

## A New Day for Women's Health at the Food and Drug Administration December 2008

### Immediate action by the President

- ◆ Issue an executive order directing the Secretary of HHS to instruct the FDA to review and evaluate the scientific data underlying the age restriction on over-the-counter access to EC to ensure that the FDA's policy is based on sound science rather than politics. (*Supporting documentation and proposed language attached.*)
- ◆ Appoint an FDA Commissioner with a demonstrated track record of leadership in the field, knowledge of and commitment to the work of the FDA and experience in managing multilayered networks of experts with respect and integrity. The new Commissioner should articulate and demonstrate a commitment to standing by evidence-based findings of the FDA's scientific and medical staff and make clear that such findings will not be suppressed, distorted, or manipulated to advance a political agenda.

### Immediate action by the FDA

- ◆ Reestablish the Office of Women's Health as a direct report to the Commissioner.

### Currently pending women's health decisions at the FDA

- ◆ Contraception/HIV Prevention On December 11, the Obstetrics and Gynecology Devices Panel of the Medical Devices Advisory Committee recommended approval of an application for the FC2 Female Condom, sponsored by the Female Health Company. This device is indicated to help prevent HIV/AIDS and unintended pregnancy. It is the first contraceptive or HIV prevention product publicly considered by the agency since the election. We're now waiting for a decision by the agency and expect it will come the first few months of 2009.
- ◆ Grandfathered products in need of safety review Last month, the AP published an analysis showing that Medicaid paid nearly \$198 million from 2004 to 2007 for more than 100 drugs that have never been approved by the FDA. These are mostly drugs that were on the market before FDA got authority to require rigorous review and the agency tries to handle them with case by case enforcement. One example of particular concern in women's health is an estrogen/testosterone combination marketed to women at menopause. The National Women's Health Network filed a citizen petition in August 2006, calling for the FDA to stop marketing these products which have not been evaluated for safety and efficacy as would be required today prior to marketing. In 2003, the FDA concluded that there is no substantial evidence of efficacy for the labeled indication, and the 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. (*Petition attached.*)



## Ongoing women's health concerns related to the FDA

- ◆ Safety of dietary supplements As more women have learned about the health risks of conventional hormone therapy drugs, many have started looking for natural alternatives, such as dietary supplements, and these products are heavily marketed to women at and around the age of menopause. While the Dietary Supplement Health and Education Act limits the FDA's authority over dietary supplements, the agency is responsible for several safety aspects of these products and has failed to exercise adequate oversight with respect to quality control, manufacturing standards and taking action against unsafe products on the market.
  
- ◆ Postmarket safety monitoring The FDA has an extremely weak track record when it comes to ensuring that manufacturers meet their commitments to conduct safety monitoring after a product is approved. The agency needs to do a better job of this across the board, and we urge attention to this area, while noting the reproductive health products should not be held to a more stringent standard than other drugs and medical devices.
  - Based on the research made public to date, the **HPV vaccine** appears to be highly effective and very safe. As with any new product, there isn't any data about its long-term safety, and it is critical for the FDA to ensure that the sponsor follow through on promises to conduct follow-up research with the people who participated in previous studies as well as additional safety monitoring of women who are vaccinated.
  
  - In 2005 the FDA approved two **silicone gel breast implants** even though FDA scientists had concluded that neither company provided sufficient data to answer questions on the safety of the products and the agency's outside scientific advisors had recommended against approval of one of the applications. This decision culminated a 15 year-long struggle between the FDA and the implant manufacturers who resisted calls for long-term studies of the device. The FDA has asked implant manufacturers to keep the clinical trials going until they have collected 10 years worth of data. (The approvals were based on 2-3 years of data.) These measures could help protect women's health and answer important outstanding questions about the safety of silicone gel breast implants.
  
  - To date the FDA has done a good job of carefully considering possible safety concerns that have been raised about mifepristone, the abortion pill, and appropriate monitoring should continue. In August 2008, a Government Accountability Office report on the FDA's approval and oversight of mifepristone found that FDA's actions have been consistent with actions taken for other drugs similarly approved.



