FDA
TALK PAPER
FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T92-68
Dec. 9, 1992

Mike Shaffer
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INTERNATIONAL HARMONIZATION TASK FORCE REPORT COMPLETED

We are receiving inquiries about the recently completed report of FDA's International Harmonization Task Force. The report outlines current agency involvement in harmonization activities and, among other things, calls for enhanced agency participation in international efforts to develop regulatory standards for foods, drugs and other products. This will help assure the safety and quality of U.S. imports, permit faster access by U.S. patients to therapies available overseas and allow more efficient use of FDA resources. The report also emphasizes that international requirements for FDA-regulated products should be science based and not unnecessarily restrict trade.

The following can be used to answer inquiries.

FDA participates in international harmonization activities primarily to assure that consumer protection standards and requirements are met, to safeguard U.S. public health and facilitate the availability of safe and effective products.

In recent years, FDA has been increasingly involved in international efforts to reduce trade barriers with the aim of ensuring that health and safety standards are adequately protected. FDA was represented in North American Free Trade Agreement negotiations, has participated in the Uruguay Round negotiations of the General Agreement on Tariffs and Trade (GATT) and has worked with the Commission of the European Communities (EC) as it moves toward its single internal market.

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The task force report makes recommendations for future agency activities and calls for continuing discussions in these and other forums to encourage international cooperation, such as in the Andean, Caribbean, Korean and Japanese markets.

The report addresses the need for adequate resources to carry out international programs and cites increased costs, such as those required for conducting foreign inspections, as a driving force for international collaborative efforts to harmonize manufacturing standards and enforcement.

One of the mechanisms for agreements with foreign countries is the Memorandum of Understanding (MOU). FDA has already made considerable progress working through MOUs, especially for Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) requirements.

In the area of food safety, FDA participates with international organizations such as the United Nations Food and Agriculture Organization (FAO), the World Health Organization (WHO) and the Codex Alimentarius Commission (Codex), a joint FAO/WHO-sponsored organization that sets international food standards. In the area of foods, FDA has 22 MOUs with such countries as Australia, Canada, Finland and Mexico. The agreement with Mexico, for example, includes mutual technical cooperation to prevent the import of products with impermissible pesticide residues. FDA represents the United States on six of seven commodity committees and all seven general subject committees of Codex that are directed at ensuring a "level playing field" in international food trade.

Since 1985, FDA has inspected more than 1600 foreign manufacturing plants in more than 50 countries that supply bulk drugs for the production of prescription drugs sold here. The agency also has formal agreements with Canada, Sweden and Switzerland that provide for the mutual recognition of

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GMP inspection programs and reports and is exploring the possibility of agreements with Japan, Australia, the EC and others.

Standards applicable to biological products, such as vaccines and various biotechnology-related products, are increasingly developed in coordination with international groups, including the Council of Europe, the International Society for Blood Transfusion, WHO and others.

In the medical devices area, the agency currently has 181 people working on 371 standards development projects with 32 different organizations, in particular the International Organization for Standardization. Approximately 1600 firms import medical devices that require some form of preclearance by FDA.

FDA and the Canadian Bureau of Veterinary Drugs have already agreed to recognize each other's regulations where possible and to consult prior to implementing any future regulations involving animal drugs and feeds. Additional agreements with other organizations are being developed.

FDA is involved in a major effort to harmonize the technical requirements for new drugs and biologics among the EC, Japan and the United States, through participation in the International Conference on Harmonization. Further, FDA is studying the feasibility and benefits of conducting joint reviews of drug, biological and other product applications with its foreign counterpart agencies. Three drugs for use in treating patients with AIDS -- atovaquone, dideoxyinosine (ddI) and dideoxycytidine (ddC) -- were recently approved following joint reviews with Canada.

The report will be available shortly from the National Technical Information Service (NTIS), 5285 Port Royal Rd., Springfield, Va. 22161, telephone (703) 487-4650. The order number is PB 93-128155.

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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P85-12
FOR IMMEDIATE RELEASE
April 9, 1985

Food and Drug Administration
Bruce Brown -- (301) 443-3285
(Home) -- (301) 384-0426

The Food and Drug Administration today instructed manufacturers and distributors of the drug DHEA, which is promoted as a "natural" weight reduction product, to discontinue selling it because it has not been reviewed for safety and effectiveness.

DHEA, known as dehydroepiandrosterone or dehydroandrosterone, is a steroidal hormone which has been sold nationwide without prescription in retail stores and through the mails for weight management, enhanced sex life and longer life. It has been promoted in recently popular books on extending human life. But no evidence has been submitted to FDA which substantiates those claims.

FDA is writing makers and distributors that DHEA is an unapproved new drug and that they must stop selling it and must provide FDA with information about its manufacture and distribution. If the companies fail to comply within 10 days of receipt of the letter, FDA will consider regulatory actions against the products and companies.

FDA has few adverse reaction reports on the drug, but said the risks from long-term use are unknown. DHEA may be manufactured from human urine. Scientific studies have not established what effect reintroducing into the body this concentrated bodily excess might have, FDA said.

No applications to conduct human studies with DHEA or to market it were submitted to FDA by the companies now selling it. The substance is considered a drug because under the Federal Food, Drug and Cosmetic Act, a substance that is offered for a nonfood purpose and that is intended or advertised to affect the body's normal functioning is classified as a drug. All new drugs require premarket approval.

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TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T91-65
Oct. 21, 1991

Brad Stone
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FDA TO INSPECT AIDS "BUYERS CLUBS"

Recently officials from FDA's Office of AIDS Coordination and Office of Regulatory Affairs met with representatives from several major AIDS "buyers clubs." The term "buyers clubs" is loosely used to describe groups which distribute drugs and other products purportedly useful in treating AIDS and related diseases. The meetings were held to inform these buyers clubs that the agency will soon initiate a series of inspections of these clubs in order to more fully determine the nature and scope of their activities. These inspections are designed to be primarily exploratory, and are not intended to precipitate any immediate regulatory action against these groups.

These groups apparently vary widely in their procurement and distribution practices. Some may sell these products at little or no cost to clients, while others may be selling similar products at a considerable profit. These groups may also differ dramatically as to the type of products they sell and the degree of quality assurance associated with these products.

In the past few months, an increasing number of reports have indicated possible violations by some buyers clubs. Therefore, FDA is looking at buyers clubs to determine whether some violations are occurring, and if so, what steps might be taken to rectify these problems.

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FDA has notified buyers clubs throughout the U.S. that these inspections are part of the effort to gain greater knowledge about their operations, but do not represent a crackdown action against them. In the event that FDA inspections do reveal activities that may be violative, the agency, whenever possible, will work with buyers clubs to resolve these problems without the use of regulatory sanctions.

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FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T95-46
Sept. 7, 1995

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FDA WARNS AIDS BUYERS' CLUBS NOT TO SELL THALIDOMIDE

We have been receiving inquiries about FDA's letters to three AIDS buyers' clubs warning them to stop their illegal sale of thalidomide. The warning letters were issued after several months of agency communication with the organizations about the serious risks associated with the uncontrolled distribution and use of thalidomide. The following can be used to respond to inquiries:

Thalidomide was marketed in Europe and other parts of the world in the 1950s and 1960s as a tranquilizer and became notorious for causing severe fetal malformations when taken by pregnant women to reduce nausea. The drug, which was not approved for use in the United States, was linked worldwide to the birth of an estimated 7,000-12,000 babies without properly developed arms and legs.

Since then, thalidomide has been used in clinical trials, studying the drug to treat *erythema nodosum leprosum*, a serious inflammatory condition in leprosy patients. The drug also is

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being investigated in clinical trials as a possible treatment for several other conditions.

In recent months, FDA became aware that three AIDS buyers' clubs are illegally selling thalidomide to people with AIDS who are not participating in clinical trials. FDA regards this distribution of thalidomide as an unacceptable risk to both male and female AIDS patients and to the public health at large.

Thalidomide poses potential adverse effects on fetal development and on an individual patient's nervous and immune systems. Use of thalidomide requires appropriate medical supervision and informed consent, which are not usually available outside carefully monitored clinical trials. In addition, illegal distribution of thalidomide by buyers' clubs is likely to hinder enrollment in the clinical trials, thereby delaying the determination of whether the drug is safe or effective for treating these illnesses.

Thalidomide's possible new uses are being investigated in the United States in clinical trials for aphthous ulcers, which are painful, HIV-related open sores in the mouth and throat, and for a wasting syndrome associated with AIDS.

FDA allows AIDS patients with aphthous ulcers who are not eligible to enroll in larger clinical trials to obtain thalidomide through their doctors. This allowance, through

carefully monitored single-patient INDs (Investigational New Drug applications), is based on preliminary data indicating that the drug may be effective in treating aphthous ulcers.

For patients suffering HIV wasting, FDA has authorized an expanded access protocol in connection with Celgene Corp.'s thalidomide clinical trials for this indication. At this time, the data on thalidomide as a treatment for AIDS-associated wasting are limited. The expanded access protocol and Celgene's placebo-controlled trial for HIV wasting are designed to determine if thalidomide is safe and effective for wasting. During this period of investigation, the recently authorized protocol substantially expands access of the drug to HIV-wasting patients.

Two drugs, Bristol-Myers Squibb's Megace and Roxane Laboratories' Marinol, currently are approved for marketing for AIDS-related wasting and appetite stimulation, respectively. In addition, FDA earlier this year made available Serono Corp.'s human growth hormone (Serostim) for treating AIDS wasting through a treatment IND. FDA's treatment IND regulations offer a mechanism that allows drug developers to provide earlier and wider access to investigational therapies while further data are being developed in clinical trials.

