Food & Drug Administration News

FDA Approves Depo Provera, injectable contraceptive

P92-31 Food and Drug Administration

FOR IMMEDIATE RELEASE Susan Cruzan - (301) 443-3285

The Food and Drug Administration today announced the approval of Depo Provera, an injectable contraceptive drug.

The drug, which contains a synthetic hormone similar to the natural hormone progesterone, protects women from pregnancy for three months per injection. The hormone is injected into the muscle of the arm or buttock where it is released into the bloodstream to prevent pregnancy. It is more than 99 percent effective.

"This drug presents another long-term, effective option for women to prevent pregnancy," said FDA Commissioner David A. Kessler, M.D. "As an injectable, given once every three months, Depo Provera eliminates problems related to missing a daily dose."

Depo Provera is available in 150 mg. single dose vials from doctors and clinics and must be given on a regular basis to maintain contraceptive protection. If a patient decides to become pregnant, she discontinues the injections.

As with any such products, FDA advises patients to discuss the benefits and risks of Depo Provera with their doctor or other health care professional before making a decision to use it.

Depo Provera's effectiveness as a contraceptive was established in extensive

studies by the manufacturer, the World Health Organization and health agencies in other countries. U.S. clinical trials, begun in 1963, also found Depo Provera effective as an injectable contraceptive.

The most common side effects are menstrual irregularities and weight gain. In addition, some patients may experience headache, nervousness, abdominal pain, dizziness, weakness or fatigue. The drug should not be used in women who have acute liver disease, unexplained vaginal bleeding, breast cancer or blood clots in the legs, lungs or eyes.

The labeling advises doctors to rule out pregnancy before prescribing the drug, due to concerns about low birth weight in babies exposed to the drug.



Recent data have also demonstrated that long-term use may contribute to osteoporosis. The manufacturer will conduct additional research to study this potential effect.

Depo Provera was Developed in the 1960s and has been approved for contraception in many other countries. The UpJohn Company of Kalamazoo, Mich., which will market the drug under the name, Depo Provera Contraceptive Injection, first submitted it for approval in the United States in the 1970s.

At that time, animal studies raised questions about its potential to cause breast cancer. Worldwide studies have since found the overall risk of cancer, including breast cancer in humans, to be minimal if any.



New Rules Speed Approval of Drugs for Life-Threatening Illnesses

P92-37 Food and Drug Administration

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The Food and Drug Administration today announced that it will soon publish new rules to shed the approval of drugs for patients with serious or life-threatening illnesses, such as AIDS, cancer and Alzheimer's disease.

"These final rules will help patients who are suffering the most serious illnesses to get access to new drugs months or even years earlier than would otherwise be possible," said HHS Secretary Louis W. Sullivan, M.D. "The effort to accelerate FDA review for these drugs has been a long-term commitment and indeed a hallmark of this administration."

These rules establish procedures for the Food and Drug Administration to approve a drug based on "surrogate endpoints" or markers. They apply when the drug provides a meaningful benefit over currently available therapies. Such endpoints would include laboratory tests or physical signs that do not in themselves constitute a clinical effect but that are judged by qualified scientists to be likely to correspond to real benefits to the patient.

Use of surrogate endpoints for measurement of drug efficacy permits approval earlier than if traditional endpoints -- such as relief of disease symptoms or prevention of disability and death from the disease -- are used.

The new rules provide for therapies to be approved as soon as safety and effectiveness, based on surrogate endpoints, can be reasonably established.

The drug's sponsor will be required to agree to continue or conduct postmarketing human studies to confirm that the drug's effect on the surrogate endpoint is an indicator of its clinical effectiveness.

One new drug -- zalcitabine (also called ddC) -- was approved June 19, using a model of this process, for treating the human immunodeficiency virus, HIV, the cause of AIDS.

Accelerated approval can also be used, if necessary, when FDA determines that a drug, judged to be effective for the treatment of a disease, can be used safely only under a restricted distribution plan.

"The new rules will help streamline the drug development and review process without sacrificing goad science and rigorous FDA oversight," said FDA commissioner David A. Kessler, M.D. "While drug approval will be accomplished faster, these drugs and biological products must still meet safety and effectiveness standards required by law."



The new procedures also allow for a streamlined withdrawal process if the postmarketing studies do not verify the drug's clinical benefit, if there is new evidence that the drug product is not shown to be safe and effective, or if other specified circumstances arise that necessitate expeditious withdrawal of the drug or biologic.