**Review Policies that Restrict Access to Emergency Contraception (EC) and Eliminate Restrictions that Lack Scientific Support.** We urge the President to direct relevant agencies to reexamine Bush Administration policies that have blocked or limited women's access to EC ... the President should direct the Secretary of HHS to instruct the FDA to review and evaluate the scientific data underlying the age restriction on over-the-counter access to EC, to ensure that the FDA's policy is based on sound science rather than politics.

### **FDA Plan B<sup>®</sup> Over-the-Counter Status**

#### ➤ **Legal Authority for FDA to Grant Over-the-Counter Status**

The federal Food, Drug, and Cosmetic Act (FDCA) established the Food and Drug Administration within the Department of Health and Human Services.<sup>49</sup> FDA's mission is to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner..." and "with respect to such products, protect the public health by ensuring that—human . . . drugs are safe and effective."<sup>50</sup>

The Secretary of Health and Human Services, acting through the Commissioner of the FDA, is charged by the FDCA with implementing the requirements of the FDCA, "providing overall direction" to the FDA, and "research relating to foods, drugs, cosmetics, and devices in carrying out this Act."<sup>51</sup>

By law, FDA may approve a switch from prescription to over-the-counter status if use of the drug is safe and effective for self-medication in accordance with proposed labeling.<sup>52</sup> FDA manuals of policies and procedures, as well as federal regulations, delineate the procedure by which a drug is switched from prescription to over-the-counter status. The authority to approve an OTC switch application ultimately rests with the Secretary of Health and Human Services.<sup>53</sup>

#### ➤ **Suggested Language for Presidential Memorandum to the Secretary of Health and Human Services**

*Subject: Restrictions on Plan B<sup>®</sup> Approval*

On August 24, 2006, the Food and Drug Administration (FDA) approved Plan B<sup>®</sup>, an emergency contraceptive pill, for restricted sale as an over-the-counter product.<sup>54</sup> It is available without a prescription for consumers 18 years and older, and by prescription only for women 17 years and younger.

Independent evidence, including a review by the U.S. Government Accountability Office, suggests that the FDA based its assessment of a switch from prescription to over-the-counter status on factors other than whether use of the drug is safe and effective for self-medication in accordance with proposed labeling. Accordingly, I hereby direct that you promptly instruct the FDA to review and evaluate the scientific data underlying the decision to switch Plan B<sup>®</sup> from prescription to over-the-counter status only for consumers 18 years and older, and to take appropriate steps to ensure that FDA's decision is consistent with the scientific and medical evidence.

You are hereby authorized and directed to publish this memorandum in the *Federal Register*.

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<sup>49</sup> 21 U.S.C. § 393(a).

<sup>50</sup> 21 U.S.C. § 393(b)(1) and (2)(b).

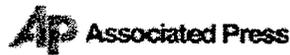
<sup>51</sup> 21 U.S.C. § 393(d).

<sup>52</sup> See 21 U.S.C. § 353(b)(1); 21 C.F.R. § 310.200(b) (2005).

<sup>53</sup> Cite.

<sup>54</sup> See Memorandum from Steven Galson, MD, MPH, Director, Center for Drug Evaluation and Research, to NDA 21-045, S-011, Subject: Plan B<sup>®</sup> (Aug. 24, 2006).



**AP IMPACT: Govt pays millions for unapproved drugs**

By RICARDO ALONSO-ZALDIVAR and FRANK BASS – Nov 23, 2008

WASHINGTON (AP) — Taxpayers have shelled out at least \$200 million since 2004 for medications that have never been reviewed by the government for safety and effectiveness but are still covered under Medicaid, an Associated Press analysis of federal data has found. Millions of private patients are taking such drugs, as well.

The availability of unapproved prescription drugs to the public may create a dangerous false sense of security. Dozens of deaths have been linked to them.

The medications date back decades, before the Food and Drug Administration tightened its review of drugs in the early 1960s. The FDA says it is trying to squeeze them from the market, but conflicting federal laws allow the Medicaid health program for low-income people to pay for them.

The AP analysis found that Medicaid paid nearly \$198 million from 2004 to 2007 for more than 100 unapproved drugs, mostly for common conditions such as colds and pain. Data for 2008 were not available but unapproved drugs still are being sold. The AP checked the medications against FDA databases, using agency guidelines to determine if they were unapproved. The FDA says there may be thousands of such drugs on the market.