Information on ongoing clinical trials of thalidomide for

AIDS-related conditions can be obtained from the AIDS Clinical Trials Information Service by calling 1-800-TRIALS-A.

This week's agency warning letters were sent to three buyers' clubs that are known to be selling thalidomide: LifeLink of Arroyo Grande, Calif., Healing Alternatives of San Francisco, and PWA Health Group of New York City. The organizations have 15 days to respond to the letters and cease their sale of thalidomide or they may face regulatory action.

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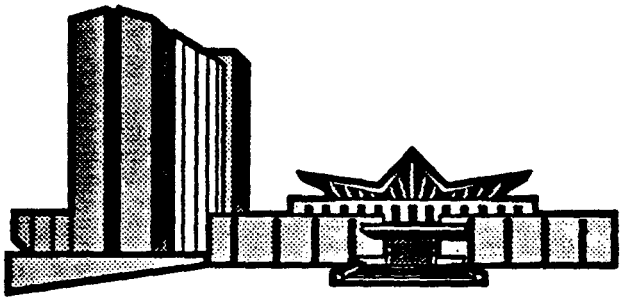
CLINICAL ALERT NEWS

National Library of Medicine
National Institutes of Health
8600 Rockville Pike
Bethesda, MD 20894



Date: February 10, 1993

TO:

Medical Library Director

FROM:

National Library of Medicine
National Network of Libraries of Medicine

NOTES:

Please distribute this important clinical information to the health care professionals in your institution.

Problems or Questions? Call National Network of Libraries of Medicine at 1-800-272-4787

A NOTE TO PHYSICIANS

NATIONAL INSTITUTES OF HEALTH
National Institute of Allergy and Infectious Diseases
Bethesda, Maryland 20892

February 1, 1993

IMPORTANT THERAPEUTIC INFORMATION ON TREATMENT OF HIV INFECTION IN HIV-INFECTED PATIENTS WHO ARE INTOLERANT OF OR HAVE FAILED ZIDOVUDINE THERAPY

Purpose of this Document

This document provides information on the results of a recently completed clinical trial that compared ddI and ddC in HIV-infected patients who were intolerant of or who had failed zidovudine therapy. Application of these results beyond this specific patient population can not be supported by this study. The study was conducted by the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA), which is part of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. This information is provided to you, as a health care practitioner, to serve as preliminary information while a manuscript is being readied for submission to a peer-reviewed medical journal.

Introduction and Background

The CPCRA was established in 1989 to involve community physicians and their patients in studies of treatments for HIV. A unique feature of this program is its community-based focus for evaluating the effectiveness of a broad spectrum of therapies and treatment regimens. The CPCRA is comprised of 17 research units, consisting of consortiums of primary care physicians and nurses, located in 13 U.S. cities. These research units represent a significant geographic, racial and risk group diversity. Through this diversity, the CPCRA extends greater opportunity for participation in clinical research to those persons underrepresented in traditional, university-based HIV studies.

Study Design

The CPCRA ddI/ddC study was designed to answer the important clinical question of which one of the currently available nucleoside analogues should be given to a patient who can no longer tolerate or has failed ZDV therapy. The study was an open-label comparison of ddI and ddC with progression of disease, including death, and tolerance of the study drugs as the main endpoints.

The CPCRA ddI/ddC study opened in December 1990 and enrolled 467 patients by September 20, 1991, exceeding target accrual three months earlier than projected. All patients were followed for at least one year after the last patient was enrolled. The protocol ended follow-up on September 20, 1992.

Study Population

Study Population: 230 patients were randomized to receive ddI and 237 to receive ddC. Ten percent of the patients were women and two-thirds were white. Nearly a quarter of the patients enrolled had

a history of injection drug use. The average age was 38 years. Approximately 63% of patients were ZDV intolerant, 48% of them because of hematologic intolerance. Intolerant patients had used ZDV an average of 14 months, whereas those failing ZDV had used it an average of 23 months. Approximately 66% of patients had a prior AIDS diagnosis. The median CD4+ cell count of the enrolled patients was very low, 37 cells per cubic millimeter. The use of concomitant medications at baseline was similar in the two groups.

Results

Main Endpoint

Disease progression, including death, occurred in 156 ddI patients and 150 ddC patients (rate per 100 person years: 92.3 for ddI vs 86.4 for ddC; relative risk = 0.93, p-value = 0.56). Thus, there is no statistically significant difference between the two treatments based on this endpoint. The ddI group reported 100 deaths while the ddC group had 87 and the difference between the groups is approaching, but does not reach, a statistically significant level (relative risk 0.76, p-value = 0.072).

There were small, not statistically significant differences in several characteristics with known prognostic value for progression of HIV disease and survival: number of CD4+ cells, AIDS diagnosis and Karnofsky score. These small baseline imbalances in important prognostic factors between the two groups, especially for Karnofsky score, indicate that the ddC group may have been, by chance, slightly more ill than the ddI group. It may be difficult to distinguish the effect of the treatments under study from any inherent differences in those baseline characteristics. Adjusted analysis is done in order to make sure that any differences in outcome have not been influenced by those random baseline differences.

When analysis of these results was performed adjusting for these prognostic characteristics, the risk of progression of disease including death is in the direction of favoring ddC, although still not statistically significant ($p = 0.11$). The adjusted risk of death alone, however, does indicate an advantage for ddC ($p = 0.002$).

Disseminated *Mycobacterium avium* infection (MAI) infection was the most common non-fatal first event in both treatment groups (ddI=24 vs ddC=27), with *Pneumocystis carinii* pneumonia (PCP) and candidiasis following. Longitudinal analysis of data on CD4+ cells show that the average change after 2 months for those receiving ddI was significantly greater than for those receiving ddC. Between months 2 and 18, CD4+ cell counts declined in both groups.

Toxicity

While on initial study drug, at least one adverse experience was reported by 67% of patients on ddI and 66% on ddC. Many patients had multiple adverse experiences. Although the number and rates for patients with at least one adverse experience were similar in the two groups, the nature of these experiences were different. Peripheral neuropathy was seen significantly more frequently in patients receiving ddC (32 on ddI vs 69 on ddC, $p<0.001$), while stomatitis occurred only in ddC (8 patients). Pancreatitis was seen only in patients on ddI (4 patients). Diarrhea (48 vs 9, $p<0.001$) and abdominal

TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T92-22
April 21, 1992

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ADVISORY COMMITTEE RECOMMENDS APPROVAL OF DDC AS COMBINATION AIDS THERAPY

FDA is receiving numerous inquiries concerning recommendations by the Antiviral Drug Products Advisory Committee on dideoxycytidine (DDC), an experimental therapy for treating patients at advanced stages of infection with the AIDS virus.

On April 21, a majority of the committee, a panel of outside experts, recommended that FDA approve DDC for use in combination with zidovudine (AZT), an approved treatment for people with AIDS. However, the committee recommended against DDC's approval as monotherapy in treating AIDS patients who are intolerant to, or who have not responded to AZT and didanosine (DDI) -- the other approved therapy for AIDS.

The committee made its recommendations after reviewing data and analyses presented by FDA reviewers, clinical researchers from the National Institute of Allergy and Infectious Diseases (NIAID) and representatives of the drug's manufacturer, Hoffmann-LaRoche Inc. of Nutley, N.J. The data presented involved several studies, some of which examined DDC's use as a single agent, and others that looked at it in combination with AZT therapy.

In determining DDC's effectiveness as monotherapy, the committee considered a study conducted jointly by Hoffmann-LaRoche and the AIDS Clinical Trial Group (ACTG) of NIAID, that compared AIDS patients treated with DDC to similar patients treated with AZT. This study, designated

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N3300/ACTG 114, indicated that the patients given AZT did better than patients on DDC in terms of their length of survival and the avoidance of serious opportunistic infections.

In their presentation before the committee, researchers for Hoffmann-LaRoche contended that data from this study as well as other large-scale DDC protocols suggested that some patients on DDC did appear to derive some quality of life benefits from the drug --for example, weight gain. The committee was interested in these data, but not convinced that these benefits were clear and well substantiated. Therefore, the committee determined, after a careful assessment of the risks and potential benefits, that an approval for DDC monotherapy was not warranted at this time.

The committee considered several small studies that dealt with the efficacy of combination DDC/AZT therapy. These studies compared patient groups given combination DDC/AZT therapy to patient groups treated with AZT. The majority of these studies used only groups containing patients who had not previously been treated with AZT.

The results of these trials indicated that the combination therapy had a beneficial effect in some patients. This effect was gauged through measuring patients' CD4 helper cell levels. CD4 helper cells are white blood cells important in the immune system that are destroyed by the AIDS virus. Healthy individuals normally have CD4 helper cell counts of 1,000 or more, while those at advanced stages of AIDS infection usually have counts of 200 or less. Both FDA and its Antiviral Products Advisory Committee have agreed with many researchers that an increase in CD4 cell counts can indicate a beneficial effect on a patient's immune system.

The results from these studies were augmented by data from a study by

AZT's manufacturer, the Burroughs Wellcome Co. of Research Triangle Park, N.C. This randomized study produced results consistent with those found in the smaller Hoffmann-La Roche studies.

The committee in its recommendation concluded that data from these studies, when considered together, warranted FDA's approval of DDC for use in combination with AZT. Although most of the DDC/AZT combination therapy trials involved patients who had not previously received AZT therapy, the committee chose not to recommend a specific indication for the therapy's use. The committee deferred this matter to FDA, but urged that the benefits of DDC/AZT combination therapy be studied in persons already treated with AZT so that the most effective means for using combination therapy could be determined.

