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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 77 N-0240; DESI 1786]

Certain Single-Entity Coronary Vasodilators Containing Isosorbide
Dinitrate; Opportunity for a Hearing

AGENCY : Food and Drug Administration, HHS.

ACTION : Notice.

SUMMARY: The Food and Drug Administration (FDA) is proposing to withdraw approval of 25 abbreviated new drug applications (ANDA's) for certain single-entity coronary vasodilator drug products containing isosorbide dinitrate. FDA is offering the holders of the applications an opportunity for a hearing on the proposal. The basis for the proposal is that the sponsors of these products have failed to submit acceptable data on bioavailability and bioequivalence.

DATES : Requests for a hearing are due by (insert date 30 days after date of publication in the FEDERAL REGISTER); data and information in support of hearing requests are due by (insert date 60 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: A request for hearing, supporting data, and other comments are to be identified with Docket No. 77N-0240 and submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857.

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Comments in response to this notice, identified with the reference number DESI 1786 and a request for applicability of this notice to a specific product, should be directed to the Division of Prescription Drug Compliance and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pi., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Mary E. Catchings,
Center for Drug Evaluation and Research (HFD-7),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-594-2041.

SUPPLEMENTARY INFORMATION:

I. Background

In a notice (DESI 1786) published in the FEDERAL REGISTER of February 25, 1972 (37 FR 4001), FDA announced its evaluation of reports received from the National Academy of Sciences/National Research Council, Drug Efficacy Study Group on certain coronary **vasodilator** drugs. FDA classified isosorbide dinitrate drug products as: Probably effective for the treatment and prevention of **anginal** attacks when administered sublingually, and possibly effective for their **labeled** indications relating to the

management, prophylaxis, or treatment of anginal attacks when administered orally.

In notices published in the FEDERAL REGISTER of December 14, 1972 (37 FR 26623), July 11, 1973 (38 FR 18477), August 26, 1977 (42 FR 43127), October 21, 1977 (42 FR 56156), and September 15, 1978 (43 FR 41282), FDA temporarily exempted certain single-entity coronary vasodilators, including isosorbide dinitrate, from the time limits established for the Drug Efficacy Study Implementation (DESI) program. The notices established conditions for marketing these products and identical, similar, or related products § 310.6 (21 CFR 310.6) whether or not they had been marketed and whether or not they were subjects of approved new drug applications (NDA's). FDA required manufacturers and distributors to have ANDA's (conditionally approved, pending the results of ongoing studies) to market a product not the subject of NDA's. If at least one drug sponsor was conducting clinical studies on a chemical entity, FDA permitted the marketing of all firms' products containing the same chemical entity in a similar dosage form, provided each product met the other conditions. Not all sponsors, therefore, were required to conduct clinical studies. Because bioavailability is specific for an individual product, however, FDA required each firm to conduct a bioavailability study on its own product.

In a notice published in the FEDERAL REGISTER of August 3, 1984 (49 FR 31151), after completing its review of the clinical studies submitted for single-entity isosorbide dinitrate, FDA announced its conclusions that these drugs are effective. The notice set forth the marketing and labeling conditions for the products. Additionally, FDA required the submission of supplements providing acceptable in vitro dissolution tests and in vivo bioavailability/bioequivalence studies. The August 3, 1984, notice stated that supplements not fully approved within 1 year would be subject to proceedings to withdraw the previous approval and to remove the products from the market. This deadline was extended to June 26, 1987, in a notice published in the FEDERAL REGISTER of December 26, 1985 (50 FR 52856) .

The sponsors of the drug products listed in section II of this document are not in compliance with the notices of August 3, 1984, and December 26, 1985, in that they either have not submitted any bioavailability/bioequivalence data or have not submitted additional data on incomplete or inadequate studies. Accordingly, this notice reclassifies the products listed in section II of this document as lacking substantial evidence of effectiveness, proposes to withdraw approval of the applications, and offers an opportunity for a hearing on the proposal.