Medicaid officials acknowledge the problem, but say they need help from Congress to fix it. The FDA and Medicaid are part of the Health and Human Services Department, but the FDA has yet to compile a master list of unapproved drugs, and Medicaid — which may be the biggest purchaser — keeps paying.

"I think this is something we ought to look at very hard, and we ought to fix it," said Medicaid chief Herb Kuhn. "It raises a whole set of questions, not only in terms of safety, but in the efficiency of the program — to make sure we are getting the right set of services for beneficiaries."

At a time when families, businesses and government are struggling with health care costs and 46 million people are uninsured, payments for questionable medications amount to an unplugged leak in the system.

Sen. Charles Grassley, R-Iowa, has asked the HHS inspector general to investigate.

That unapproved prescription drugs can be sold in the United States surprises even doctors and pharmacists. But the FDA estimates they account for 2 percent of all prescriptions filled by U.S. pharmacies, about 72 million scripts a year. Private insurance plans also cover them.



The roots of the problem go back in time, tangled in layers of legalese.

It wasn't until 1962 that Congress ordered the FDA to review all new medications for effectiveness. Thousands of drugs already on the market were also supposed to be evaluated. But some manufacturers claimed their medications were "grandfathered" under earlier laws, and even under the 1962 bill.

Then, in the early 1980s, a safety scandal erupted over one of those medications. E-Ferol, a high potency vitamin E injection, was linked to serious reactions in some 100 premature babies, 40 of whom died.

In response, the FDA started a program to weed out drugs it had never reviewed scientifically. Yet some medications continued to escape scrutiny.

Sometimes, the medications do not help patients. In other cases, the FDA says, they have made people sicker, maybe even killed them. This year, for example, the FDA banned injectable versions of a gout drug called colchicine after receiving reports of 23 deaths. Investigators found the unapproved drug had a very narrow margin of safety, and patients easily could receive a toxic dose leading to complications such as organ failure.

Critics say the FDA's case-by-case enforcement approach is not working.

"The FDA does not appear to have a systematic mechanism to report these drugs out," said Jon Glaudemans, senior vice president of Avalere Health, a health care industry information company, "and there doesn't seem to be a systematic process by which health insurance programs can validate their status. And everyone is pointing the finger at someone else as to why we can't get there."

In most cases, doctors, pharmacists and patients are not aware the drugs are unapproved.

"Over the years, they have become fully entrenched in the system," said Patti Manolakis, a Charlotte, N.C., pharmacist who has studied the issue. Only a few unapproved drugs are truly essential and should remain on the market, she added.

Tackling the problem is made harder by confusing — and sometimes conflicting — laws, regulations and responsibilities that pertain to different government agencies.

Medicaid officials said their program, which serves the poor and disabled, is allowed to pay for unapproved drugs until the FDA orders a specific medication off the market. But that can take years.

Compare that with Medicare, the health care program for older people.

Medicare's prescription program is not supposed to cover unapproved drugs. Medicare has purged hundreds of such medications from its coverage lists, but continues to find others.



It might be easier to sort things out if the FDA compiled a master list of unapproved drugs, but the agency hasn't. FDA officials say that would be difficult because many manufacturers do not list unapproved products with the agency. Yet, the AP found many that were listed — a possible starting point for a list.

Among the drugs the AP's research identified were Carbofed, for colds and flu; Hylira, a dry skin ointment; Andehist, a decongestant, and ICAR Prenatal, a vitamin tablet. Medicaid data show the program paid \$7.3 million for Carbofed products from 2004 to 2007; \$146,000 for Hylira; \$4.8 million for Andehist products, and \$900,000 for ICAR.

Grassley said the system is failing taxpayers and consumers.

"The problem I see is bureaucrats don't want to make a decision," Grassley said. "There is no reason why this should be such a house of mirrors when so much public money is being spent." Grassley is considering introducing legislation to ensure that consumers are told when a medication is unapproved.

FDA officials say they tell Medicaid and Medicare when the agency moves to ban an unapproved drug, so the programs can stop paying.