The committee strongly urged that ACTG 155 -- a large ongoing double-blind, randomized clinical trial which compares patient groups on combination therapy with patient groups being treated with either AZT or DDC -- should continue. Some interested parties had asked that the codes helping to ensure the objectivity of the trial be broken, so that clinical data gathered so far can be analyzed. The committee argued that such action would be premature and would irrevocably harm any chance to acquire reliable efficacy data on DDC/AZT combination therapy.

Although the committee's recommendations for approval are not binding upon FDA, they will be given a very serious consideration in the agency's review of the new drug application for DDC. The amount of time needed to consider an advisory committee's recommendations varies widely depending on a number of factors, but FDA intends to act quickly in its evaluation of this drug and has devoted extraordinary resources to this effort.

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In the meantime, the drug is being made widely available, through a series of protocols sponsored by Hoffmann-LaRoche, to physicians treating AIDS patients and others at advanced stages of infection with the AIDS virus who cannot participate in controlled clinical studies of the drug. Physicians interested in these protocols can contact the company at 1-800-DDC-21HIV, Monday through Friday, from 9 a.m. to 8 p.m., Eastern Time.

FDA regularly calls on its 40 advisory committees to address specific issues or problems concerning FDA-regulated products.

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FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T88-6
Jan. 14, 1988

Brad Stone/Don McLearn
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UPDATE ON EXPERIMENTAL AIDS THERAPIES AND VACCINES

Since Acquired Immune Deficiency Syndrome or AIDS was observed and recognized by medical scientists at the Centers for Disease Control and around the world in 1981, FDA and its sister agencies in the Public Health Service and the Department of Health and Human Services have made the fight against this dreaded disease their top priority. Less than three years later, in 1984, scientists at the National Cancer Institute in Bethesda, Md., and at the Pasteur Institute of Paris, isolated the Human Immunodeficiency Virus (HIV) and identified it as the source of AIDS.

Much about HIV and AIDS remains a mystery to scientists. Nevertheless, substantial progress has been made over the past few years in (1) discovering the basic character of HIV, (2) developing diagnostic methods and devices for detecting HIV infection, and (3) examining possible approaches to preventing and treating AIDS. The following information may help answer questions about potential AIDS therapies and vaccines now being studied. This Talk Paper updates T87-58 (Dec. 2, 1987).

There is as yet no cure for AIDS and no vaccine to prevent the disease. In the absence of such basic tools, medical scientists are concentrating on developing three distinct types of drug treatments -- drugs to stop the multiplication of Human Immunodeficiency Virus, drugs to boost the immune system, and drugs to treat AIDS-associated opportunistic infections which are responsible for the lethal effects of AIDS.

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A widely held notion -- that FDA actually does the clinical testing of drugs before they are marketed -- is incorrect. Pharmaceutical manufacturers, the National Institutes of Health and other research institutions across the country do the testing. It is FDA's responsibility to review and analyze the results of the testing to see if a drug is safe and effective for commercial use by the general public.

However, in the case of drugs to treat AIDS and AIDS-related diseases, FDA has taken a number of steps to encourage testing through the incentives of the "orphan" drug program and to streamline the agency's drug review process so that when AIDS drugs do come to the agency, they can get the most timely review possible. In addition, the agency works closely with manufacturers of promising therapies during drug development to assure that the studies conducted provide the information necessary for new drug approval.

NEW DRUG APPLICATIONS (NDAs)

FDA has given all potential AIDS drugs a 1-AA classification -- the highest possible priority -- in FDA's drug review system. The agency's expedited review of zidovudine (marketed as Retrovir and more commonly known as AZT), which became the first approved treatment for AIDS, served as the prototype for the new 1-AA classification.

The agency reviewed and approved zidovudine's new drug application (NDA) in less than four months -- 107 days -- after its submission.

There are no NDA's currently pending before the agency for drugs to directly treat AIDS.

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INVESTIGATIONAL NEW DRUGS (INDs)

FDA has approved more than 100 on-going human studies to test potential AIDS drugs. In many cases, FDA has granted permission to begin these trials within five days of receiving an application. This was true, for example, of a recent request by the National Institute for Allergy and Infectious Diseases (NIAID) to test AL-721. (Unless FDA notifies a sponsor of problems within 30 days, a sponsor can go ahead with its research plan.)

At present, IND studies involve more than 40 different anti-viral or immuno-modulating drugs. In a few studies, two or more experimental therapies are being used in combination.

Under federal laws to protect trade secret and confidential commercial information, FDA employees are prohibited from publicly discussing or acknowledging the status of experimental drugs. However, due to the intense public interest in AIDS, many of the sponsors of experimental AIDS therapies now undergoing FDA-sanctioned clinical testing have made some information about their therapies available. The following is a list of potential AIDS therapies publicly acknowledged by their sponsors to be now under study. Requests for additional information on any of these products should be directed to the IND sponsor.

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IND--EXPERIMENTAL ANTI-VIRAL AGENTS

EXPERIMENTAL TREATMENT	SPONSOR
Ansamycin (rifabutin)	Adria Laboratories, Dublin, Ohio (614) 764-8100
Ribavirin	Viratek/ICN Pharmaceuticals, Costa Mesa, Calif. (800) 556-1937
ddC (Dideoxycytidine)	Hoffmann-La Roche Inc., Nutley, N.J. (201) 235-5000
HPA-23	Rhone-Poulenc, Monmouth Junction, N.J. (201) 297-0100
AL 721	Matrix Laboratories, Fort Lee, N.J. (201) 944-0444
	National Inst. of Allergy & Infectious Diseases, Bethesda, Md. (301) 496-5717
Foscarnet	National Inst. for Allergy & Infectious Diseases, Bethesda, Md. (301) 496-5717
UA001	Ueno Fine Chemicals Industry Ltd., New York, N.Y. (301) 452-8666

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EXPERIMENTAL IMMUNO-MODULATING AGENTS

EXPERIMENTAL TREATMENT	SPONSOR
DTC (Imuthiol)	Merieux Institute, Miami, Fla. (305) 593-9577
Thymopentin	Ortho Pharmaceuticals, Raritan, N.J. (201) 524-8895
Thymostimuline	Serono Laboratories Inc., Randolph, Mass. (800) 225-5185
Methionine-enkephalin	National Jewish Hospital, Denver, Colo. (303) 398-1907
AS-101	Scientific Testing Inc., New Brunswick, N.J. (212) 230-9500
Peptide-T*	National Inst. of Mental Health, Bethesda, Md. (301) 443-4515
Isoprinosine	Newport Pharmaceuticals, Newport Beach, Calif. (714) 642-7511
Alpha Interferon*	Hoffmann-La Roche Inc., Nutley, N.J. (201) 235-5000
Tumor Necrosis Factor*	Genentech Inc., San Francisco, Calif. (415) 266-1000
Gamma Interferon*	Genentech Inc., San Francisco, Calif. (415) 266-1000
Imreg-I*	IMREG Inc., New Orleans, La. (504) 523-2875
Interleukin-II*	Hoffmann-La Roche Inc., Nutley, N.J. (201) 235-5000
Ampligen*	HEM Research, Philadelphia, Pa. (215) 999-0080, and E.I. Dupont de Nemours and Co. Wilmington, Delaware (302) 992-4747
Anti-alpha interferon serum*	Advanced Biotherapy Concepts Inc., Los Angeles, Calif. (213) 474-1774
r-GM-Colony Growth Stimulating Factor*	Sandoz Pharmaceuticals Corp. East Hanover, N.J. (201) 386-7500, and Schering-Plough Corp. Kenilworth, N.J. (201) 558-4000

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OPPORTUNISTIC INFECTION AND CANCER AGENTS

In addition to the fight to develop drugs to deal directly or indirectly with HIV itself, there is an intense search for drugs to treat opportunistic infections and cancers that are often lethal to AIDS patients who -- with a depleted immune system -- have no way of fighting them off.

Experimental drugs for these conditions include anti-infectives which will act directly against an infection, immuno-modulators to boost the body's own immune system and anti-neoplastics to act directly against cancers.

The most prevalent forms of opportunistic infections and cancers include:

Pneumocystis carinii pneumonia (PCP) -- a severe lung infection found in nearly 80 percent of all AIDS patients at some time in the course of the disease.

Candidiasis -- A fungal infection of the mouth and esophagus.

Kaposi's Sarcoma (KS) -- A malignant tumor condition common in AIDS patients.

Cytomegalovirus (CMV) -- An opportunistic infection that can cause blindness and/or death in AIDS patients.

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There are a number of drugs which are approved or being developed for these conditions. Perhaps the best example is the anti-infective drug pentamidine**, produced by LyphoMed Inc. of Rosemont, Ill., used in the treatment of PCP pneumonia. Using an expedited review procedure, FDA approved pentamidine for commercial marketing in just over six months.

PENDING NEW DRUG APPLICATIONS (NDAs)

The following are drugs for AIDS-associated conditions that have pending new drug applications (NDAs):

NDA--EXPERIMENTAL IMMUNO-MODULATING AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
r-alpha-interferon*	Hoffmann-La Roche Inc. Nutley, N.J. (201) 235-5000	Kaposi's Sarcoma
r-alpha-2b interferon*	Schering-Plough Corp. Kenilworth, N.J. (201) 558-4000	Kaposi's Sarcoma

NDA--EXPERIMENTAL ANTI-NEOPLASTIC AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
None		

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NDA--EXPERIMENTAL ANTI-INFECTIVE AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
ganciclovir (DHPG)	Syntex Corporation Palo Alto, Calif. (415) 855-5050	Cytomegalovirus/ life or sight threatening

INVESTIGATIONAL NEW DRUGS (IND) FOR OPPORTUNISTIC INFECTIONS AND CANCERS

FDA has approved more than 80 on-going human studies to test potential drugs for opportunistic infections and cancers. At present these studies involve nearly 30 different agents. In several cases, separate human trials are being conducted with the same proposed AIDS therapy to test its effect on different AIDS conditions. In a few cases, two or more experimental therapies are being used in combination.

