

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 troleanomycin). 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 50-69 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 that