Articles

## Research Shows Promise for Preventing or Slowing Blindness due to Retinal Disease

National Retinitis Pigmentosa Foundation

### Neutrophilic Factors Rescue Photoreceptor Cells in Animal Tests

Baltimore, MD - Researchers at the University of California San Francisco and Regeneron Pharmaceuticals, Inc. [NASDAQ: REGN] have discovered that certain naturally occurring substances known as neurotrophic factors can prevent the degeneration of light-sensing cells in the retina of the eye. The

degeneration of these cells, known as photoreceptors, is a major cause of visual impairment

This research, published to in the December issue of the Proceedings of the National Academy of Science (PNAS), holds promise for people who may lose their sight due to progressive retinal degeneration -- currently, no drug treatment for retinal degeneration exists. It is estimated that 2.5 million Americans have severe vision loss due to age-related macular degeneration and 100,000 Americans are affected by retinitis pigmentosus, a hereditary disease that causes blindness. In addition, each year more than 15,000 people undergo surgical procedures to repair retinal detachments and other retinal traumas.

The research was funded in part by the RP (Retinitis Pigmentosa) Foundation Fighting Blindness, Regeneron Pharmaceuticals and the National Eye Institute. It was conducted by Drs. Matthew M. LaVail, Kazuhiko Unoki, Douglas Yasurnura, Michael T. Matthes and Roy H. Steinberg at UCSF, arld Dr. C;eorge Yancoooulos, Regeneron's Vice President for Discovery. Regeneron holds an exclusive license for this research from UCSF.

In the research described in the PNAS , a light-damage model was used to assess the survival-promoting activity of a number of naturally occurring substances. Experimental rats were exposed to constant light for one week. Eyes that had not been treated with an effective factor lost most of their photoreceptor cells -- the rods and cones of the retina -- after light exposure. Brain Derived Neurotrophic Factor (BDNF) and Ciliary Neurotrophic Factor (CNTF) were particularly effective in this model without causing unwanted side effects; other factors such as Nerve Growth Factor (NGF) and Insulin-like Growth Factor (IGF-1) were not effective in these experiments.

Discussing the research, Dr. Jesse M. Cedarbaum, Regeneron's Director of

Clinical Research, said, "BDNF's ability to rescue neurons in the retina that have been damaged by light exposure may hold promise for the treatment of age-related macular degeneration, one of the leading causes of vision impairment, and for retinal detachment. Following detachment, permanent vision loss may



result frorn the death of detached retinal cells. It is possible that BDNF could play a role in rescuing those cells once the retina has been reattached surgically."

"Retinitis pigmentosa is a slowly progressing disease that causes the retina to degenerate over a period of years or even decades. Vision decreases to a small tunnel of sight and can result in total blindness. It is our hope that research on growth factors will provide a means to slow the progression and preserve useful vision throughout life," stated Jeanette S. Felix, Ph.D., Director of Science for the RP Foundation Fighting Blindness.

In addition to the work described , Regeneron is developing BDNF in conjunction with Aingen Inc. [NASDAQ:AMGN] as a possible treatment for peripheral neuropathies associated with diabetes and cancer chemotherapy, motor neuron diseases, Parkinson's disease, and Alzheimer's disease. By itself, Regeneron is testing CNTF in patients with arnyotrophic lateral sclerosis (commonly known as Lou Gehrig's disease).

Regeneron Pharlnaceuticals, Inc., based in Tarrytown, New York, is a leader in the discovery and development of biotechnology-based compounds for the treatment of neurodegenerative diseases, peripheral neuropathies and nerve injuries, which affect more than seven million Americans. Drs. LaVail and Steinberg of UCSF are consultants to Regeneron.

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# Affluent Diet Increases Risk Of Heart Disease

Research Resources Reporter

written by Mary Weideman

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National Institutes of Health

High-fat, high-calorie diets rapidly increase risk factors for coronary heart disease in native populations of developing countries that have traditionally consumed diets low in fat. These findings, according to investigators at the Oregon Health Sciences University in Portland, have serious implications for public health in both industrialized and developing countries.

"This study demonstrates why we can develop coronary heart disease and have higher blood cholesterol and triglyceride levels. It shows also the importance of diet and particularly the potential of the diet to increase body weight, thereby leading to a whole host of other health problems in developing countries and affluent nations as well," explains principal investigator Dr. William E. Connor, head of the section of clinical nutrition and lipid metabolism at Oregon Health Sciences University.

Over the past 25 years Dr. Connor and his team have characterized the food and nutrient intakes of the Tara humara Indians in Mexico, while simultaneously documenting various aspects of Tarahumara lipid metabolism. These native Mexicans number approximately 50,000 and reside in the Sierra Madre Occidental Mountains in the state of Chihuahua. The Tarahumaras have coupled an agrarian diet to endurance racing. Probably as a result, coronary

heart disease, which is so prevalent in Western industrialized nations, is virtually non existent in their culture. Loosely translated, the name Tarahumara means "fleet of foot," reflecting a tribal passion for betting on "kickball" races, in which participants run distances of 100 miles or more while kicking a machete-carved wooden ball.