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INFECTIVE AGENTS

EXPERIMENTAL AGENT	SPONSOR	INDICATION
Trimetrexate**	Warner-Lambert Company Morris Plains, N.J. (201) 540-2000 (NIAID also)	Pneumocystis carinii pneumonia (treatment)
Elflornithine (DMFO)**	Merrell-Dow Pharmaceuticals Inc. (513) 984-9111	Pneumocystis carinii pneumonia (treatment)
Aerosol Pentamidine**	Fisons Corporation Bedford, Md. (617) 275-1000	Pneumocystis carinii pneumonia (treatment)
	LyphoMed Melrose Park, IL (312) 345-6170	Pneumocystis carinii pneumonia (treatment and prophylaxis)
Foscarnet	Astra Pharmaceuticals Products Inc., Westboro, Ma. (617) 366-1100	Cytomegaloviral retinitis
Ansamycin (in combination with other drugs)	Adria Laboratories, Dublin, Ohio (614) 764-8100	k-Mycobacterium avium intracellulare disease infection (an organism closely related to Mycobacterium tuberculosis)
Spiramycin	Rhone-Poulenc Inc. Monmouth Junction, N.J. (201) 297-0100	Cryptosporidiosis (a eukaryotic organism that can cause severe chronic diarrhea)
Piritrexim	Burroughs Wellcome Co. Research Triangle Park, N.C. (919) 248-3000	Pneumocystis carinii pneumonia (treatment)
Immune Globulin IG-IV*	Sandoz Pharmaceuticals Corp., East Hanover, N.J. (201) 386-7500, and Alpha Therapeutics, Los Angeles, Calif. (213) 227-7526	Treatment or prevention of various opportunistic infections
Cryptosporidiosis Immune Globulin (from cows' milk)*	National Institute of Allergy & Infectious Diseases, Bethesda, Md. (301) 496-5717	Cryptosporidiosis

-MORE-

Fluconazole	Pfizer Inc., New York, N.Y. (212) 573-2323	Cryptococcol Meningitis

IND--EXPERIMENTAL IMMUNO-MODULATING AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
r-Interleukin-2 analogue*	Cetus Corp. Emeryville, Calif. (415) 420-3232	Kaposi's Sarcoma
Lymphoblastoid interferon*	Burroughs Wellcome Co. Research Triangle Park, N.C. (919) 248-3000	Kaposi's Sarcoma
r-beta-ser Interferon*	Triton Biosciences Alameda, Calif. (415) 769-5200	Kaposi's Sarcoma

IND--EXPERIMENTAL ANTI-NEOPLASTIC AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
Piritrexim Isethionate	Burroughs Wellcome Co. Research Triangle Park, N.C. (919) 248-3000	Kaposi's Sarcoma
Doxorubicin (see note below)	National Institute of Allergy and Infectious Diseases, Bethesda, Md. (301) 496-5717	Kaposi's Sarcoma
Menogaril	National Cancer Institute Bethesda, Md. (301) 496-6641	Kaposi's Sarcoma
M-BACOD	National Institute of Allergy and Infectious Diseases, Bethesda, Md. (301) 496-5717	Primary Lymphoma

Note: Doxorubicin is an approved commercially available anti-cancer agent. This is an experimental use of the drug.

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VACCINES:

At present, the Public Health Service has recommended certain steps that individuals can take to avoid exposure to HIV infection. Theoretically, one of the most effective ways to prevent the spread of this infectious disease would be through vaccination. However, because of the nature of the HIV, scientists predict vaccines against it will take a number of years to develop. But there has already been a good deal of progress in the search for such vaccines.

On Aug. 18, 1987, FDA sanctioned the first human testing of a candidate vaccine against HIV in the United States. The vaccine is manufactured by MicroGeneSys Inc. of West Haven, Conn. Study of the vaccine is being conducted by the National Institute of Allergy and Infectious Diseases at its Clinical Center in Bethesda, Md. (301) 496-5717, and through its extramural program which includes a network of vaccine evaluation units at medical schools across the country.

On Nov. 25, 1987, FDA approved a second experimental vaccine for human testing. The vaccine, produced by Bristol-Myers Co. of New York, N.Y., is made from vaccinia virus into which genes for the surface or envelope proteins from HIV have been inserted by recombinant DNA techniques.

In the future, FDA will continue to encourage the development of drugs and vaccines against HIV and HIV-related opportunistic infections, and will update this Talk Paper on a regular basis.

-MORE-

* These products are considered biologic products. Interferon products also have anti-infective and immune-modulating properties.

** These products have been designated for Orphan Drug status under FDA's Orphan Products Development Program. This program provides tax and other financial incentives for the development of potential therapies for serious, but relatively rare diseases.

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FDA
TALK PAPER
FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T87-22
April 9, 1987

Brad Stone
(301) 443-3285

UPDATE ON EXPERIMENTAL AIDS THERAPIES

On March 20, the drug zidovudine, commonly known as AZT, became the first FDA-approved treatment for AIDS. It is currently being marketed under the trade name Retrovir. Since that approval, there have been a number of requests for information on potential AIDS therapies that are under clinical research .

The following is a list of proposed treatments for AIDS that have received investigational new drug exemptions (IND) from the agency, permitting clinical studies. This list of INDs for testing AIDS therapies contains those treatments that have been publicly acknowledged by their sponsors. Under FDA's Freedom of Information regulations, information on therapies currently under consideration at FDA is regarded as trade secret and confidential, and as such is not ordinarily releasable without the consent of the sponsor. Therefore, experimental treatments that have not been acknowledged or publicized by their sponsors are not included on this list.

It is important to note that the drugs listed below have not been approved by the agency. Their listing indicates only that sponsors have shown these drugs to be sufficiently safe for clinical testing. Many essential safety and efficacy questions concerning these drugs must be resolved through clinical testing before they can receive FDA approval for commercial distribution.

This list includes the name of the drug, its therapeutic category and its IND sponsor(s). Requests for additional information on any of the experimental AIDS treatments listed below should be directed to its IND sponsor.

(MORE)

IMMUNO-MODULATING AGENTS

EXPERIMENTAL TREATMENT	SPONSOR
Thymopentin	Ortho Pharmaceuticals/ Raritan, N.J.
Thymostimuline	Serono Laboratories, Inc./ Braintree, Mass.
Methionine-enkephalin	National Jewish Hospital/ Denver, Colo.
Isoprinosine	Newport Pharmaceuticals/ Newport Beach, Calif.

ANTI-VIRAL AGENTS

EXPERIMENTAL TREATMENT	SPONSOR
Ansamycin	Adria Laboratories/ Dublin, Ohio
Ribavirin	Viratek/ICN Pharmaceuticals/ Costa Mesa, Calif.
DDC (Dideoxycytidine)	National Cancer Institute/ Bethesda, Md.
HPA-23	Rhone-Poulenc/ Monmouth Junction, N.J.

(MORE)

ANTI-VIRAL AGENTS continued--

EXPERIMENTAL TREATMENT	SPONSOR
AL 721	Matrix Laboratories/ New York, N.Y.
Foscarnet	National Inst. for Allergies & Infectious Disease/ Bethesda, Md.

BIOLOGICAL PRODUCTS

EXPERIMENTAL TREATMENT	SPONSOR
Alpha interferon	Hoffmann-La Roche Inc./ Nutley, N.J.
Gamma interferon	Genentech, Inc./ San Francisco, Calif.
Imreg-I	IMREG, Inc./ New Orleans, La.
Interleukin-II	Hoffmann-La Roche Inc./ Nutley, N.J.
Poly IC12U	HEM Research/ Rockville, Md.

(MORE)

BIOLOGICAL PRODUCTS continued --

EXPERIMENTAL TREATMENT	SPONSOR	
Immune Globulin IG-IV	Sandoz Pharmaceuticals Corp./	East Hanover, N.J.
	Alpha Therapeutics/	Los Angeles, Calif.

NOTE ON AIDS VACCINES:

Currently there are several investigational new biologic applications before FDA from sponsors seeking permission to begin clinical human testing of their AIDS vaccines. The sponsors for two of these AIDS vaccines have publicized their IND submissions:

The Institute for Immunological Disorders in Houston, Texas has submitted an application to test Alpha I Therapeutic as an AIDS vaccine. FDA's Office of Biologics Research and Review has reviewed and responded to this application with a request to the sponsor for additional information on the drug's characterization and safety.

Bristol-Myers's Oncogen Division has more recently submitted an IND application to test another potential AIDS vaccine. FDA is now reviewing that application.

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Abbott Changes Direction on Clarithromycin Prophylaxis Trial

Gordon Nary

The AIDS Clinical Trial Group (ACTG) and Community Programs for Clinical Research on AIDS (CPCRA) clarithromycin (Biaxin®) placebo-controlled prophylaxis trial against *Mycobacterium avium* complex (MAC) as reported in *PAACNOTES* (volume 3, number 5) was scrapped when the rifabutin prophylaxis trial data was announced in January by Adria. Rifabutin's statistical significance over placebo in preventing or delaying MAC nullified the use of a placebo in any MAC prophylaxis trial.

While there are tentative plans to redesign a new ACTG trial comparing rifabutin with clarithromycin and azithromycin, and other discussions of a possible clarithromycin-rifabutin combination prophylaxis trial, Abbott has decided to test the effectiveness of clarithromycin as a sole prophylactic agent against MAC on its own without waiting several months for a new ACTG trial.

