposed to the risks associated with exogenous estrogens and testosterone, without deriving the therapeutic benefit either product purports to provide.

The known risks associated with exogenous androgen use (including testosterone) include:⁴

1. liver toxicity which can result in a number of ailments including:
 - a. hepatitis due to accumulation of bile in the liver
 - b. peliosis hepatitis, a life threatening accumulation of blood in the liver
 - c. liver cancer
2. increased risk for invasive breast cancer
3. reduction in high-density lipoproteins
4. fluid retention leading to worsening heart failure and hypertension
5. abnormal hair growth
6. acne
7. deepening of the voice
8. hair loss
9. clitoral enlargement (usually not reversible after drug discontinuation)
10. amenorrhea
11. paresthesia
12. increased or decreased libido
13. headache
14. anxiety
15. depression

In addition, the risks associated with long-term testosterone use are largely unknown because of a paucity of research in this area; scientists have concluded that more research is needed before evidence-based conclusions can be drawn.⁵

The continued marketing of Estratest and Syntest for moderate to severe vasomotor symptoms puts the health of women exposed to these products at significant risk not only due to exposure to exogenous testosterone but to exogenous estrogen as well. The risks of estrogen use have been well documented in the Women's Health Initiative, specifically, stroke, dementia, heart attack, breast cancer, and blood clots.⁶ The use of Estratest or Syntest increases a woman's risk by exposing her to exogenous estrogen for a longer period of time than if she had stopped after failure of estrogen only. In addition, exposing a woman to the unknown risks associated with exogenous testosterone for no therapeutic purpose is dangerous.

While the FDA has never conducted a safety review of Estratest or Syntest, it did review a testosterone product for another indication in women who were already taking estrogen and found significant safety concerns. In December of 2004, the FDA Advisory Committee for Reproductive Health Drugs reviewed an application for Intrinsa, a testosterone transdermal system (TTS) for the treatment of Female Sexual Desire Disorder. To assist in the assessment of Intrinsa, Dr. Kate Gelperin, a medical officer in the Office of Drug Safety, testified about the Adverse Event Reporting System (AERS) data that the FDA has collected on Estratest since both Intrinsa and Estratest contain testosterone.⁷ Dr. Gelperin found 226 reports in the AERS database on Estratest that met the regulatory definition of "serious"; this definition included events that were significant enough to be considered life-threatening, requiring or prolonging hospitalization, or other medically important events. The most frequently reported problems associated with Estratest included:

1. breast cancer
2. depression
3. headache
4. cerebrovascular accident
5. coronary artery occlusion
6. dizziness
7. chest discomfort
8. glaucoma
9. 'hypoesthesia

10. pain

11. ovarian cancer

Other less serious events included acne. While Dr. Gelperin noted in her testimony that these reports cannot be "...regard[ed]... in any sense [as] confirming a hypothesis," they do form an adequate basis for serious safety questions about the use of Estratest and Syntest.⁷ In the absence of answers to these questions, these products should not continue to be marketed and prescribed to women. Taking on the risk of the conditions that Dr. Gelperin described might be acceptable if estrogen/testosterone products offered a unique therapeutic benefit for vasomotor symptoms. However, in light of the fact that FDA has concluded that there is not substantial evidence that estrogen/testosterone products are effective for the labeled indication, the risks associated with their use are not acceptable.

The FDA's Reproductive Health Drugs Advisory Committee voted unanimously to recommend against approval of Intrinsa.⁷ Committee members cited concerns about the safety of long-term exposure to exogenous testosterone, especially in groups of women in whom exposure had not been adequately studied. These same safety concerns should also apply to Estratest and Menogen, which expose a woman to as much as *eight times* the amount of testosterone as Intrinsa (Table 1).

Table 1. Comparison of doses of Intrinsa to doses of Estratest & Syntest.

Product	Testosterone	Estrogens
Intrinsa	300 mcg	0
Estratest	2.5mg	1.25mg
Estratest H.S.	1.25mg	0.625 mg
Syntest	2.5mg	1.25mg
Syntest H.S.	1.25mg	0.625 mg

3. Many Women Exposed: The Use of Estratest is Widespread

Estratest has been on the U.S. market since 1964 without ever having received FDA product approval; yet women have been led to believe that Estratest is a safe, FDA-approved product because their health care practitioners can prescribe it. Solvay even uses the number of prescriptions as part of its marketing materials for Estratest by stating, "More than 36 million prescriptions filled." (See Attachment #1) Data from the Nurses' Health Study indicate that use of Estratest rose exponentially from 1988 to 2000.⁸ In 2000, Estratest was the 199th most prescribed drug in the United States. In 2004, one year after the FDA announced Estratest lacked efficacy for vasomotor symptoms, sales of the drug reached \$119 million in the North American market.⁹ Women continue to be prescribed a drug with labeled indications that FDA has stated are not supported by scientific evidence, because FDA has not stopped the company from marketing it.

