

and the final decision of the Commission shall be issued by May 8, 1998.

By the Commission.
Joseph C. Polking,
Secretary.

[FR Doc. 97-829 Filed 1-13-97; 8:45 am]

BILLING CODE 6730-01-M

FEDERAL RESERVE SYSTEM

Notice of Proposals To Engage in Permissible Nonbanking Activities or To Acquire Companies That Are Engaged in Permissible Nonbanking Activities

The companies listed in this notice have given notice under section 4 of the Bank Holding Company Act (12 U.S.C. 1843) (BHC Act) and Regulation Y, (12 CFR Part 225) to engage *de novo*, or to acquire or control voting securities or assets of a company that engages either directly or through a subsidiary or other company, in a nonbanking activity that is listed in § 225.25 of Regulation Y (12 CFR 225.25) or that the Board has determined by Order to be closely related to banking and permissible for bank holding companies. Unless otherwise noted, these activities will be conducted throughout the United States.

Each notice is available for inspection at the Federal Reserve Bank indicated. Once the notice has been accepted for processing, it will also be available for inspection at the offices of the Board of Governors. Interested persons may express their views in writing on the question whether the proposal complies with the standards of section 4 of the BHC Act, including whether consummation of the proposal can "reasonably be expected to produce benefits to the public, such as greater convenience, increased competition, or gains in efficiency, that outweigh possible adverse effects, such as undue concentration of resources, decreased or unfair competition, conflicts of interests, or unsound banking practices" (12 U.S.C. 1843). Any request for a hearing on this question must be accompanied by a statement of the reasons a written presentation would not suffice in lieu of a hearing, identifying specifically any questions of fact that are in dispute, summarizing the evidence that would be presented at a hearing, and indicating how the party commenting would be aggrieved by approval of the proposal.

Unless otherwise noted, comments regarding the applications must be received at the Reserve Bank indicated

or the offices of the Board of Governors not later than January 29, 1997.

A. Federal Reserve Bank of New York (Christopher J. McCurdy, Senior Vice President) 33 Liberty Street, New York, New York 10045:

1. *Canadian Imperial Bank of Commerce*, Toronto, Canada; to engage *de novo*, through its wholly owned subsidiary, CIBC Investment Corporation, New York, New York ("Company"), in trading for its own account, for purposes other than hedging, in futures, options, and options on futures contracts based on certain securities indices and money market instruments. Canadian Imperial proposes that Company would conduct these activities throughout the world. See *Swiss Bank Corporation*, 81 Fed. Res. Bull. 185 (1995).

Board of Governors of the Federal Reserve System, January 8, 1997.

Jennifer J. Johnson,

Deputy Secretary of the Board.

[FR Doc. 97-828 Filed 1-13-97; 8:45 am]

BILLING CODE 6210-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 96N-0512]

Hoechst Marion Roussel, Inc., and Baker Norton Pharmaceuticals, Inc.; Terfenadine; Proposal To Withdraw Approval of Two New Drug Applications and One Abbreviated New Drug Application; 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 two new drug applications (NDA's) and one abbreviated new drug application (ANDA) for drug products containing terfenadine. NDA 18-949 (Seldane) and NDA 19-664 (Seldane-D) are held by Hoechst Marion Roussel (HMR), Inc., P.O. Box 9627, Kansas City, MO 64134-0627. ANDA 74-475 is held by Baker Norton Pharmaceuticals, Inc., 4400 Biscayne Blvd., Miami, FL 33137. On July 25, 1996, FDA approved HMR's NDA 20-625 for fexofenadine hydrochloride (Allegra). Fexofenadine is the active metabolite of terfenadine that is responsible for the desired beneficial properties of terfenadine. When patients take terfenadine, parent terfenadine is ordinarily present in their blood at very

low concentrations, because the terfenadine molecule is metabolized to form fexofenadine. Fexofenadine is responsible for providing patients with essentially all the clinical benefits of taking terfenadine. If terfenadine's metabolism is inhibited, either by another drug or by intrinsic liver disease, the level of parent terfenadine can rise to levels that can cause serious side effects in people as a result of the effect of parent terfenadine on cardiac potassium channels. Inhibition of these channels causes delayed cardiac repolarization (prolonged electrocardiographic QT interval) and increases the risk of a characteristic kind of ventricular tachycardia called torsades de pointes and possibly the risk of other rhythm abnormalities. Fexofenadine hydrochloride, however, has not been shown to affect cardiac potassium channels and has been shown not to cause prolongation of the electrocardiographic QT interval, even at larger-than-recommended doses. Based on all data to date, fexofenadine hydrochloride appears to lack parent terfenadine's risk of serious cardiovascular adverse events. The basis for the proposed withdrawal of the applications is a finding that the availability of fexofenadine hydrochloride provides patients with an alternative that can provide essentially all the benefits of terfenadine, because it is identical in molecular structure to the metabolized (active) form of terfenadine, without the serious and potentially fatal risks associated with terfenadine when terfenadine's metabolism is inhibited either by another drug or by intrinsic liver disease. Because of the availability of fexofenadine hydrochloride, terfenadine is not shown to be safe for use under the conditions of use that formed the basis upon which the applications were approved.