II. ANDA'S Subject to This Notice

1. ANDA 85-783; Isordil Chewable Tablets containing 10 milligrams (mg) of isosorbide dinitrate per tablet; Wyeth-Ayerst Laboratories (formerly held by Ives Laboratories, Inc.) , P.O. Box 8299, Philadelphia, PA 19101.
2. ANDA 86-045; Isosorbide Dinitrate Tablets containing 5 mg of the drug per tablet; Bolar Pharmaceutical Co., Inc., 130 Lincoln St., Copiague, NY 11726.
3. ANDA 86-186; Isosorbide Dinitrate (controlled release, colored) Capsules containing 40 mg of the drug per capsule; Eon Labs Manufacturing, Inc. (formerly held by The Vitarine Co., Inc.), 227-15 North Conduit Ave., Laurelton, NY 11413.
4. ANDA 86-191; Isosorbide Dinitrate (sublingual) Tablets containing 5 mg of the drug per tablet; Bolar.
5. ANDA 86-224; Isosorbide Dinitrate (controlled release) Tablets containing 40 mg of the drug per tablet; Geneva Pharmaceuticals, Inc. (formerly held by Cord Laboratories, Inc.) , 2555 West Midway Blvd., P.O. Box 446, Broomfield, CO 80038-0446.
6. ANDA 86-362; Isosorbide Dinitrate (sublingual) Tablets containing 2.5 mg of the drug per tablet; Bolar.
7. ANDA 86-388; **Sorbitrate** (chewable) Tablets containing 10 mg of isosorbide dinitrate per tablet; Zeneca Pharmaceuticals, 1800 Concord Pike, Wilmington, DE 19897.

8. ANDA 86-788; Isosorbide Dinitrate (controlled release, green) Tablets containing 40 mg of the drug per tablet; Forest Laboratories, Inc., 919 Third Ave., New York, NY 10022.

9. ANDA 86-790; Isosorbide Dinitrate (controlled release, yellow) Tablets containing 40 mg of the drug per tablet; Forest.

10. ANDA 87-314; Isosorbide Dinitrate (chewable) Tablets containing 10 mg of the drug per tablet; D. M. Graham Laboratories, Inc., 58 Pearl St., P.O. Box P, Hobart, NY 13788.

11. ANDA 87-414; Isosorbide Dinitrate (controlled release scarlet/clear) Capsules containing 40 mg of the drug per capsule; Eon Labs.

12. ANDA 87-461; Isosorbide Dinitrate (controlled release orange/clear) Capsules containing 40 mg of the drug per capsule; Eon Labs.

13. ANDA 87-477; Isosorbide Dinitrate (sublingual) Tablets containing 2.5 mg of the drug per tablet; Ascot Hospital Pharmaceuticals, Inc. , 8055 North Ridgeway Ave., Skokie, IL 60076.

14. ANDA 87-482; Isosorbide Dinitrate (controlled release) Tablets containing 40 mg of the drug per tablet; Ascot.

15. ANDA 87-507; **Isosorbide** Dinitrate (controlled release white/amethyst) Capsules containing 40 mg of the drug per capsule; Eon Labs.

16. ANDA 87-558; Isosorbide Dinitrate (controlled release) Tablets containing 40 mg of the drug per tablet; Par Pharmaceutical, Inc., One Ram Ridge Rd., Spring Valley, NY 10977.

17. ANDA 87-680; Isosorbide Dinitrate (controlled release white/clear) Capsules containing 40 mg of the drug; Eon Labs.

18. ANDA 87-694; Isosorbide Dinitrate (sublingual) Tablets containing 5 mg of the drug per tablet; Vanguard Labs, Inc. , P.O. Box 1268, Glasgow, KY 42142-1268.

19. ANDA 87-700; Isosorbide Dinitrate (sublingual) Tablets containing 2.5 mg of the drug per tablet; Vanguard.

20. ANDA 88-074; Sorbitrate Tablets containing 20 mg of isosorbide dinitrate per tablet; Zeneca.

21. ANDA 88-428; Isosorbide Dinitrate (controlled release) Tablets containing 20 mg of the drug per tablet; Forest.

22. ANDA 88-589; Isosorbide Dinitrate Tablets containing 5 mg of the drug per tablet; Barr Laboratories, Inc. , Two Quaker Rd ., P. O. Box 2900, Pomona, NY 10970-0519.

