



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-1998-P-0083 (formerly 76N-0377); DESI 7661]

Drugs for Human Use; Drug Efficacy Study Implementation: Estrogen-Androgen Fixed-Combination Drug Products; Syntest D.S. and Syntest H.S. Tablets; Withdrawal of Hearing Requests; Final Resolution of Drug Efficacy Study Implementation 7661

AGENCY: Food and Drug Administration, Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing that all outstanding hearing requests for estrogen-androgen fixed-combination drug products under Docket FDA-1998-P-0083 (formerly 76N-0377) (DESI 7661) have been withdrawn. Therefore, as proposed in the April 14, 2003, notice of opportunity for hearing (NOOH), FDA finds that the products subject to this proceeding have not been shown to be effective for use under the conditions of use prescribed, recommended, or suggested in the labeling. Shipment in interstate commerce of any product identified in this docket (DESI 7661), or any identical, related, or similar (IRS) product, that is not the subject of an approved new drug application (NDA) or abbreviated new drug application (ANDA) is unlawful as of the date of this notice.

DATES: This notice is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500 between 9 a.m. and 4 p.m., Monday through Friday. Publicly available submissions may be seen in the docket.

The most relevant background documents regarding this matter are available in the docket. However, additional background documents are available upon request (see FOR FURTHER INFORMATION CONTACT).

FOR FURTHER INFORMATION CONTACT: Amber McKinley, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 5172, Silver Spring, MD 20993-0002, 301-796-0061, e-mail: Amber.McKinley@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require that “new drugs” (21 U.S.C. 321(p)) be proven effective for their labeled indications, as well as safe, in order to obtain FDA approval (Drug Amendments of 1962 (Pub. L. 87–781)). These amendments also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962. FDA contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that had been approved only for safety between 1938 and 1962. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and reevaluated the reports and published its findings in *Federal Register* notices. FDA’s administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the approximately 3,400 products specifically reviewed by the NAS/NRC, as well as the even larger number of products that were IRS (see 21 CFR 310.6(b)(1)) to the approved drug products and that had entered the market without FDA approval. All drugs covered by the DESI review are “new drugs” under the FD&C Act.

II. Final Resolution of Hearing Request Regarding Estrogen-Androgen Fixed-Combination Drug Products Under Docket FDA-1998-P-0083 (formerly 76N-0377); DESI 7661

In a *Federal Register* notice published on September 8, 1972 (37 FR 18225), FDA announced its evaluation of reports received from the NAS/NRC under DESI 7661 regarding five fixed-combination drug products containing an estrogen and an androgen. FDA stated in that notice that it found these drugs to be effective “for the prevention of postpartum breast engorgement” and “for the menopausal syndrome in those patients not improved by estrogen alone.” With respect to the first indication, on December 17, 1998, FDA withdrew approval of estrogen-containing drug products insofar as they were indicated for postpartum breast engorgement, because estrogens were not shown to be safe for this use (63 FR 69631).¹ Given FDA’s findings in the December 17, 1998, *Federal Register* notice, the remainder of this notice focuses on the second indication in the September 1972 notice, i.e. “for the menopausal syndrome in those patients not improved by estrogen alone.”

In the *Federal Register* of September 29, 1976 (41 FR 43112), FDA announced that the menopausal indication for fixed-combination drugs containing an estrogen and an androgen (including the five drug products identified in the September 8, 1972, notice) was revised to read:

Moderate to severe vasomotor symptoms associated with the menopause in those patients not improved by estrogen alone (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions).

Id. at 43113.

In 1981, in response to requests from the sponsors, FDA determined that the effectiveness finding in the September 29, 1976, notice could be applied to two fixed-combination drug products that were not listed in the 1976 notice but were being marketed at the time: (1) conjugated estrogens and methyltestosterone, and (2) esterified estrogens and methyltestosterone. See 68 FR 17953, 17954 (April 14, 2003).

¹ For additional background information leading to the 1998 *Federal Register* notice, see 68 FR 17953 (April 14, 2003).