DATES: A hearing request is due on February 13, 1997; data and information in support of the hearing request are due on March 17, 1997.

ADDRESSES: A request for hearing, supporting data, and other comments are to be identified with docket no. 96N-0512 and submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

For information on medical/scientific issues: John K. Jenkins, Center for Drug Evaluation and Research (HFD-570), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-

1050.

For general information concerning this notice: David T. Read, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301-594-2041.

SUPPLEMENTARY INFORMATION:**I. Background**

Terfenadine is an antihistamine, indicated for the relief of symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation. Terfenadine was the first antihistamine approved in the United States that was not associated with more somnolence than placebo in clinical trials. The absence of an increased risk of somnolence over placebo is an important safety advantage to many people who use antihistamines. NDA 18-949 for Seldane tablets (terfenadine 60 milligrams (mg)) was approved by FDA on May 8, 1985. NDA 19-664 for Seldane-D tablets (terfenadine 60 mg and the decongestant pseudoephedrine hydrochloride 120 mg) was approved by FDA on August 19, 1991.

Other antihistamines now available in the United States that were not associated with more somnolence than placebo in clinical trials are astemizole (Hismanal) and loratadine (Claritin), approved on December 29, 1988, and April 12, 1993, respectively. Most significant to this proceeding, on July 25, 1996, FDA approved HMR's NDA 20-625 for fexofenadine hydrochloride 60 mg capsules (Allegra). Fexofenadine is the metabolite of terfenadine responsible for its desired antihistaminic efficacy. Fexofenadine hydrochloride was also not associated with more somnolence than placebo in clinical trials.

After the approval of terfenadine in 1985, there began to be reports of certain serious cardiac adverse events associated with terfenadine use in patients taking certain antimicrobials or with significant liver dysfunction. Very little parent terfenadine normally circulates in the plasma because orally administered terfenadine undergoes extensive first pass metabolism by a specific cytochrome P-450 isoenzyme (CYP3A4). This metabolic pathway may be impaired in patients with liver dysfunction (e.g., alcoholic cirrhosis) or who are taking drugs such as ketoconazole, itraconazole, or macrolide antimicrobials (e.g., clarithromycin, erythromycin, or troleandomycin). These drugs are all inhibitors of the cytochrome P-450 isoenzyme.

Interference with the normal metabolism of terfenadine can lead to elevated plasma terfenadine levels. At these elevated levels, terfenadine can delay cardiac repolarization (prolong the electrocardiographic QT interval) because of its effects on cardiac potassium channels. The delayed cardiac repolarization increases the risk of serious ventricular tachyarrhythmias, most characteristically a kind of ventricular tachycardia called torsades de pointes. This arrhythmia can cause dizziness and syncope when it is short-lived, but it may persist and degenerate into unstable ventricular tachycardia or ventricular fibrillation. Ventricular fibrillation is fatal if not promptly reversed. These serious and possibly fatal events can occur at the recommended dose of terfenadine if it is taken along with other medications that interfere with its metabolism or if it is administered to someone with significant hepatic dysfunction.

In an effort to inform the medical and patient communities about the serious and potentially fatal cardiac adverse effects associated with inappropriate use of terfenadine, the labeling for Seldane and Seldane-D have been revised many times. In 1992, terfenadine labeling was revised to include a prominent boxed warning cautioning against its use in certain settings, particularly with the drugs that inhibit its metabolism. In addition, "Dear Health Care Professional" letters warning health care practitioners of the serious risk of inappropriate use of terfenadine were issued by the sponsor in 1990, 1992, and 1996.

Although the revised labeling and "Dear Health Care Professional" letters have significantly reduced the inappropriate prescribing of terfenadine together with the drugs that block its metabolism, such prescribing and dispensing has not been eliminated and almost certainly cannot be. Three recently published studies indicate that coprescription and codispensing of medications contraindicated with terfenadine continues to occur (Refs. 1, 2, and 3). The Cavuto study also demonstrates that the computerized drug-interaction screening programs used by many pharmacists, who are the last line of defense against prescribing errors, do not completely prevent prescribing and filling of prescriptions for potentially dangerous combinations of terfenadine and contraindicated drugs.

Terfenadine is an antihistamine that is intended to be used when symptoms of seasonal allergic rhinitis occur. Patients often do not consume all of the pills they receive in a prescription of

terfenadine for a single episode of seasonal allergic rhinitis, and may keep the remaining pills for later use when needed, as patients often do with over-the-counter antihistamines. Because of the nature of seasonal allergies, a long period of time (e.g., from early fall to spring) can elapse between the time the drug and any associated warning from a health care practitioner or pharmacist is received and the time terfenadine is used. Such intermittent dosing of terfenadine increases the probability that some patients may be taking one of the contraindicated medications, such as one of the frequently prescribed antimicrobials listed above, at the same time the patient self-diagnoses his or her seasonal allergy symptoms and takes the remaining terfenadine from the pill container in the medicine chest.