The typical Tarahumara diet consists primarily of pinto beans, tortillas, and pinole, a drink made of ground roasted corn mixed with cold water, together with squash and gath ered fruits and vegetables. The Tara humaras also eat small amounts of game, fish, and eggs. Their food contains approximately 12 percent of total calories as fat of which the majority (69 percent) is of vegetable origin. Dietician Martha McMurry, a coinvestigator in the study, describes their diet as simple and very rich in nutrients while low in cholesterol and fat.

The Tarahumaras have average plasma cholesterol levels of 121 mg/ dL, low-density lipoprotein (LDL)-cholesterol levels of 72 mg/dl, and high-density lipoprotein (HDL)-cholesterol levels of 32 to 42 mg/dl. All of those values are in the good, low-risk range, according to the researchers. Elevated cholesterol and LDL-cholesterol levels are considered risk factors for heart



disease. HDL-cholesterol is considered beneficial. In previous studies the Tarahumaras had been found to be at low risk for cardiac disease, although able to respond to high-cholesterol diets with elevations in total and LDL-cholesterol.

Clinical Research Center dietitian McMurry and coinvestigator Maria Teresa Cerqueira established a metabolic unit in a Jesuit mission school

building near a community hospital in the small village of Sisoguichi. Food was weighed, cooked, and fed to the study participants under the investigators' direct supervision, ensuring that subjects ate only food stipulated by the research protocol. Fasting blood was drawn twice weekly, and plasma samples were frozen and shipped to Dr. Connors laboratory for cholesterol, triglyceride, and lipoprotein analyses. Regular measurements included participant body weight, height, and triceps skin fold thickness.

Thirteen Tarahumaras, five women and eight men, including one adolescent, were fed their native diet for 1 week, followed by 5 weeks of an "affluent" diet. "In this study we went up to a concentration of dietary fat that was 40 percent of total calories. This is the prototype of the holiday diet that many Americans consume a diet high in fat, sugar, and cholesterol, low in fiber," elaborates Dr. Conners. Such dietary characteristics are reflected in the cholesterol-saturation index, or CSI, recently devised research dietitian Sonja Conner working with Dr. Connor. "The CSI is a single number that incorporates both the amount of cholesterol and the amount of saturated fat in the diet. CSI indicates the diet's potential to elevate the cholesterol level, particularly the LDL," Dr. Connor explains. The Tarahumaran diet averages a very low CSI of 20; Dr. Connor's "affluent" diet used in the study ranks a CSI of 149.

The experimental design of this study reflects the importance of establishing baseline plasma lipid levels, typical of the native diet, before exposing subjects to the experimental diet. The standard curve relating dietary food intake to plasma cholesterol demonstrates a leveling off, or plateau, for consumption of large amounts of fat. Changes in dietary fat and/or cholesterol in this range have little effect on plasma levels. "You

must have the baseline diet almost free of the variables you are going to put into the experimental diet. The Framingham study, for example, did not discriminate on the basis of diet between individuals who got heart disease because the diet was already high in fat. All subjects were already eating on a plateau," Dr. Connor says.

After 5 weeks of consuming the "affluent" diet, the subjects' mean plasma cholesterol levels had in creased by 31 percent, primarily in the LDL fraction, which rose 39 percent. HDL-cholesterol increased by 31 per cent, and LDL to HDL ratios changed therefore very little. Plasma triglyceride levels increased by 18 percent, and subjects averaged an 8-pound gain in weight. According to Dr. Connor, lipid changes occurred surprisingly soon, yielding nearly the same results after 7 days of affluent diet as after 35 days.



The increase in HDL carries broad dietary implications for industrialized nations. "We think HDL-cholesterol increased because we increased the amount of dietary fat over the fat content used in the previous Tarahumara metabolic study. In that study we saw no change in HDL levels after raising the dietary cholesterol but keeping the fat relatively consistent with native consumption. In the present study we increased fat intake to 40 percent of the total calories. We reached the conclusion in the Tarahumara study that HDL reflects the amount of dietary fat in general and not the amount of dietary cholesterol. HDL must increase to help metabolize the fat, and it increased quite a bit in this study," Dr. Connor explains.

Low HDL in the Tarahumarans is not typically an important predictor of

coronary heart disease because they do not normally consume large amounts of fat or cholesterol. HDL remains an important predictor to Americans because of their usual high fat intake.

