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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 78N-0280; DESI Nos. 740, 1543, and 7661]

Estrogens for Postpartum Breast Engorgement; Withdrawal of Approval of the Labeled Indication for Postpartum Breast Engorgement in Estrogen-Containing Drug Products; Final Order

AGENCY : Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY : The Food and Drug Administration (FDA) is withdrawing approval of estrogen-containing drugs insofar as they are indicated for use in postpartum breast engorgement. The basis for the action is that estrogens are not shown to be safe for that use.

EFFECTIVE DATE: (Insert date of publication in the FEDERAL REGISTER.)

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: For many years, estrogen-containing drug products were used to suppress postpartum breast

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engorgement. By the 1970's, however, the use of estrogens was shown to be associated with an increased risk of puerperal thromboembolism. Moreover, estrogen dosages for the suppression of postpartum breast engorgement were higher than for other labeled indications. The risk of thromboembolism was first evaluated by the FDA Obstetrics and Gynecology Advisory Committee, now called the Advisory Committee for Reproductive Health Drugs (the Committee), on July 15 and 16, 1976. At that time, the Committee recommended that estrogen drug products indicated for the suppression of postpartum breast engorgement contain an insert stating that the risk of thromboembolism should be considered in conjunction with the risk-free alternative of the use of breast binding and mild analgesics. On January 31, 1978, after additional risk evaluation, the Committee recommended that estrogen-containing drug products' indication for the suppression of postpartum breast engorgement be withdrawn.

In a notice of opportunity for hearing (NOOH) published in the FEDERAL REGISTER of October 24, 1978 (43 **FR** 49564), the agency proposed to withdraw approval of all new drug applications (NDA's) for estrogen-containing drug products labeled for use in postpartum breast engorgement approved either before or after the Drug Amendments of 1962 (Pub. L. 87-781) . The NOOH also applied to any identical, similar, or related drug product whether or not

it was the subject of an NDA. The NOOH listed the following NDA's:

1. NDA 0-740; Di-Ovocyclin Injection containing estradiol dipropionate; Ciba Pharmaceutical Co., Division Ciba Giegy Corp. , 556 Morris Ave., Summit, NJ 07901.

2. NDA 4-039; Stilbestrol Ect. containing diethylstilbestrol; Eli Lilly & Co., Box 618, Indianapolis, IN 46206.

3. NDA 4-041; Stilbestrol Tablets and Injection containing diethylstilbestrol; Eli Lilly & Co.

4. NDA 4-056; Stilbestrol Tablets, Injection, and Suppositories containing diethylstilbestrol; E. R. Squibb & Sons, Inc. , Box 4000, Princeton, NJ 08540.

5. NDA 4-073; Stilbestrol Perles, Injection and Suppositories containing diethylstilbestrol; The Upjohn co., 7171 Portage Rd., Kalamazoo, MI 49002.

6. NDA 4-782; Premarin Tablets containing conjugated estrogens; Ayerst Laboratories, Division of American Home Products Corp., 685 Third Ave., New York, NY 10017.

7. NDA 4-823; Estrone Injection containing estrone; Abbott Laboratories, 14th and Sheridan Rd., North Chicago, IL 60064.

8. NDA 5-159; Diethylstilbestrol Dipropionate Tablets containing diethylstilbestrol dipropionate; BlueLine Laboratories, Inc. , 302 South Broadway, St. Louis, MO 63102.

9. NDA 5-233; Diethylstilbestrol Tablets containing diethylstilbestrol; High Chemical co., 1760 North Howard St., Philadelphia, PA 19122.
10. NDA 5-292; Estinyl Tablets containing ethinyl estradiol; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033.
11. NDA 7-661; AE Tablets and Tylosterone Tablets containing diethylstilbestrol and methyltestosterone; Eli Lilly & co.
12. NDA 8-099; Tylosterone Injection containing diethylstilbestrol and methyltestosterone; Eli Lilly & Co.
13. NDA 8-102; Tace Tablets and Capsules containing chlorotrianisene; Merrell-National Laboratories, Division of Richardson-Merrell Inc., 110 East Amity Rd., Cincinnati, OH 45215.
14. NDA 8-579; Vallestril Tablets containing methallenestril; Searle Laboratories, Division of G. D. Searle & co., Box 5100, Chicago, IL 60680.
15. NDA 9-402; Delestrogen Injection, Delestrogen 4X Injection, and Delestrogen 2X Injection containing estradiol valerate; E. R. Squibb & Sons, Inc.
16. NDA 9-545; Deladumone Injection containing testosterone enanthate and estradiol valerate; E. R. Squibb & Sons, Inc.

17. NDA 10-597; Tace-Androgen Capsules containing chlorotrianisene and methyltestosterone; Merrell-National Laboratories .

18. NDA 11-444; Tace Capsules containing chlorotrianisene and Tace with Ergonovine Capsules containing chlorotrianisene and ergonovine maleate; Merrell-National Laboratories.

19. NDA 16-235; Tace 72-Milligram Capsule containing chlorotrianisene; Merrell-National Laboratories.

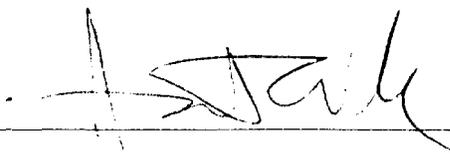
20. NDA 16-768; Estrovis Tablets containing quinestrol; Warner Chilcott Laboratories, Division Warner Lambert Co., 201 Tabor Rd., Box W, Morris Plains, NJ 07950.

In response to the NOOH, Merrell-National Laboratories, Parke-Davis, E. R. Squibb & Sons, Inc., Byk-Gulden, Inc., and the American College of Obstetricians and Gynecologists (the College) requested hearings, but the firms voluntarily agreed to remove the indication from their labeling. Since then, the College and the firms, or their respective successors in interest, have withdrawn their hearing requests. (The approvals of NDA 7-661, NDA 8-099, and NDA 9-545 were withdrawn in a FEDERAL REGISTER notice of October 29, 1998 (63 FR 58053) ; the approval of NDA 10-597 was withdrawn in a FEDERAL REGISTER notice of June 25, 1993 (58 FR 34466); the approval of NDA 16-768 was withdrawn in a FEDERAL REGISTER notice of March 27, 1996 (61 FR 13506).)

Therefore, for reasons stated in the NOOH of October 24, 1978, as well as the reasons discussed above, the Director of the Center for Drug Evaluation and Research hereby withdraws approval of any estrogen-containing drug product insofar as it is labeled for the suppression of postpartum breast engorgement. - (In the FEDERAL REGISTER of January 17, 1995 (60 FR 3404), FDA withdrew approval of bromocriptine mesylate for the indication of the

prevention of physiological lactation, i.e., postpartum breast engorgement; today's action means, therefore, that no product is currently approved for this indication.) This notice is issued under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10(a) (1)) and redelegate to the Director of the Center for Drug Evaluation and Research (21 CFR 5.82) .

Dated: November 30, 1998



Janet Woodcock
Director
Center for Drug Evaluation and
Research

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