This problem of concomitant use is further compounded by the growing list of medications known to inhibit the metabolism of terfenadine, many of which are taken for chronic medical conditions and may be prescribed by health care practitioners other than the practitioner who prescribed the terfenadine. Labeling changes and even perfect performance by prescribers and close attention by pharmacists, therefore, cannot completely eliminate the risks of serious cardiac adverse events associated with the inappropriate use of terfenadine.

Very low to undetectable blood levels of parent terfenadine are found in patients taking the recommended dose of terfenadine. For this reason, parent terfenadine appears to have very little, if any, impact on the therapeutic efficacy that is associated with terfenadine use.

The discovery of terfenadine's ability to delay cardiac repolarization and its associations with serious and sometimes fatal cardiac adverse events when used inappropriately led to evaluation of its principal active metabolite as a potentially safer alternative antihistamine. It was discovered that the metabolite that is responsible for the desired therapeutic effect of terfenadine, fexofenadine, does not affect cardiac potassium channels. The agency, therefore, encouraged HMR to initiate the development of a drug product with only the active metabolite fexofenadine as the active antihistamine. Even at doses considerably in excess of those recommended for use, fexofenadine hydrochloride has not been shown to prolong the QT interval. It therefore should not have, and has not been shown to have, the serious cardiovascular adverse events potentially associated with unmetabolized terfenadine. No new

adverse reaction, not already associated with terfenadine, would be expected because the many people who have taken terfenadine have been, in fact, exposed primarily to fexofenadine manufactured by their body.

An NDA for fexofenadine hydrochloride was approved by FDA on July 25, 1996. Nearly 5 months of marketing of this product in the United States have not resulted in any reports of serious cardiac arrhythmias.

Prior to the approval of fexofenadine hydrochloride, the agency considered terfenadine to be safe (i.e., its benefits outweighed its risks) despite terfenadine's known serious adverse effects when its metabolism was blocked and despite the availability of alternative antihistamines that, like terfenadine, were not associated with greater somnolence than placebo in clinical trials. This is because the agency recognizes that responses to drugs are not uniform among individuals and, for reasons that are often unclear and difficult to discover, some patients may respond better, with respect to therapeutic effectiveness or tolerance, to one drug than to another. Terfenadine certainly provided a unique therapeutic benefit when it was the only available antihistamine that was not associated with more somnolence than placebo in clinical trials, and it continued to provide a benefit and choice to patients even after the approval of astemizole and loratadine (e.g., some patients may have found that terfenadine provided some advantage over either of the other two products or may have been unable to tolerate the alternative medications for a variety of medical reasons, including drug allergy). So long as terfenadine represented a unique molecule, the agency concluded that terfenadine's risks, which had been greatly reduced by labeling changes and public awareness, were acceptable in light of its benefits. It is only now, when there is an alternative that is identical to the molecule that provides the therapeutic benefits of terfenadine, that terfenadine's benefits do not outweigh its risks. This is because essentially all of its benefits can be obtained with fexofenadine hydrochloride without the cardiovascular risk caused by QT prolongation.

Currently, there is no combination of fexofenadine hydrochloride and pseudoephedrine approved for marketing in the United States. Although the absence of a fexofenadine hydrochloride/pseudoephedrine combination product may be inconvenient for patients currently taking Seldane-D, there are available

over-the-counter extended-release pseudoephedrine 120 mg products that could be taken with fexofenadine hydrochloride to provide symptomatic relief comparable to that provided by Seldane-D for the treatment of seasonal allergic rhinitis. The minor inconvenience to patients of having to take separate fexofenadine hydrochloride and extended-release pseudoephedrine doses is more than offset by the cardiac safety advantage of fexofenadine hydrochloride over terfenadine.

Accordingly, the Director of the Center for Drug Evaluation and Research concludes with respect to NDA 18-949 (terfenadine 60 mg) that: (1) Prior to the approval of fexofenadine hydrochloride, terfenadine provided a unique therapeutic alternative for which the risks associated with the use of terfenadine were acceptable; (2) terfenadine provides no therapeutic benefit to any patient population that is not also provided by fexofenadine hydrochloride, because fexofenadine hydrochloride is identical in molecular structure to terfenadine's therapeutically active metabolite; (3) current data demonstrate that fexofenadine hydrochloride lacks the serious cardiovascular risks associated with misuse of terfenadine, and approximately 5 months of marketing experience with fexofenadine hydrochloride in the United States has not resulted in any reports of serious cardiac arrhythmias; (4) despite the many interventions undertaken by the agency and by HMR (three "Dear Health Care Professional" letters, multiple labeling changes, and extensive education campaigns), residual coprescribing, codispensing, and concomitant use of terfenadine with a growing list of medications that inhibit its metabolism continues and cannot be expected to be completely eliminated; and (5) terfenadine, therefore, is no longer shown to be safe for use under the conditions that formed the basis upon which the application was initially approved. The Director also finds that ANDA 74-475 refers to NDA 18-949 (Seldane, 60 mg terfenadine oral tablets) as the listed drug. The Director further finds that the conclusions set out above for NDA 18-949 apply with respect to NDA 19-664 (terfenadine 60 mg and pseudoephedrine 120 mg), and that the inconvenience to patients of taking separate doses of fexofenadine hydrochloride and extended-release pseudoephedrine is more than offset by the cardiac safety advantage of fexofenadine hydrochloride over terfenadine. The Director is proposing to

withdraw approval of NDA 18-949 and NDA 19-664 in accordance with section 505(e)(2) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355(e)(2)). The Director is proposing to withdraw approval of ANDA 74-475 in accordance with section 505(j)(5) of the act.