According to Andre Pernet, Ph.D., vice president, Anti-Infective Research and Development at Abbott Laboratories, Abbott is conducting their own dose-ranging trial so that "physicians and patients can have critical MAC prophylaxis data as quickly as possible and use the most effective available agent to prevent this increasingly life-threatening complication of HIV disease."

The new dose-ranging trial will compare 500 mg and 1000 mg daily dosage of clarithromycin in patients with HIV disease who have a CD4 count of less than 100 and who have not had a previous episode of MAC. Patients will stay in the study for up to two years after the last patient is enrolled or until there is a positive blood culture for MAC, whichever occurs first.

Abbott is actively seeking HIV treatment centers with clinical trial experience that have 100 or more eligible patients. Clinical trial centers interested in participating in the new trials should contact Physicians Association for AIDS Care at 1-800-243-3059 for additional information.

Hoffman-La Roche Announces Two New ddC Expanded-Access Programs

Gordon Nary

On February 20, 1992 Hoffman-La Roche Inc. announced plans for two new programs to make HIVID® (zalcitabine, ddC) available. Roche will continue its existing expanded access program for patients who have either developed an intolerance or failed zidovudine (ZDV).

A new open-label program will be implemented within the next two weeks. Rapid enrollment will be enhanced through the use of streamlined entry criteria and limited data collection, much of which can be done over the phone. Symptomatic HIV-infected individuals with $CD4^+$ cell counts of 300 or less or asymptomatic individuals with $CD4^+$ cell counts of 200 or less who cannot participate in controlled clinical trials will be eligible to receive HIVID® for combination therapy. Physicians should call the ddC Coordinating Center at 1-800-332-2144 between 9 a.m. and 8 p.m. (EST) for enrollment information. HIVID® will be provided free of charge to all eligible persons.

In the second program, Roche is planning to provide HIVID® for combination therapy in healthier HIV-infected individuals with $CD4^+$ cell counts up to 500. At press time the information on this proposed trial was nebulous. Roche is attempting to integrate some disparate recommendations from AIDS activists. However, Food and Drug Administration's (FDA's) attempted crackdown on buyer's clubs who may be selling ddC of questionable purity is forcing some creative attempts to meet the growing demand for the antiviral by patients and physicians. [An investigative report on FDA's probe of buyers clubs is scheduled for the March/April issue of *PAACNOTES*]

Fluconazole As Effective As Amphotericin B for Initial Episodes of Cryptococcal Meningitis

Gordon Nary

In the January 9, 1992 issue of *The New England Journal of Medicine*, study investigators found that oral fluconazole (Diflucan®) is as effective as intravenous doses of amphotericin B as a treatment for AIDS patients with an initial episode of cryptococcal meningitis. In addition, the patients taking fluconazole had fewer drug-related side effects.

The standard therapy for treating an initial episode of cryptococcal meningitis is intravenous amphotericin B, but the drug's use can result in serious adverse reactions including impairment of kidney function and suppression of bone marrow, as well as milder side effects such as fever and nausea. In this study, patients on fluconazole experienced fewer drug-related side effects, although some patients had drug-associated gastrointestinal symptoms, skin rashes, and, less frequently, elevation of liver enzymes.

Of the 194 patients in the trial, 131 received fluconazole (200 mg/day) and 63 received amphotericin B (0.4-0.5 mg/day per kilogram of body weight). Treatment was successful in 44 of 131 fluconazole recipients (34 percent); and in 25 of the 63 amphotericin B recipients (40 percent).

Rates of death due to cryptococcal meningitis did not differ significantly for the two groups (14 percent for the amphotericin B group vs. 18 percent for the fluconazole group). However, the death rate during the first two weeks of therapy was higher in the fluconazole group (15 percent vs. 8 percent).

Patients tolerated fluconazole much better than amphotericin B: 73 percent of fluconazole recipients reported no adverse effects, as compared with 37 percent of amphotericin B recipients. Severe side effects forced discontinuation of the drug in 8 percent of amphotericin B recipients, as compared with two percent of fluconazole recipients.

Treatment Issues Oct 1993

continued from previous page

be able to destroy many RNA strands. According to Hybridon, GEM-91 first binds to the target RNA strand, then activates a cellular enzyme (RNAseH) which destroys the strand, leaving the drug free to attack more RNA.

Even if GEM-91 fails in humans, Hybridon is positioned to be a leading player in antisense research. Hybridon has already synthesized GEM-92, its second generation product. Also, the company claims broad patent rights over all antisense approaches to AIDS, although this has not been tested in the courts.

In addition, Hybridon believes it has resolved manufacturing issues. The company was recently awarded a patent that covers new, more efficient methods of antisense production and has started construction of a large manufacturing facility. The company believes that it will have sufficient supply of the compound to meet the needs of clinical research.

Conclusion

Since the genes of HIV have been extensively studied by molecular biologists, researchers can design antisense compounds aimed at specific mRNA molecules that produce proteins essential to HIV's survival. Although very few clinical trials have actually begun, and clinical efficacy is a long way from certain, the pharmaceutical industry has devoted significant resources to this burgeoning field. Its proponents believe antisense will radically transform medicine and open up the possibility for new treatments for AIDS and other viral diseases.

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continued from page 5

ples came from the San Francisco area, New York, and Los Angeles. Of the 101 samples analyzed, 59 contained MDMA only. Twenty-four samples contained MDMA with other substances, usually MDA, a closely related but more toxic compound, or chemical precursors from MDMA's manufacturing process, usually methylamine. Fifteen samples contained MDA alone or with its own chemical precursors. One sample "contained a nondescript amphetamine." Two samples contained no MDMA, MDA, or other known drugs; the constituents in these two samples could not be identified.

Analysis Anonymous ceased operations before MDMA was criminalized. It is unknown what effect, if any, criminalization may have had on the purity of MDMA samples. Treatment Issues was unable to obtain information on the purity of MDMA now available on the street.

CONCLUSION

MDMA is a popular illicit drug widely used by some urban populations, including gay men and some HIV-infected people. Inadequate data describe the extent of MDMA use. MDMA is associated with increased risk of HIV infection in men who have sex with men. Although rare, MDMA use has been linked to serious toxicities and death. While no data support the belief that MDMA causes brain damage, scientific studies have not adequately addressed this question. MDMA addiction has not been described in humans, although it has been observed in two species of primates. MDMA is a street drug with unknown purity.

FDA Reviews ddC

by Derek Link

DDC APPROVED AND WITHDRAWN

In a two-day meeting full of ironic twists, the FDA Antiviral Advisory Committee voted on September 20 to fully approve ddC monotherapy and withdraw combination AZT/ddC's accelerated approval. Advisory Committee decisions carry no official authority, although FDA usually follows them. The monotherapy approval was based on CPCRA 002, an open-label, non-randomized comparison of ddC and ddI in advanced AIDS patients who were intolerant or failing AZT. Hoffmann LaRoche, the New Jersey-based affiliate of the Swiss drug company that manufactures ddC, also submitted data from earlier monotherapy studies, the ddC monotherapy control arm of ACTG 155, and the ddC expanded access program to support the approval. During the vote, Fred Gordin, MD, VA Medical Center in Washington DC, a committee member said, "we use ddC monotherapy as salvage therapy in advanced patients. This brings the indication in line with its clinical use."

In a separate decision, the committee voted to withdraw ddC combination therapy's accelerated approval. Accelerated approval is a new regulatory mechanism which allows marketing approval before a drug's clinical efficacy has been established. AZT/ddC combination therapy obtained the first accelerated approval in June 1992. Committee members cited several reasons for the withdrawal including insufficient data supporting efficacy of the combination, lack of ddC access problems, and doubts that accelerated approval could be implemented after ddC received a full monotherapy approval.

TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T92-7
Feb. 6, 1992

Brad Stone
(301) 443-3285

FDA URGES BUYERS CLUBS TO END SALES OF UNDERGROUND DDC

On Feb. 5, 1992, FDA informed AIDS buyers clubs throughout the United States that FDA-sponsored laboratory analysis of samples of unauthorized, or underground, versions of dideoxycytidine (DDC) -- an experimental AIDS treatment -- showed potentially serious variations in product potency and quality. The agency has determined that these results indicate that underground DDC is produced under poor manufacturing conditions and that the overall safety and purity of underground DDC is suspect. As a result, FDA has strongly urged buyers clubs to cease the sale or distribution of underground DDC and to notify their clientele of FDA's findings.

The term "buyers club" is loosely used to describe groups which facilitate patient access to drugs and other products purportedly useful in treating AIDS and related diseases.

In January 1992, the agency received reports that the amounts of DDC contained in some capsules of the underground product were far higher or lower than labelled. In response to these reports, FDA undertook to do its own analysis of the product, collected samples from various buyers clubs and had its laboratory analyze these samples.

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FDA's analysis confirmed wide variations among the individual samples of tested underground DDC. Some individual capsules were shown to contain no DDC at all, while others contained more than twice the labelled amount. Variations from labelled dosage levels were also found when the individual units from each buyers club were combined into a composite sample for each site; one composite contained only half the expected content.

FDA is concerned about these results because a significant variation from recommended dosage levels of DDC could put patients at risk of injury, particularly if the levels were too high. Excessive levels of DDC are known to cause nerve damage in the hands and feet. Although the excess potency found in FDA's analysis of the sampled underground DDC was short of the levels certain to produce these conditions, it nevertheless could increase patient risk of experiencing some serious adverse reactions.

Moreover, FDA believes that the significant inconsistency found in these samples reflects lapses in manufacturing practices that could be associated with increased risk of product contamination or other problems. At a minimum, these findings demonstrate that it is not possible to assure the quality or safety of these products.