23. ANDA 88-590; Isosorbide Dinitrate Tablets containing 5 mg of the drug per tablet; Barr.

24. ANDA 88-591; Isosorbide Dinitrate Tablets containing 20 mg of the drug per tablet; Barr.

25. ANDA 88-592; Isosorbide Dinitrate (sublingual) Tablets containing 2.5 mg of the drug per tablet; Barr.

III. Notice of Opportunity for a Hearing

On the basis of all available data and information, the Director of the Center for Drug Evaluation and Research is unaware of any adequate and well-controlled clinical investigation, conducted by experts who are qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355), 21 CFR 314.126, and 21 CFR part 320 that demonstrates effectiveness (i.e., bioavailability/bioequivalence) of the drugs that are in compliance with the conditions established for continued marketing.

Therefore, notice is given to the holders of the ANDA's listed previously and to a 11 other interested persons that the Director of the Center for Drug Evaluation and Research proposes to issue an order under section 505(e) of the act withdrawing approval of the applications and all amendments and supplements thereto on the ground that new information before her with respect to the drug products, evaluated together with the evidence available to her when the applications were approved, shows there is a lack of substantial evidence that the drug products will have the effect they purport or are represented to have under the conditions of use prescribed, recommended, or suggested in the labeling.

In addition to the holders of the applications specifically named in section II of the document, this notice of opportunity for hearing applies to all persons who manufacture or distribute a drug product, not the subject of an approved application, that is identical, related, or similar to a drug product named previously, as defined in § 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice of opportunity for hearing to determine whether it covers any drug product that they manufacture or distribute. Such persons may request an opinion on the applicability of this notice to a specific drug product by writing to the Division of Prescription Drug Compliance and Surveillance (address given above) .

This notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in § 310.6); e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act (21 U.S.C. 321(P)) or because it is exempt from part or all of the new drug provisions of the act under the exemption for products marketed before June 25, 1938, in section 201(p) of the act, or under section 107(c) of the Drug Amendments of 1962, or for any other reason.

In accordance with section 505 of the act and the regulations issued under it (21 CFR parts 310 and 314), an applicant and all other persons subject to this notice are hereby given an opportunity for hearing to show why approval of the applications should not be withdrawn.

An applicant or any other person subject to this notice who decides to seek a hearing shall file: (1) On or before (insert date 30 days after date of publication in the FEDERAL REGISTER), a written notice of appearance and request for hearing, and (2) on or before (insert date 60 days after date of publication in the FEDERAL REGISTER), the data, information, and analyses relied on to demonstrate that there is a genuine issue of material fact to justify a hearing, as specified in § 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for a hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, other comments, and a grant or denial of a hearing are contained in §§ 314.151 and 314.200 and in 21 CFR part 12.

The failure of an applicant or any other person subject to this notice to file a timely written notice of appearance and request for hearing, as required by § 314.200, constitutes an **election** by that person not to use the opportunity for a hearing concerning the action proposed and a waiver of any contentions

concerning the legal status of that person's drug product(s) .
Any new drug product marketed without an approved new drug
application is subject to regulatory action at any time.

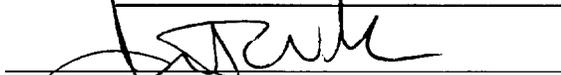
A request for a hearing may not rest upon mere allegations
or denials, but must present specific facts showing that there is
a genuine and substantial issue of fact that requires a hearing.
If it conclusively appears from the face of the data,
information, and factual analyses in the request for hearing that
there is no genuine and substantial issue of fact which precludes
the withdrawal of approval of the application, or when a request
for hearing is not made in the required format or with the
required analyses, the Commissioner of Food and Drugs will enter
summary judgment against the person(s) who requests the hearing,
making findings and conclusions, and denying a hearing.

All submissions under this notice of opportunity for a
hearing are to be filed in four copies. Except for data and
information prohibited from public disclosure under 21 U.S.C.
331(j) or 18 U.S.C. 1905, the submissions may be seen in the

Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505 (21 U.S.C. 355)) and under authority delegated to the Director of the Center for Drug Evaluation and Research (21 CFR 5.82).

Dated: March 3, 1999



Janet Woodcock
Director
Center for Drug Evaluation
and Research

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