II. Notice of Opportunity for a Hearing

The Director has evaluated the information discussed above and, on the grounds stated, is proposing to withdraw approval of NDA 18-949, NDA 19-664, and ANDA 74-475. Therefore, notice is given to HMR and Baker Norton Pharmaceuticals, Inc. that the Director proposes to issue an order under section 505(e)(2) of the act, withdrawing approval of NDA 18-949 and NDA 19-664, and all amendments and supplements thereto, and under section 505(j)(5) of the act, withdrawing approval of ANDA 74-475, and all amendments and supplements thereto. The Director finds that new evidence of clinical experience, not contained in NDA 18-949 and NDA 19-664 or not available to the Director until after the applications were approved, evaluated together with the evidence available to the Director when the applications were approved, shows that terfenadine is not shown to be safe for use under the conditions which formed the basis upon which the applications were approved. The Director also finds that ANDA 74-475 refers to the drug that is the subject of NDA 18-949.

In accordance with section 505 of the act and part 314 (21 CFR part 314), HMR and Baker Norton Pharmaceuticals, Inc. are hereby given an opportunity for a hearing to show why approval of the NDA's should not be withdrawn.

An applicant who decides to seek a hearing shall file: (1) On or before February 13, 1997, a written notice of appearance and request for hearing, and (2) on or before March 17, 1997, 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 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 products. Any new drug product marketed without an approved new drug application is subject to regulatory action at any time.

III. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Thompson, D. and G. Oster. "Use of Terfenadine and Contraindicated Drugs," *Journal of the American Medical Association*, 275(17):1339-1341, 1996.

2. Cavuto, N. J., R. L. Woosley, and M. Sale. "Pharmacies and Prevention of Potentially Fatal Drug Interactions" (letter), *Journal of the American Medical Association*, 275(14):1086-1087, 1996.

3. Carlson, A. M., and L. S. Morris. "Coprescription of Terfenadine and Erythromycin and Ketoconazole: An Assessment of Potential Harm," *Journal of the American Pharmaceutical Association*, NS36(4):263-269, 1996.

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 a hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, 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 who requests the hearing, making findings and conclusions, and denying a hearing.

All submissions pursuant to 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: January 7, 1997.

Janet Woodcock,

Director, Center for Drug Evaluation and Research.

[FR Doc. 97-714 Filed 1-10-97; 8:45 am]

BILLING CODE 4160-01-F

National Institutes of Health

Consensus Development Conference on Breast Cancer Screening For Women Ages 40-49

Notice is hereby given of the NIH Consensus Development Conference on "Breast Cancer Screening For Women Ages 40-49," which will be held January 21-23, 1997, in the Natcher Conference Center of the National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. The conference begins at 8:30 a.m. on January 21, at 8 a.m. on January 22, and at 9 a.m. on January 23.

A number of randomized clinical trials have shown clearly that early detection of breast cancer by mammography, with and without clinical breast examination at regular intervals ranging from 1 year to 33 months, reduces breast cancer mortality in women ages 50-59 by about a third. However, the picture is not as clear for women 40-49 years of age, and worldwide experts continue to examine the data regarding the use of mammography in this age group. Follow-up data from the Swedish, Canadian, Edinburgh (U.K.), and health Insurance Plan of New York clinical trials will be presented at the conference in an attempt to help clarify these issues.

This conference will bring together the investigators who have conducted the randomized clinical trials, epidemiologists, statisticians, radiologists, oncologists, and other experts, as well as representatives of the public, to present and discuss the latest data and data analyses.

After 1½ days of presentations and audience discussion, an independent, no-Federal consensus panel will weigh the scientific evidence and write a draft statement that it will present to the audience on the third day. The consensus statement will address the following key questions:

- Is there a reduction in mortality from breast cancer due to screening women ages 40 to 49 with mammography, with or without physical examination? If so, how large is the benefit? How does it change with age?
- What are the risks associated with screening women ages 40-49 with mammography and with physical examination?
- Are there other benefits? If so, what are they? How do they change with age?
- What is known about how the benefits and risks of breast cancer screening differ based on known risk factors for breast cancer?

—What are the directions for future research?

The primary sponsors of this conference are the National Cancer Institute and the NIH Office of Medical Applications Research. The conference is cosponsored by the National Institute on Aging, the NIH Office of Research on Women's Health, and the Centers for Disease Control and Prevention.

Advance information on the conference program and conference registration materials may be obtained from Hope Levy Cott, Technical Resources International, Inc., 3202 Tower Oaks Blvd., Suite 200, Rockville, Maryland 20852, (301) 770-3153, or by sending e-mail to confdept@tech-res.com.