In view of these concerns, FDA has notified buyers clubs that underground DDC poses an unacceptable risk to public health, that sales and distribution of the product should cease immediately and that they should inform their clientele about the potential problems associated with these products. FDA will work in cooperation with buyers clubs in this effort and will take other appropriate steps to protect the public health.

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Unlike underground DDC, the authorized version of DDC is manufactured under strictly regulated conditions that ensure consistent product quality. Nevertheless, it is an experimental drug whose safety and efficacy are still under evaluation by FDA. The agency is currently reviewing, on an expedited basis, a new drug application for DDC submitted in October 1991 by the drug's authorized manufacturer, Hoffmann-La Roche of Nutley, N.J.

In the meantime, more than 3,500 patients are enrolled in FDA-sanctioned clinical trials of the drug being conducted by the National Cancer Institute, the National Institutes of Health and Hoffmann-La Roche. In addition, DDC is being made available to more than 6,000 patients with AIDS and advanced AIDS-related complex who fail to benefit from or are unable to tolerate treatment with the approved AIDS treatment, zidovudine, commonly called AZT.

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TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T91-29
June 13, 1991

Sharon Snider
(301) 443-4177

DDC Receives Treatment IND Status

The Food and Drug Administration recently approved the release of the experimental AIDS drug dideoxycytidine (DDC) under a "Treatment IND." The following may be used to answer questions:

Treatment IND regulations provide a mechanism for drug developers to provide to patients promising investigational therapies that have been studied in humans and that may be effective. DDC is being made available to patients with AIDS and advanced AIDS-related complex who fail to benefit from or are unable to tolerate treatment with the approved AIDS treatment, zidovudine, commonly called AZT.

AZT reduces the incidence of life-threatening infections and prolongs survival in people with AIDS and advanced AIDS-related complex. However, despite its benefits, AZT can cause severe anemia in some patients, requiring physicians to either reduce the dose or discontinue the drug altogether. In addition, the disease may continue to progress while patients are on therapy.

DDC, which is being developed by Hoffmann-La Roche Inc. of Nutley, N.J., belongs to the same chemical class of drugs as AZT. Clinical studies underway in 3,500 patients by the National Cancer Institute, the National

-MORE-

Institutes of Health, and Hoffmann-La Roche indicate that DDC does not cause anemia and some of the other adverse effects associated with AZT. However, the effectiveness of DDC has not yet been fully established, and it has been associated with other adverse effects, some of which may be severe.

The most serious adverse effects of DDC are nerve damage in the hands and feet and inflammation of the pancreas. The former condition, called peripheral neuropathy, is usually reversible after treatment with DDC is stopped. Other common adverse effects of the drug are skin rash and mouth ulcers.

Under the Treatment IND, eligible AIDS patients will be able to receive DDC through a protocol administered and funded by Hoffmann-La Roche. Patients may request DDC from their physicians. If they qualify for treatment, they will be given DDC in tablet form. Patients will be monitored by their physicians monthly for six months and bi-monthly thereafter.

DDC was previously made available to patients who were not able to tolerate treatment with AZT or dideoxyinosine (DDI) through an open label protocol.

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FDA
TALK PAPER
FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

Arthur Whitmore
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T95-58
Nov. 7, 1995

FDA PANEL RECOMMENDS APPROVAL OF 3TC WITH AZT TO TREAT AIDS

The Food and Drug Administration's Anti-Viral Drugs Advisory Committee yesterday recommended that the agency grant accelerated approval for the drug lamivudine, or 3TC, for use in combination with AZT (zidovudine) in treating AIDS and HIV infection. The following may be useful in answering questions:

Both AZT and 3TC are members of the nucleoside analogue class of drug compounds, and both inhibit the replication of HIV, the virus that causes AIDS. AZT was approved by the agency in 1987. It was the first drug approved for the treatment of HIV infection. 3TC and AZT are manufactured by Glaxo-Wellcome Inc. of Research Triangle Park, N.C. The registered trade name for 3TC is Epivir; for AZT, Retrovir.

The committee based its recommendation on data from four controlled, randomized clinical trials evaluating laboratory measures of infection in adults. Data were also presented from ongoing open-label protocols for children and adults.

In the four controlled trials, 974 HIV-infected subjects were randomized to receive either combined therapy with 3TC and AZT, 3TC as a single therapy, AZT as a single therapy, or combined therapy

-more-

with AZT with ddC (Roche's anti-AIDS nucleoside analogue, which received accelerated approval in 1992). Patients included those with and without prior AZT therapy.

The primary marker of drug effect was changes in CD4 cell counts (a reflection of immune system strength). Secondary measures included assessments of the amount of HIV in patients' blood. Duration of the trials was 24 weeks. Baseline CD4 cell counts of patients at time of enrollment ranged from 100 to 500. (Values greater than 800 are normal for healthy individuals.) Doses of 3TC were 150 milligrams or 300 milligrams twice a day.

In patients who had no prior AZT therapy, the 3TC/AZT combination treatment was associated with an average increase in CD4 counts of about 50 above baseline. In patients previously on AZT therapy, the 3TC/AZT combination was associated with a CD4 increase of about 30 above baseline. Duration of this effect is not fully determined, although generally it lasted for at least 24 weeks.

Adverse events observed in patients on the AZT/3TC regimen were similar to those associated with other nucleoside analogue AIDS drugs. They included nausea, diarrhea, anemia, neutropenia, pancreatitis (especially in children who had received prior nucleoside analogue therapy) and neuropathy. Some of the more severe adverse reactions required withdrawal from therapy.

3TC has been studied in humans since April 1991. Since October 1993, the drug has been available to patients outside of

controlled clinical trials under an open-label protocol. More than 35,000 patients have received the drug under this expanded access program.

Approval of the 3TC/AZT application would be granted as an accelerated approval, a regulatory mechanism under which the agency may grant early marketing status for a product based on laboratory markers used to measure drug activity, rather than on clinical endpoints. Only products treating serious diseases and providing meaningful therapeutic benefit over existing treatments can qualify for an accelerated approval.

To grant accelerated approval, the agency must conclude that responses of markers in trials are probable predictors of clinical benefit. In the case of the 3TC/AZT marketing application, laboratory markers are the CD4 cell counts and assessments of amount of HIV in patients' blood.

Manufacturers of products granted accelerated approval must demonstrate within a reasonable period of time that the product provides true clinical benefit -- such as delay in death or reduction in opportunistic infections -- or the agency may withdraw accelerated approval. Trials designed to demonstrate clinical benefits of the 3TC-AZT treatment regimen are currently ongoing in adult and pediatric patients.

Information on ongoing clinical trials testing drugs for HIV infection may be obtained from the National Institute of Health's AIDS Clinical Trial Information Service at 1-800-TRIALS-A.

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FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

T95-62
Nov. 15, 1995

Arthur Whitmore
(301) 443-3285

FDA PANEL RECOMMENDS APPROVAL OF NEW AIDS DRUG

FDA's Antiviral Drugs Advisory Committee on Nov. 7 recommended that the agency grant accelerated approval for saquinavir for treating advanced HIV infection in combination with nucleoside analogue drugs. Saquinavir is manufactured by Roche Pharmaceuticals under the trade name Invirase. The following may be useful for answering questions.

Saquinavir is a protease inhibitor, a new class of compounds under study for treating HIV. Protease inhibitors interrupt a key step in the chemical sequence by which HIV replicates.

Controlled clinical trials on saquinavir enrolled 936 HIV-infected patients and tracked changes in CD4 cell counts (the number of these infection-fighting cells per ml in patients' blood) in subjects on three combinations of drugs: saquinavir with AZT, saquinavir with ddC, and saquinavir with both AZT and ddC. Saquinavir doses ranged from 75 to 600 mg three times a day. Analyses of CD4 counts were conducted over 16 weeks, and patients had the option of continuing treatment. Patients with CD4 counts ranging from 0 to 500 before treatment were enrolled in the trials. (Values greater than 800 are normal in healthy individuals.)

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AZT and ddC are AIDS drugs of the nucleoside analogue class of compounds, which also inhibit HIV replication. AZT, or zidovudine, was approved in 1987 and is manufactured by Glaxo-Wellcome Inc. under the trade name Retrovir; ddC, or zalcitabine, received accelerated approval in 1992 and is manufactured by Roche under the trade name Hivid.

Over 16 weeks, CD4 cell counts increased an average of 30-40 cells above baseline levels among patients on saquinavir in combination with ddC or AZT or AZT plus ddC. The increases were larger in patients who were previously untreated with nucleoside analogues. Saquinavir doses of less than 600 mg three times a day did not produce discernable CD4 increases, even when used in combination with AZT.

Few adverse events were associated with saquinavir, and for most patients the drug was well tolerated.

Approval of the saquinavir marketing application would be granted as an accelerated approval, a regulatory mechanism under which the agency bases early marketing approval for a product on laboratory markers like CD4 cell counts, rather than on clinical endpoints such as delay in death or reduction of opportunistic infections.

Manufacturers of products granted accelerated approval must demonstrate within a reasonable period of time that the product provides true clinical benefit or the agency may withdraw the accelerated approval. Trials designed to demonstrate clinical benefits of saquinavir in combination with other nucleoside analogues are currently enrolled in adult and pediatric patients.

Information on ongoing clinical trials testing drugs for HIV infection may be obtained from the Public Health Service's AIDS Clinical Trial Information Service at 1-800-TRIALS-A.