"The situation is complicated by the fact that Medicaid and Medicare have a different regulatory regime than FDA does," said FDA compliance lawyer Michael Levy. "There are products that we may consider to be illegally marketed that could be legally reimbursed under their law."

The FDA began its latest crackdown on unapproved drugs two years ago and has taken action against nine types of medications and dozens of companies. Typically, the agency orders manufacturers to stop making and shipping drugs, and it also has seized millions of dollars' worth of medications. But federal law does not provide fines for selling unapproved drugs, and criminal prosecutions are rare.

Some manufacturers of unapproved drugs say their products predate FDA regulation and are "grandfathered in."

"These are drugs that don't require an FDA approval," said Bill Peters, chief financial officer of Hi-Tech Pharmacal in Amityville, N.Y. "These are products with active ingredients that have been on the market for a long time." The company is moving away from older products, Peters said, and its new market offerings are FDA-approved.

Levy said the FDA is skeptical that any drugs now being sold are entitled to "grandfather" status. To qualify, they would have to be identical to medications sold decades ago in formulation and other important aspects.

The agency is targeting drugs linked to fraud, ones that do not work and, above all, those with safety risks. While the crackdown has helped, it does not appear to have solved the problem.



The gout drug banned by the FDA this February is not the only recent case involving safety problems.

Last year, the FDA banned unapproved cough medicines containing hydrocodone, a potent narcotic. Some had directions for medicating children as young as age 2, although no hydrocodone cough products have been shown to be safe and effective for children under 6.

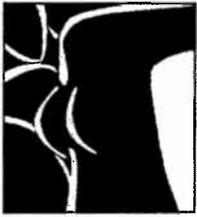
In a 2006 case, the agency received 21 reports of children younger than 2 who died after taking unapproved cold and allergy medications containing carbinoxamine, an allergy drug that also acts as a powerful sedative. Regulators banned all products that contained carbinoxamine in combination with other cold medicines.

"We as Americans have a belief that all the prescription drugs that are available to us have been reviewed and approved by the FDA," said Manolakis, the pharmacist. "I think the presence of these drugs shows we have a false sense of security."

On the Net:

- FDA's unapproved drugs page: <http://tinyurl.com/4tv2sb>

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**NATIONAL  
WOMEN'S  
HEALTH  
NETWORK**

A VOICE FOR WOMEN, A NETWORK FOR CHANGE

0429 6 05 22 P1:37

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

CP 1

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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.<sup>1,2</sup>

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."<sup>3</sup> 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:<sup>4</sup>

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.<sup>5</sup>



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.<sup>6</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>7</sup> 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.<sup>8</sup> In 2000, Estratest was the 199<sup>th</sup> 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.<sup>9</sup> 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."*<sup>10</sup>

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,

Cynthia Pearson  
Executive Director

Amy Allina  
Program Director

Kristen Suthers  
Menopause & Aging Program Specialist

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

<sup>2</sup> 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>

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

<sup>4</sup> 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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<sup>5</sup> Morley, J.E. & Perry, H.M. Androgens and women at the menopause and beyond. *Journals of Gerontology: Medical Sciences* 2003, 58A:409-416.

<sup>6</sup> 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>

<sup>7</sup> 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>

<sup>8</sup> 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.

<sup>9</sup> 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](http://www.solvay-investors.com/static/wma/pdf/3/5/8/6/Solvay_RA2004_FULL_ENok3.pdf)

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

# Turn on estrogen-androgen powered therapy

NWHN Citizen Petition Attachment # 1

## A long history of estrogen-androgen therapy

- ESTRATEST® Brand Tablets is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause in those patients not improved by estrogen alone<sup>13</sup>

## A trusted choice

- Over 38 years of marketed experience
- More than 36 million prescriptions filled\*

\*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.

Make **ESTRATEST® Brand Tablets** your first choice when hot flashes and night sweats persist despite taking estrogen alone

- Safety and efficacy for this class of compounds was confirmed by the National Academy of Sciences<sup>14</sup>
- This product has not obtained FDA pre-market approval applicable for new drugs
- **ESTRATEST® does not contain a progestogen and women with an intact uterus need to have an opposing progestogen<sup>13</sup>**

Safety

Tolerability