The consensus statement will be submitted for publication in professional journals and other publications. In addition, the statement will be available beginning January 23, 1997, from the NIH Consensus Program Information Center, P.O. Box 2577, Kensington, Maryland 20891, phone 1-888-NIH-CONSENSUS (1-888-644-2667), and from the NIH Consensus Development Program site on the World Wide Web at <http://consensus.nih.gov>.

Dated: January 7, 1997.

Ruth L. Kirschstein,
Deputy Director, NIH.

[FR Doc. 97-850 Filed 1-13-97; 8:45 am]

BILLING CODE 4140-01-M

John E. Fogarty International Center for Advanced Study in the Health Sciences; Notice of Meeting of the Fogarty International Center Advisory Board

Pursuant to Public Law 92-463, as amended, notice is hereby given of the thirty-fifth meeting of the Fogarty International Center (FIC) Advisory Board, February 4, 1997, in the Lawton Chiles International House (Building 16 at the National Institute of Health.

The meeting will be open to the public from 8:30 a.m. to 12:00 p.m.

The agenda will include a report by the Director, FIC; a report on the Recommendations of the External Advisory Panel to Review NIH/FIC International Programs followed by a discussion of the recommendations led by the Director, NIH; a report on the December Meeting of the Advisory Committee to the Director, NIH; a presentation on the recommendations of a review panel on the FIC AIDS International Training and Research Program; and a report on the International Conference on Malaria tha

N18949
(Terfenadine)

T98-10 Seldane and Generic Terfenadine Withdrawn from Market

T98-10 Ivy Fleischer Kupec: 301-827-6242
Feb. 27, 1998 Broadcast Media: 301-827-3434
Consumer Inquiries: 800-532-4440

SELDA NE AND GENERIC TERFENADINE WITHDRAWN FROM MARKET

Hoescht Marion Roussel and Baker Norton Pharmaceuticals have voluntarily discontinued distribution and marketing of all terfenadine-containing antihistamine product lines in the United States.

Terfenadine-containing products, such as Seldane and Seldane-D, have been associated with rare, but serious heart problems when taken with certain other drugs, including certain antibiotics and antifungals.

In January 1997, FDA proposed removing all terfenadine products from the marketplace because of the approval of a safer alternative drug: Allegra (fexofenadine hydrochloride). Fexofenadine hydrochloride provides exactly the same benefits of terfenadine, but it does not cause a potentially fatal heart condition when taken with certain other commonly prescribed medications. At that time, FDA advised patients currently taking Seldane, Seldane-D and generic terfenadine products to talk to their health care providers about switching to alternative medications. Following the approval of Allegra-D in December 1997 and with the prior approval of Allegra, Hoescht Marion Roussel announced its plans to discontinue distribution and marketing of the drugs' predecessors, Seldane and Seldane-D from the marketplace as of Feb. 1. Likewise, the manufacturer of generic terfenadine, Baker Norton Pharmaceuticals, also has discontinued U.S. distribution and marketing of its product.

As a result, terfenadine-containing products will soon disappear from pharmacies as existing supplies are depleted. FDA again reminds consumers and health care providers who have used these products, that equally safe and effective alternative drug products are available.

FDA will continue the administrative procedures to finalize the permanent withdrawal of all terfenadine-containing products.

####

T97-67 Allegra-D, Manufacturer to Withdraw Seldane from Marketplace

T97-67 Ivy Fleischer Kupec: 301-827-6242
Dec. 29, 1997 Broadcast Media: 301-827-3434
Consumer Inquiries: 800-532-4440

FDA APPROVES ALLEGRA-D,
MANUFACTURER TO WITHDRAW SELDANE FROM MARKETPLACE

FDA today announced the approval of the prescription antihistamine/decongestant Allegra-D (fexofenadine/pseudoephedrine) extended release tablet. With the approval of this drug and the prior approval of Allegra, the manufacturer has announced its plans to remove the drugs' predecessors, Seldane and Seldane-D (terfenadine-containing products), from the marketplace. The following can be used to answer questions:

Fexofenadine, an active ingredient in Allegra and Allegra-D, is the primary active derivative of terfenadine produced in the body when Seldane and Seldane-D are taken. Fexofenadine provides nearly all of terfenadine's beneficial effects but does not appear to cause a potentially fatal heart condition when taken with some other commonly prescribed medications.

In January, FDA proposed removing all terfenadine products from the marketplace because of the approval of a safer alternative drug: fexofenadine. At that time, FDA advised patients currently taking Seldane, Seldane-D and generic terfenadine products to talk to their doctors about switching to alternative medications. In September, the manufacturer added increased warnings on Seldane and Seldane-D's label to give health care providers and consumers who still used terfenadine-containing products the latest available information about these risks, while FDA continued the administrative process of removing these products from the market.

Controlled clinical studies have demonstrated that the twice-daily dose of fexofenadine/pseudoephedrine combination tablet significantly reduced the intensity of sneezing, nasal congestion, and itchy nose, mouth, throat and eyes that typically appear with seasonal allergies.

Allegra-D is indicated for adults and children age 12 and older. The most common adverse events reported during clinical trials of Allegra-D included: headache (13 percent), insomnia (12.6 percent) and nausea (7.4 percent).