Syntest, a generic form of Estratest that has been on the market since 1997, is also labeled for the relief of moderate to severe vasomotor symptoms that don't respond to treatment with exogenous estrogen alone. Similar to Estratest, no application for Syntest has ever been submitted to the FDA, neither a New Drug Application (NDA) nor an Abbreviated New Drug Application (ANDA) that is commonly used for generic drugs.

Despite a lack of efficacy evidence for the labeled indication, Solvay and Breckenridge continue to circumvent the FDA regulatory process and market these products. Both companies depend on the public's lack of knowledge of the products' equivocal regulatory status to create the impression that these estrogen/testosterone combination products are like most prescription products available in the United States and have been determined to be safe and effective by an FDA review of evidence. In the late 1990's, Breckenridge and Solvay went to court over Breckenridge's right to produce and market Syntest (which was then known as Menogen). In its written opinion on the case, the appellate court stated that lawyers for both Solvay and Breckenridge sought to mislead the court and the public about the regulatory status of both Estratest and Syntest (Menogen), respectively.

*"It seems obvious to this court that this last-moment motion to dismiss.....resulted from Solvay's realization that it was caught misrepresenting Estratest's regulatory status and wishes to avoid a published opinion that would alert the world to its misdeeds. Careful review of the record has uncovered a pattern of conduct by both parties' attorneys designed to mislead and confuse the court regarding the regulatory status of Estratest and Menogen.....In this case, the lawyers for both parties have frustrated the system of justice.....because they wanted to avoid an unpleasant truth about their clients' conduct."*¹⁰

These court transcripts demonstrate that both Solvay and Breckenridge have gone to significant effort and expense to keep the truth about the regulatory status of these products out of the public domain.

Given the known health risks associated with Estratest and Syntest, the significant safety questions that have yet to be examined and the lack of any established therapeutic benefit for the labeled indications, the National Women's Health Network petitions the FDA to order Solvay and Breckenridge to cease marketing Estratest and Syntest, respectively.

III. Environmental Impact Statement

The petitioners believe that the actions requested in this Petition provide no significant environmental impact. The requested actions will not introduce any substance into the environment and are categorically excluded pursuant to 21 CFR 25.30.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petition which is unfavorable to the petition.

Signed,

A large, stylized handwritten signature in black ink, consisting of several overlapping loops and a long horizontal stroke at the end.

Cynthia Pearson
Executive Director

A handwritten signature in black ink, appearing to be 'Amy Allina', with a distinct loop and a horizontal tail.

Amy Allina
Program Director

A handwritten signature in black ink, appearing to be 'Kristen Suthers', with a large initial 'K' and a long horizontal tail.

Kristen Suthers
Menopause & Aging Program Specialist

¹ Federal Register DOCID: fr14ap03-60. April 14, 2003 (Volume 68, Number 71).

² Transcript of Advisory Committee for Reproductive Health Drugs, December 2, 2004. Accessed June 20, 2006 at: <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4082T1.pdf>

³ Federal Register DOCID: fr14ap03-60. April 14, 2003 (Volume 68, Number 71).

⁴ Tamimi, RM, et al. Combined Estrogen and Testosterone Use and Risk of Breast Cancer in Postmenopausal Women. *Archives of Internal Medicine* 2006, 166:1483-1489.

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⁵ Morley, J.E. & Perry, H.M. Androgens and women at the menopause and beyond. *Journals of Gerontology: Medical Sciences* 2003, 58A:409-416.

⁶ National Institutes of Health. Women's Health Initiative: WHI Publications & Events. Accessed June 21, 2006 at: <http://www.nhlbi.nih.gov/whi/references.htm#des>

⁷ Transcript of Advisory Committee for Reproductive Health Drugs, December 2, 2004. Accessed June 20, 2006 at: <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4082T1.pdf>

⁸ Tamimi, RM, et al. Combined Estrogen and Testosterone Use and Risk of Breast Cancer in Postmenopausal Women. *Archives of Internal Medicine* 2006, 166:1483-1489.

⁹ Solvay, Inc. Global Annual Report, 2004. Accessed June 20, 2006 at: http://www.solvay-investors.com/static/wma/pdf/3/5/8/6/Solvay_RA2004_FULL_ENok3.pdf

¹⁰ See: *Breckenridge v. Solvay*. LEXSEE 1999 US APP LEXIS 8815. Case No. 98-4606, United States Court of Appeals, Eleventh Circuit, May 11, 1999.

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*According to IMS Health's National Prescription Audit (NPA), Estratest and Estratest H.S. have combined for over 36.34 million prescriptions from January 1965 through August 2003.

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- Safety and efficacy for this class of compounds was confirmed by the National Academy of Sciences¹⁴
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