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FDA

Press Office
Food and Drug Administration
U.S. Department of Health and Human Services

NOTE TO CORRESPONDENTS/AIDS UPDATE
Nov. 30, 1988

Brad Stone
(301) 443-3285

INTERFERON APPROVED FOR KAPOSI'S

On Nov. 21, 1988, FDA approved the use of alpha interferon to treat Kaposi's Sarcoma -- a cancer which primarily affects AIDS patients. (See Press Release P88-35, Nov. 21, 1988.) Additionally, ganciclovir has been given treatment IND status, and DHEA, a new experimental therapy for AIDS, has been given the go-ahead for clinical testing:

The approval for alpha interferon is based in part on a study by the National Institute of Allergy and Infectious Diseases to be published in the Nov. 26 issue of the medical journal Lancet.

Kaposi's Sarcoma is most often manifested by the appearance of large purplish lesions on the skin, but internal lesions can develop throughout the body. Although the disease is rarely the immediate cause of death for AIDS patients, it can greatly weaken the patient's physical condition.

In several human studies, 40 to 45 percent of certain patients with Kaposi's Sarcoma who received high doses of alpha interferon responded with a significant reduction in the size of their tumors. These patients tended to be at less advanced stages of AIDS.

Schering Corp. of Kenilworth, N.J., and Hoffmann-La Roche of Nutley, N.J., will market slightly different molecular versions of the licensed

-MORE-

alpha interferon treatment for this indication under the Intron-A and Roferon brand names, respectively.

NIAID is conducting additional studies. Volunteers at early stages of HIV infection are being sought for a study comparing treatment with alpha interferon plus zidovudine (commonly known as AZT) to treatment with zidovudine or alpha interferon alone. Interested individuals should call Victoria Davey, R.N., at (301) 496-7196.

Reported adverse reactions to alpha interferon include flu-like symptoms.

GANCICLOVIR -- Treatment IND status was granted to ganciclovir -- an experimental therapy for AIDS patients with sight-threatening cytomegalovirus (CMV) retinitis, an eye infection that can lead to blindness. NIAID is sponsoring this treatment IND, as well as a controlled clinical trial of the drug with Syntex Corp. of Palo Alto, Calif.

Treatment IND status allows for expanded distribution of experimental therapies for immediately life-threatening or serious conditions before marketing approval has been granted, after safety and some degree of efficacy have been demonstrated in clinical testing. Trimetrexate, a drug to treat certain AIDS patients with Pneumocystis carinii pneumonia was given this status in Feb. 1988.

Patients with immediately sight-threatening CMV retinitis will be eligible under this treatment IND. Patients with CMV retinitis that is not threatening sight will be eligible for a controlled clinical trial of ganciclovir, in which patients will receive either immediate or later therapy, with very close monitoring for clinical deterioration.

Physicians and patients interested in either protocol can call the Ganciclovir Study Center at (301) 497-9888.

On Nov. 7, 1988, FDA granted permission for initial clinical testing of DHEA, a proposed anti-viral treatment for AIDS. The trials will be sponsored by the drug's sponsor, the Elan Corporation of Atlanta, Ga. (404) 534-8239.

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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P85-12
FOR IMMEDIATE RELEASE
April 9, 1985

Food and Drug Administration
Bruce Brown -- (301) 443-3285
(Home) -- (301) 384-0426

The Food and Drug Administration today instructed manufacturers and distributors of the drug DHEA, which is promoted as a "natural" weight reduction product, to discontinue selling it because it has not been reviewed for safety and effectiveness.

DHEA, known as dehydroepiandrosterone or dehydroandrosterone, is a steroidal hormone which has been sold nationwide without prescription in retail stores and through the mails for weight management, enhanced sex life and longer life. It has been promoted in recently popular books on extending human life. But no evidence has been submitted to FDA which substantiates those claims.

FDA is writing makers and distributors that DHEA is an unapproved new drug and that they must stop selling it and must provide FDA with information about its manufacture and distribution. If the companies fail to comply within 10 days of receipt of the letter, FDA will consider regulatory actions against the products and companies.

FDA has few adverse reaction reports on the drug, but said the risks from long-term use are unknown. DHEA may be manufactured from human urine. Scientific studies have not established what effect reintroducing into the body this concentrated bodily excess might have, FDA said.

No applications to conduct human studies with DHEA or to market it were submitted to FDA by the companies now selling it. The substance is considered a drug because under the Federal Food, Drug and Cosmetic Act, a substance that is offered for a nonfood purpose and that is intended or advertised to affect the body's normal functioning is classified as a drug. All new drugs require premarket approval.

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Press Office
Food and Drug Administration
U.S. Department of Health and Human Services

NOTE TO CORRESPONDENTS
May 31, 1990

Brad Stone
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MAY UPDATE/FDA SANCTIONS NEW DDC STUDY

On May 2, FDA sanctioned a new study primarily designed to evaluate the safety of the experimental anti-viral drug dideoxycytidine, or DDC. The following can be used to answer the questions that frequently are asked:

This protocol allows access to DDC for patients with AIDS or advanced ARC who can tolerate neither zidovudine, the standard treatment, nor didanosine (DDI), an experimental anti-viral drug currently available to certain patients through clinical testing and expanded access protocols. In addition, the protocol allows access to patients who have had progression of disease while on zidovudine and who were also DDI intolerant.

Zidovudine, commonly called AZT, can cause severe anemia and low white blood cell counts, especially in patients with advanced disease. DDI is associated with gastrointestinal problems, painful nerve damage to the feet (peripheral neuropathy) and, less commonly, severe damage to the pancreas that can be fatal.

All patients enrolled in the study will receive DDC. Patients will be assigned one of two doses of DDC, in order to compare the relative safety of the two dosage regimens and to provide some information about their efficacy.

Early clinical trials indicated that DDC at higher doses caused painful peripheral neuropathy in most patients after several months. Therefore,

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patients who have peripheral neuropathy, including those who may have developed it as an adverse reaction to DDI, will be excluded from entering this new study.

Because ongoing studies have shown that DDC-induced peripheral neuropathy may be more common in patients with advanced disease who are already intolerant to zidovudine, the study has been designed to allow an increasing number of patients to enroll as more information is acculmulated about the safety of the drug. The first group of patients eligible for the new DDC study will be carefully monitored by clinicians who have experience with this potentially toxic drug. Gradually, the study will enroll additional patients should the drug appear to be adequately tolerated by this patient population.

The manufacturer of DDC, Hoffmann-La Roche Inc. of Nutley, N.J., applied for the study on April 11, 1990. The company will provide the drug free of charge to physicians with enrolled patients.

Beginning June 25, 1990, physicians wishing to enter a patient in this study may call toll-free at 1-800-DDC-21HIV, Monday through Friday, from 9 a.m. to 8 p.m., Eastern Time. The company anticipates that physicians who apply for participation in the protocol should begin to receive the drug for their patients shortly thereafter.

Controlled comparison studies of DDC in patients at advanced stages of infection with the AIDS virus began in the summer of 1989. These studies, as well as the new DDC study, use lower doses of the drug than those initially tested. Most of these studies compare patients receiving DDC with those receiving zidovudine, the only approved treatment for AIDS virus infection. Patient enrollment for these studies is still open.

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Physicians, patients and others interested in these protocols involving DDC or in other experimental AIDS drugs can call 1-800 TRIALS-A, a toll-free service of the U.S. Public Health Service, from 9 a.m. to 7 p.m., Eastern Time, Monday through Friday.

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Press Office
Food and Drug Administration
U.S. Department of Health and Human Services

NOTE TO CORRESPONDENTS/AIDS UPDATE
Dec. 4, 1990

Brad Stone
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TRIALS SANCTIONED FOR STUDY OF POTENTIAL AIDS VACCINE

FDA granted permission for clinical testing of two additional experimental inactivated virus vaccines designed to fight against infection with the human immunodeficiency virus (HIV) -- the virus that causes AIDS.

One of these experimental agents, a gp120 vaccine developed by Genentech Inc. of South San Francisco, Calif., will be studied as a treatment for inhibiting the the progression of the disease in patients at early stages of infection with the AIDS virus. Fifty five people infected with the AIDS virus, but who are otherwise healthy, will be enrolled. The study will be conducted at the Walter Reed Army Institute of Research in Washington, D.C.

The other experimental vaccine, a gp160 vaccine developed by IMMUNO Ag of Vienna, Austria, will be studied to determine whether it can elicit an HIV specific immune response in healthy individuals. A clinical trial for this vaccine involving 60 HIV uninfected individuals will be sponsored by the National Institute of Allergy and Infectious Diseases.

Clinical trials for both vaccines are designed to test their safety as well as to give a preliminary indication of whether they can stimulate an immune response against the AIDS virus. Both experimental vaccines are composed of genetically engineered glycoproteins identical to the types found on the envelope or surface of the AIDS virus. Each has undergone animal testing, including studies involving chimpanzees.

These are the latest in a series of experimental HIV-1 vaccines approved for human testing in the United States. Others include two experimental vaccines developed by MicroGeneSys Inc. of West Haven, Conn., and a vaccine developed by Bristol-Myers/Squibb Co. of New York, N.Y. Another vaccine

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IND--EXPERIMENTAL ANTI-NEOPLASTIC AGENTS

EXPERIMENTAL TREATMENT	SPONSOR	INDICATION
piritrexim isethionate	Burroughs Wellcome Co. Research Triangle Park, N.C. (919) 248-3000	Kaposi's Sarcoma
doxorubicin (see note below)	National Institute of Allergy and Infectious Diseases, Bethesda, Md. (301) 496-5717	Kaposi's Sarcoma
tumor necrosis factor*	Genentech Inc. San Francisco, Calif. (415) 266-1000	Kaposi's Sarcoma
menogaril	National Cancer Institute Bethesda, Md. (301) 496-6641	Kaposi's Sarcoma
M-BACOD (with Retrovir)	National Institute of Allergy and Infectious Diseases, Bethesda, Md. (301) 496-5717	Primary Lymphoma

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* These products are considered biologic products. Interferon products also have anti-infective and immunomodulating properties.