Allegra-D is not recommended for patients with hypertension, diabetes, ischemic heart disease, increased intraocular pressure, hyperthyroidism, kidney impairment or prostate problems. Allegra-D, like other products in the same drug class, may stimulate the nervous system with convulsions or cause cardiac collapse in these patients.

Hoechst Marion Roussel of Kansas City, Mo., manufactures Seldane, Seldane-D, Allegra and Allegra-D.

###

Medical Bulletin, March 1997

FDA Medical Bulletin * March 1997 * Volume 27 Number 1

First Nonprescription Nasal Spray to Prevent, Treat Allergic Rhinitis

FDA has approved cromolyn sodium for over-the-counter marketing. It is the first nonprescription nasal spray that specifically helps prevent and treat symptoms related to nasal allergies. Cromolyn sodium, available by prescription since 1983, can be used regularly by adults and by children age 6 and older.

When used prior to allergen exposure, such as before the start of the hay fever season, cromolyn sodium is effective in diminishing allergic nasal symptoms (rhinitis). Although it is also effective for treating established allergic nasal symptoms, the full benefit may not become apparent for up to 2 weeks of treatment, so antihistamines and/or nasal decongestants may be necessary during the initial phase of treatment with cromolyn sodium nasal spray. The nasal spray is generally well tolerated, although some patients may experience local reactions that include sneezing and nasal stinging, burning, and irritation.

McNeil Consumer Products will market cromolyn sodium under the trade name Nasalcrom (Nasal Allergy Symptom Controller).

First Prescription Treatment for Oral Ulcers

FDA has approved amlexanox oral paste, 5 percent, the first prescription treatment for aphthous ulcers in people with normal immune systems. Aphthous ulcers are painful, severe canker sores in the mouth. FDA based its approval on placebo-controlled clinical trials demonstrating that amlexanox reduced the time for ulcers to heal. In general, patients improved 1 to 1-1/2 days sooner with amlexanox; pain relief was also faster. While people with AIDS do develop especially virulent forms of aphthous ulcers, the safety and effectiveness of this drug in immunocompromised individuals has not been assessed at this time.

The drug is contained in a paste that is applied directly to the ulcers four times a day, following oral hygiene after meals and before bedtime. Health care providers should advise their patients to make a return visit if the ulcers have not healed in 10 days. Some clinical trial participants reported stinging or burning where the medicine was applied and, less frequently, nausea and diarrhea.

Block Drug Company Inc. of Jersey City, New Jersey, manufactures amlexanox under the trade name Aphthasol.

Significant Devices Approved Faster

FDA approved 43 premarket approval applications (PMAs) in fiscal year 1996, 16 more than in fiscal year 1995. Half these devices are new technologies for diagnosis and treatment. Eight PMAs were reviewed in 1 year or less. Key 1996 PMA approvals in fiscal year 1996 include the following:

- o The first blood test to monitor patients for possible breast cancer recurrence: TRUQUANT by Biomira Diagnostics, Inc.
- o A new use of high-definition ultrasound as an adjunct to mammography and physical breast exams to help differentiate benign from malignant breast lesions: Ultramark 9 High Definition Ultrasound System by Advanced Technology Labs, Inc.
- o A spinal fusion implant to treat degenerative disc disease: BAK Fusion System by Spine-Tech, Inc.
- o A fiber-optic bronchial device that uses blue light to enhance the detection of abnormal lung tissue: Xillix LIFE-Lung Fluorescence Endoscopy System by Xillix Technologies Corp.
- o A semiautomatic system to aid in rescreening of Pap smears: PAPNET Testing System by Neuromedical Systems, Inc.
- o A low-density apheresis system for removing lipoprotein

cholesterol from plasma of high-risk patients: Liposorber SA-15 by Kaneka America Corp.

- o A device that uses microwave energy to treat benign prostatic hyperplasia: Prostatron by EDAP Technomed Group.
- o A stent for use in men to relieve urinary obstruction secondary to recurrent benign bulbar urethral strictures: UroLume Endourethral Prosthesis by American Medical Systems, Inc.
- o The first bioresorbable membrane to decrease the occurrence of postoperative adhesions in abdominal and pelvic surgery: Septrafilm by Genzyme Corp.
- o The first system to use laser light delivered through fiber optics to activate a light-sensitive drug to treat esophageal cancer: Photodynamic Therapy Units by QLT Phototherapeutics, Inc.
- o The first and second excimer lasers for the surgical treatment of mild to moderate nearsightedness: the S/V/S Apex Excimer Laser System by Summit Technology Inc., and the VISX Excimer Laser System, models B and C by VISX Inc.
- o A urinary insert for the control of stress incontinence in women: Reliance Urinary Control Insert and Sizing Device by Uromed Corp.
- o A device to make cleaner cytology slides for easier reading of Pap smears: ThinPrep by Cytoc Corp.
- o A ventricular assist device for use as a bridge to cardiac transplantation: Thoratec Ventricular Assist Device System by Thoratec.

For more information, contact Center for Devices and Radiological Health, CDRH, Program Operations Staff, phone (301) 594-2136, Fax (301) 443-8299.