FDA took a renewed interest in both the safety and efficacy of estrogen-androgen products while reviewing potential new safety concerns about the products. As detailed in the *Federal Register* on April 14, 2003 (68 FR 17953), an Agency review of the literature led FDA to reclassify the September 1976 effectiveness finding for estrogen-androgen fixed combination drug products to lacking substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with menopause in patients not improved by estrogen alone. At the same time, FDA also issued a Notice of Opportunity for a Hearing (NOOH) to manufacturers and distributors of drug products affected by the notice, regarding FDA's determination that such products lacked substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with menopause in patients not improved by estrogen alone. In response to the April 14, 2003, NOOH, two companies requested hearings: Syntho Pharmaceutical, Inc. (Syntho), 230 Sherwood Ave, Farmingdale, NY 11735, and Solvay Pharmaceuticals, since acquired by Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL 60064.

In response to the 2003 NOOH, Syntho filed a written notice of participation and request for a hearing on May 14, 2003, and submitted data in support of its hearing request on June 13, 2003. Syntho marketed Syntest D.S. (1.25 milligrams (mg) esterified estrogens/2.5 mg methyltestosterone) and Syntest H.S. (0.625 mg esterified estrogens/1.25 mg methyltestosterone), both labeled for use in treating moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone. In a letter dated January 31, 2011, FDA asked Syntho whether it was interested in pursuing its hearing request. Syntho affirmed its hearing request on March 1, 2011. By letter dated June 18, 2025, FDA again asked Syntho whether it wanted to pursue its hearing request regarding its Syntest D.S. and Syntest H.S. products. By letter dated August 1, 2025, Syntho stated that it had decided to withdraw its hearing request.

At the time of Solvay's 2003 hearing request, the firm marketed Estratest and Estratest HS. On January 31, 2011, FDA sent a letter to Abbott asking whether it wanted to pursue the hearing request regarding its Estratest and Estratest HS products. On June 21, 2011, Abbott responded by withdrawing the hearing request previously filed by Solvay Pharmaceuticals before its acquisition by Abbott.

III. Conclusions and Order

There are no outstanding hearing requests regarding estrogen-androgen fixed-combination drug products under Docket FDA-1998-P-0083, DESI 7661. As proposed in the April 14, 2003, NOOH, such products lack substantial evidence of effectiveness for the treatment of moderate to severe vasomotor symptoms associated with the menopause in patients not improved by estrogen alone. Shipment in interstate commerce of any drug product identified in this docket, or any IRS product, that is not the subject of an approved NDA or ANDA is unlawful as of the effective date of this notice (see EFFECTIVE DATE). Any person who wishes to determine whether this notice covers a specific product should write to Amber McKinley at the Center for Drug Evaluation and Research (see FOR FURTHER INFORMATION CONTACT). Firms should be aware that, after the applicable date of this notice (see EFFECTIVE DATE), FDA intends to take enforcement action without further notice against any firm that manufactures or ships in interstate commerce any unapproved product covered by this notice.

IV. Discontinued Products

Firms must notify the Agency of certain product discontinuations in writing under section 506C(a) of the FD&C Act (21 U.S.C. 356c). Some firms may have previously discontinued manufacturing or distributing products covered by this notice without discontinuing the listing as required under section 510(j) of the FD&C Act (21 U.S.C. 360(j)). Other firms may discontinue manufacturing or distributing listed products in response to this notice. All firms are required to electronically update the listing of their products under 510(j) of the FD&C Act to reflect

discontinuation of unapproved products covered by this notice (21 CFR 207.57(b)). Questions on electronic drug listing updates should be sent to eDRLS@fda.hhs.gov. In addition to the required update, firms can also notify the Agency of product discontinuation by sending a letter, signed by the firm's chief executive officer and fully identifying the discontinued product(s), including the product National Drug Code number(s), and stating that the manufacturing and/or distribution of the product(s) have been discontinued. The letter should be sent electronically to Amber McKinley (see FOR FURTHER INFORMATION CONTACT). FDA plans to rely on its existing records, including its drug listing records, the results of any future inspections, or other available information, when it identifies violative products for enforcement action.

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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