** These products have been designated for Orphan Drug status under FDA's Orphan Products Development Program. This program provides tax and other financial incentives for the development of potential therapies for serious, but relatively rare diseases.

TREATMENT INDs

The Treatment IND (investigational new drug) mechanism was established by FDA to allow patients suffering from serious or life-threatening conditions for which there are no satisfactory treatments to obtain promising experimental drugs that have undergone sufficient clinical testing to show they may be safe and effective.

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A series of clinical trials and expanded access protocols for the antiretroviral drug ddI, including a Treatment IND protocol, were initiated on Sept. 28, 1989 by the the National Institute of Allergy and Infectious Diseases (NIAID) and the drug's manufacturer, Bristol-Myers Company of New York. Under these protocols, approximately 2,600 persons with AIDS or AIDS Related Complex (ARC) will be enrolled in clinical trials. Simultaneously, ddI is being distributed through a Treatment IND protocol to adult patients with AIDS or advanced ARC who cannot take zidovudine because of serious drug toxicity. The drug is also being distributed under an open safety protocol for adult AIDS patients whose disease has substantially progressed despite zidovudine therapy and who have no other treatment options. In addition, ddI is being distributed under an open safety protocol to treat children who have experienced intolerance or substantial deterioration despite zidovudine (AZT) treatment.

Trimetrexate, an experimental drug for treating Pneumocystis carinii pneumonia (PCP), in Feb. 1988, became the first AIDS-related drug to be granted treatment IND status under FDA's new regulations. The new protocol allows the treatment IND's sponsor, the National Institute of Allergy and Infectious Diseases (NIAID), to provide the experimental drug therapy to AIDS patients with PCP who experience severe or life-threatening adverse reactions to the conventional treatments using the approved drugs, injectable pentamidine and trimethoprim/sulfamethoxazole.

Physicians interested in learning about the details of this distribution can contact an NIAID hotline at 1-800-537-9970 within the United States.

Physicians interested in details of the Treatment IND and open safety protocols can call the Bristol-Myers toll-free number at 1-800-662-7999 daily from 8 a.m. to 8 p.m., Eastern Time. The company will immediately

begin processing applications from physicians for their patients for the Treatment IND and open safety protocols.

On July 26, 1989, the agency approved expanded distribution of r-erythropoietin, a form of a naturally occurring protein, erythropoietin, to treat the severe anemia some AIDS patients suffer when taking zidovudine.

Under the terms of this treatment IND protocol, AZT patients who have experienced severe anemia will be eligible to receive r-erythropoietin treatment at no cost from the drug's sponsor, the Ortho Pharmaceutical Corp. of Raritan, N.J. Physicians interested in learning about the details of this treatment IND protocol can contact a hotline set up by the company at 1-800-243-7739. In addition to these treatment IND protocols, a series of clinical trials with the antiretroviral drug dideoxycytidine (ddC) have been initiated since September, 1986; approximately 800 patients have received the drug in either early phase 1/2 studies or are currently enrolled in larger phase 2/3 studies. Based on the information available from this experience, the manufacturer of ddC in patients with advanced HIV-associated disease who had "failed" or were intolerant to AZT and had "failed" ddI or were intolerant to ddI. The enrollment criteria for this protocol were amended in September, 1990 to allow direct access to ddC for patients who were failing AZT or were intolerant to ddI.

The new enrollment criteria for this protocol now parallel the expanded access program for ddI. Physicians interested in these protocols can call the sponsor at 201-235-2355.

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Press Office
Food and Drug Administration
U.S. Department of Health and Human Services

NOTE TO CORRESPONDENTS/AIDS UPDATE
May 16, 1991

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NEW DRUG APPLICATIONS (NDAs)

FDA currently has a new drug application pending for a drug to directly treat HIV infection. The drug is dideoxyinosine (ddI), sponsored by Bristol-Myers Laboratories, of Wallingford, Conn. In addition, Hoffmann-La Roche Inc., of Nutley, N.J., has publicly announced that it is in the process of submitting a new drug application for dideoxycytidine (ddC), which would also directly treat HIV infection. There are also several new drug applications pending before the agency for AIDS-related indications.

FDA has given all potential AIDS drugs a 1-AA classification -- the highest priority -- in FDA's new drug review system. The agency's expedited review of zidovudine (marketed as Retrovir and more commonly known as AZT), which became the first approved treatment for AIDS, served as the prototype for the 1-AA classification.

INVESTIGATIONAL NEW DRUGS (INDs)

FDA has approved more than 200 on-going human studies to test potential AIDS drugs. At present, investigational new drug studies involve more than 80 different anti-viral or immunomodulating drugs. Many trials are now investigating the use of two or more experimental therapies in combination.

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Due to the intense public interest in AIDS, many of the sponsors of experimental AIDS therapies now undergoing FDA-sanctioned clinical testing have made some information about their therapies available. The following is a list of potential AIDS therapies publicly acknowledged by their sponsors to be now under study. Requests for additional information on any of these products should be directed to the IND sponsor or to the AIDS Clinical Trial Information Service (1-800-TRIALS-A).

INDs FOR EXPERIMENTAL ANTI-VIRAL AGENTS

EXPERIMENTAL TREATMENT	SPONSOR
GLQ223	GeneLabs Inc., Redwood City, Calif. (415) 369-9500
SC48334	G.D. Searle & Co., Chicago, Ill., (312) 982-8651
DHEA	Elan Corp., Atlanta, Ga., (404) 534-8239
Carrisyn	Carrington Laboratories Inc., Irving, Texas (214) 541-2278
ribavirin	Viratek/ICN Pharmaceuticals, Costa Mesa, Calif. (800) 556-1937
ddI (Dideoxyinosine)**	National Cancer Institute, Bethesda, Md. (301) 496-6631
	Bristol-Myers Laboratories Wallingford, Conn. (203) 284-6000
	National Inst. of Allergy & Infectious Diseases, Bethesda, Md. (301) 496-5717
ddC (Dideoxycytidine)	Hoffmann-La Roche Inc., Nutley, N.J. (201) 235-5000
	National Cancer Institute, Bethesda, Md. (301) 496-6631
AL 721	Matrix Laboratories, Fort Lee, N.J. (201) 944-0444

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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P92-19
FOR IMMEDIATE RELEASE
June 22, 1992

Food and Drug Administration
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HHS Secretary Louis W. Sullivan, M.D., today announced that the Food and Drug Administration has approved the AIDS drug zalcitabine, commonly known as ddC. It is the third drug licensed specifically for use in treating the human immunodeficiency virus, the cause of AIDS.

Zalcitabine was approved for use in combination with the first approved AIDS drug, zidovudine -- or AZT -- as a treatment option for adult patients with advanced HIV infection who show signs of clinical or immunological deterioration.

"This drug approval represents another step forward for patients with AIDS," Dr. Sullivan said. "Zalcitabine has been rapidly developed, tested and reviewed through the cooperative efforts of scientists in the National Institutes of Health and FDA, academia and the pharmaceutical industry.

Early clinical trial data have shown that increases in CD4 cells (immune cells) were somewhat greater and more sustained in patients treated with the combination of zalcitabine and zidovudine than in those who received zidovudine alone as initial therapy. An increase in CD4 cells is believed to indicate that the body's disease-fighting capability has been at least transiently enhanced.

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ATTENTION TV BROADCASTERS: Please use open caption for the hearing impaired.

At present, however, there are no study results demonstrating enhanced survival, lowered incidence of opportunistic infections or decreased progression of HIV infection for patients treated with the combination of zidovudine and ddC.

DDC is the first drug approved under the principles and procedures of FDA's proposed accelerated drug review policy, endorsed by the White House Council on Competitiveness and announced by the Vice President on April 9. The proposal also provides for prompt removal of the drug from the market if further review determines the therapy to be ineffective.

Four studies investigating the clinical usefulness of zalcitabine are continuing, to verify the clinical benefit of the combination therapy.

"This new drug is not a cure," said James Mason, M.D., assistant secretary for health and head of the Public Health Service, "but it constitutes an important addition to the expanding group of antiviral drugs currently available, including AZT and DDI, for treating people with AIDS."

The most severe side effects observed in individuals taking zalcitabine have been in the form of neurological complications, sometimes causing tingling and pain in the hands and feet. In controlled clinical studies, 10 to 12 percent of patients discontinued treatment because of these complications. Other side effects included pancreatitis (inflammation of the pancreas), rash, oral ulcers, decreased blood platelet (blood clotting elements) counts and abnormal liver function. The side effects of the combination of zalcitabine and zidovudine are about the same as those that would be anticipated with either drug, each with significant side effects alone.

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"This approval marks an important change in FDA's drug review policy," said FDA Commissioner David A. Kessler, M.D. "In this way, we can approve drugs that are both safe and effective as quickly as possible."

The pharmacological action of zalcitabine, a chemically synthesized compound originally discovered for its antiviral activity by scientists at the National Institutes of Health in Bethesda, Md., appears to be its ability to prevent the AIDS virus from replicating or reproducing before T-cells (immune cells) are infected, thus preserving the cells' immune function.

The drug, manufactured and distributed by Hoffmann La Roche of Nutley, N.J., is administered orally every eight hours in combination with AZT. Sold under the trade name HIVID, it is expected to be commercially available immediately.

Both FDA and NIH are Public Health Service agencies within HHS.

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