FDA Proposes to Withdraw Seldane Approval

FDA has announced its intention to withdraw the approval of Seldane (terfenadine), Seldane-D (terfenadine and pseudoephedrine), and generic versions of the prescription antihistamine. The Agency has determined that drugs containing terfenadine are no longer shown to be safe because Allegra (fexofenadine) is now available. Terfenadine is a pro-drug. Fexofenadine is the active metabolite of terfenadine produced in the body, and it provides nearly all of terfenadine's therapeutic effect. It does not, however, block cardiac potassium channels or cause QT prolongation or ventricular arrhythmias, notably torsades de pointes type ventricular tachycardia, as terfenadine can at greater than usual blood levels.

Introduced in 1985, terfenadine is marketed by Hoechst Marion Roussel of Kansas City, Missouri, and was the first prescription antihistamine to relieve the symptoms of allergic rhinitis without causing drowsiness. Following its approval, FDA received reports of serious and sometimes fatal cardiac arrhythmias associated with terfenadine when it was taken with some other medications that interfere with its metabolism to fexofenadine by cytochrome P450 3A4 or when taken by patients with liver disease. These other drugs, such as erythromycin (an antibiotic) and ketoconazole (an antifungal drug), can lead to terfenadine buildup in the blood and the resulting potential for serious, sometimes fatal, cardiac arrhythmias.

Since the serious cardiac risks of terfenadine were identified, several educational campaigns have been launched by the drug's sponsor and FDA to inform health care providers and patients about the dangers of these drug interactions. These have included FDA warning statements, labeling changes, and "Dear Doctor" letters. Although these efforts have reduced inappropriate prescribing and dispensing of terfenadine with other drugs and reports of arrhythmias, such events have not been, and almost certainly cannot be, eliminated.

Prior to the approval of fexofenadine, FDA considered the benefits of terfenadine to outweigh its risks despite the serious arrhythmias that could result from its inappropriate use. Now that fexofenadine is available (approved July 1996) and provides the therapeutic benefits of terfenadine without the associated serious cardiac risks, FDA has

determined that terfenadine-containing products should be removed from the market. The Agency has provided the manufacturers of these products an opportunity to request a hearing to show that the products should not be withdrawn. In the meantime, FDA is advising health care professionals to switch patients currently taking Seldane, Seldane-D, and generic terfenadine products to alternative medications.

Medication Errors

FDA is asking the help of the medical community in reporting medication errors that result, or could result, in adverse drug events. Medication errors can be a source of significant morbidity and mortality in the health care setting. Therefore, it is important that medication errors be monitored so that similar incidents can be prevented in the future. Problems associated with devices that lead to medication errors should also be reported. FDA reviews each medication error report and, if warranted, takes appropriate action on labeling and packaging problems. In some cases, changing the design, name, or packaging of a product can help prevent medication errors.

Medication errors or potential errors may be reported in confidence to FDA's MEDWATCH program (call 1-800-FDA-1088 or fax the MEDWATCH form to 1-800-FDA-0178). When reporting a medication error to MEDWATCH, the "Product Problem" portion of the form should be completed with a description of the packaging, labeling, or device problem. We know that confidentiality is extremely important, especially in the area of reporting errors. Current federal regulations protect the identities of reporting individuals and institutions from disclosure.

The FDA Medical Bulletin will be routinely providing feedback to the medical community on some of the more significant medication errors. Here are some of the more important medication errors reported recently:

CAMPTOSAR INJECTION

(Irinotecan HCl Injection; Pharmacia and Upjohn)

FDA has received several reports, including fatalities, of accidental overdoses when the total drug content of the 5 mL vial was inadvertently given instead of 1 mL. A label change for this product has been made that includes the total drug content (100 mg/5 mL) and the concentration per milliliter (20 mg/mL).

CEREBYX INJECTION

(Fosphenytoin Sodium Injection; Parke-Davis)

FDA has received numerous reports of confusion and error resulting in overdoses and underdoses. Practitioners should be aware that this product has a unique way of expressing the dosage. The drug dosage should be prescribed in terms of its "phenytoin equivalent" (PE). Although 150 mg of fosphenytoin sodium will be administered, a prescription should be written as "fosphenytoin 100 mg PE." FDA is monitoring these reports. Certain labeling changes have recently been approved to clarify these dosing relationships.

CISPLATIN INJECTION

Several reports have been received of overdoses with cisplatin injection (Platinol-AQ; Bristol-Myers Squibb) when carboplatin was the intended agent. The flip-off seal and aluminum caps have now been imprinted "CALL DR IF DOSE > 100 MG/M2/CYCLE." In addition, a boxed warning now appears stating that doses greater than 100 mg/m² once every 3 to 4 weeks are rarely used. Other labeling enhancements include highlighting the "cis" in "cisplatin," so that it is less likely to be confused with "carboplatin," and a red stop sign to encourage verifying the dose and drug.

NAME CONFUSION

The following represent some of the name confusion reports that the Agency has received. Confusion could be due to similarities in the sound or written form of the names:

- o Amiodarone and Amrinone
- o Benadryl Dye-Free and Benadryl Allergy Liquid
- o Chlor-Trimeton and Chlor-Trimeton Non-Drowsy
- o Claritin-D and Claritin-D 24 Hour

- o Covera HS and Provera
- o Desenex Product Line
- o Excedrin PM and Excedrin
- o Leukeran (Chlorambucil) and Leucovorin (Wellcovorin)
- o Mylanta Product Line
- o Neo-Synephrine Regular Strength and 12 Hour Nasal Sprays
- o Noroxin and Neurontin
- o Norvasc and Navane
- o Norvir and Retrovir
- o Rimantadine and Ranitidine
- o Varivax (Varicella Virus Vaccine) and VZIG (Varicella-Zoster Immune Globulin)
- o Zebeta and Diabeta

Free Reprint on Using Medicines Safely

A free FDA Consumer reprint advising consumers on how to use medicines safely is available from FDA.

The reprint includes a patient check-off chart for help in taking medicines at the right time. Special sections advise patients on medication while in the hospital, protection against tampering, medication counseling, and tips for giving medicine to children.

To order "FDA Tips for Taking Medicines: How to Get the Most Benefit with the Fewest Risks," send a letter with the publication number, FDA 96-3221, to this address:

FDA
5600 Fishers Lane
Rockville, MD 20857
Attn: HFE-88 (for single copy)
Attn: HFI-40 (for 2 to 25 copies)

or

Fax your order to (301) 443-9057.

FDA Consumer is the Agency's official consumer magazine and is available at FDA's World Wide Web site (<http://www.fda.gov>).

Folate and Neural Tube Birth Defects

Reducing adverse pregnancy outcomes, such as birth defects, is an important public health goal. Recent evidence has shown a relationship between intake of the vitamin folate (folic acid, folacin) and reduction in the risk of neural tube birth defects (NTDs), the commonest of which are spina bifida and anencephaly. The defects can result in infant mortality or serious disability. Each year, about 2,500 cases of NTDs occur among about 4 million births in the United States (about 6 in 10,000 births). Because the neural tube forms between the 18th and 20th days of pregnancy and closes between the 24th and 27th days, defects in formation or closure may occur before a woman realizes that she is pregnant.

Folate is one of the B vitamins. It participates in the synthesis of amino acids and nucleotides and is particularly important in rapidly dividing and growing cells. Pregnancy increases the need for folate, as well as most other nutrients, to meet the needs of the mother and of the developing fetus. Folate is widely distributed in foods, being found at particularly high levels in dark green leafy vegetables, legumes, certain citrus fruits and juices, and organ meats such as liver. In addition, folic acid is added to virtually all ready-to-eat breakfast cereals and to many multivitamin supplements.

The U.S. Public Health Service has recommended that all women of childbearing age consume 400 micrograms (0.4 mg) of folate daily to reduce their risk of having a pregnancy affected with spina bifida or other NTDs. Adequate folate intake is important throughout the childbearing years, since about half of pregnancies in the United States are unplanned and NTDs may occur before a woman recognizes that she is pregnant.

The Public Health Service has suggested several approaches to achieve these levels:

- Improved dietary habits
- Daily use of folic acid supplements
- Fortification of the U.S. food supply

Recently, FDA announced that by January 1998, a wide range of enriched cereal-grain products will be required to add folic acid. These products include enriched flour, breads, cornmeal, noodles, macaroni, and other grain products.

Under the new rules, fortification levels will range from 0.43 to 1.4 mg per pound of product. Fortification of grain products will allow the daily intake from all sources to remain below the recommended upper limit of 1 mg of folate. Intake greater than 1 mg may mask symptoms of pernicious anemia. While it is important for women of childbearing age to maintain adequate folate intake, excessive intake should not be encouraged. Manufacturers will be allowed to make claims on the labels that the fortified products contain folic acid and that adequate intake of the nutrient may reduce the risk of NTDs. The Agency emphasizes that adequate levels of folate can be obtained by eating diets high in enriched cereal-grain products, leafy dark green vegetables, legumes, and citrus fruits and juices.

Women can also obtain adequate amounts of folate through the use of dietary supplements, many of which contain 400 micrograms of folate per tablet.

The final rules on fortification were published in the Federal Register on March 5, 1996, and will become effective January 1, 1998.

For further information, please contact Jeanne L. Rader, Office of Food Labeling, at (202) 205-5375.

Office of Women's Health Update

Women's Health: Take Time to Care

FDA's Office of Women's Health has designed a new educational outreach program called Women's Health: Take Time to Care. The program recognizes the fact that many women are so busy balancing work and family obligations that they may not take time to care for themselves. The goal is to help women take better care of themselves through educational materials aimed at improving the use of FDA-regulated products, such as medicines, health screenings, and the food label. To deliver these messages most effectively, the Office of Women's Health is involving a broad network of program partners.

Take Time to Care will introduce messages sequentially, starting with "Use Medicine Wisely." The program will target midlife and older women and place special emphasis on reaching underserved populations across the country. This spring FDA will begin the program in two cities (Hartford, CT and Chicago, IL) and roll it out nationally in the fall. If you have any questions, please send a fax to the Office of Women's Health at (301) 827-0926.

REPORT SERIOUS ADVERSE EVENTS AND PRODUCT PROBLEMS TO MEDWATCH1-800-FDA-1088