Dr. Connor recommends a diet for Americans that contains less than 20 percent of total calories as fat, less than 100 mg of cholesterol, and a CSI around 20, varying in accordance with caloric needs. Such a diet is low in meat and dairy fat, high in fiber. Dr. Connor also comments on recent suggestions that Americans adopt a "Mediterranean-style" diet. "The original Mediterranean diet, in its pristine state, consisted of a very low intake of fat and very few animal and dairy products. We are already eating a lot of meat and dairy products. Simply to continue that pattern while switching to olive oil is not going to help the situation."

The World Health Organization (WHO) is focusing much attention on the emergence of diseases such as coronary heart disease in nations and societies undergoing technological development. Dr. Connor says that coronary heart disease starts with a given society's elite, who typically eat a different diet than the average citizen. "If the pattern of afluence increases, the entire population will have have a higher incidence of coronary heart disease, which places a termendous health care burden on a society. WHO would like the developing countries to prevent coronary heart disease, so they can concentrate on other aspects of their economic development and on public health measures to improve general well-being, rather than paying for unnecessary, expensive medical technology," Dr. Connors says.

"The overall implication of this study is that humans can readily move their plasma lipids and lipoprotein values into a high-risk range within a very short time by an affluent, excessive diet. The present rate of coronary

heart disease in the United States is 30 percent less than it was 20 years ago, so a lot has been accomplished. We are changing rapidly," he concludes.



General Announcments

Publications for Health Professionals Available from NCI (1/93)

Unless otherwise noted, the following materials are provided free of charge by calling the NCI's Publication Ordering Service, 1-800-4-CANCER. Because Federal Government publications are not subject to copyright restriction, you are free to photocopy NCI material.

ANTICANCER DRUG INFORMATION SHEETS IN SPANISH/ENGLISH. Two-sided fact sheets (in English and Spanish) provide information about side effects of common drugs used to treat cancer, their proper usage, and precautions for patients. The fact sheets were prepared by the United States Pharmacopeial Convention, Inc., for distribution by the National Cancer Institute. Single sets only may be ordered.

CANCER RATES AND RISKS, 3RD EDITION (85-691). This book is a compact guide to statistics, risk factors, and risks for major cancer sites. It includes charts and graphs showing incidence, mortality, and survival worldwide and in the United States. It also contains a section on the costs of cancer. 136 pages.

(87-2778). This booklet describes what is now known about diet, nutrition, and cancer prevention. It provides information about foods that contain components like fiber,

fat, and vitamins that may affect a person's risk of getting certain cancers. It suggests ways to use that information to select from a broad variety of foods--choosing more of some foods and less of others. Includes recipes and sample menus. 39 pages.

NATIONAL CANCER INSTITUTE FACT BOOK. This book presents general information about the National Cancer Institute including budget data, grants and contracts, and historical information.



NATIONAL CANCER INSTITUTE GRANTS PROCESS (91-1222) (Revised 3/90). This booklet describes general NCI grant award procedures; includes chapters on eligibility, preparation of grant application, peer review, eligible costs, and post-award activities. 62 pages.

PHYSICIAN TO PHYSICIAN: PERSPECTIVE ON CLINICAL TRIALS. This 15-minute videocassette discusses why and how to enter patients on clinical trials. It was produced in collaboration with the American College of Surgeons Commission on Cancer.

(Revised 4/87) This booklet is designed for teachers who have students with cancer in their classrooms or schools. It includes an explanation of cancer, its treatment and effects, and guidelines for the young person's re-entry to school and for dealing with terminally ill students.

Bibliographies are included for both educators and young people. 22 pages.

UNDERSTANDING THE IMMUNE SYSTEM (92-529). This booklet describes the complex network of specialized cells and organs that make up the human immune system. It explains how the system works to fight off disease caused by invading agents such as bacteria and viruses, and how it sometimes malfunctions, resulting in a variety of diseases from allergies, to arthritis, to cancer. It was developed by the National Institute of Allergy and Infectious Diseases and printed by the National Cancer Institute. This booklet presents college level instruction in immunology. It is appropriate for nursing or pharmacology students and for persons receiving college training in other areas within the health professions. 36 pages.

CHEW OR SNUFF EDUCATOR PACKAGE (91-2976). Each package contains:

Ten copies of CHEW OR SNUFF IS REAL BAD STUFF, a brochure designed for seventh and eighth graders that describes the health and social effects of using



smokeless tobacco products. When fully opened, the brochure can be used as a poster.

One copy of CHEW OR SNUFF IS REAL BAD STUFF: A GUIDE SMOKELESS TOBACCO. This booklet is a lesson plan for

teachers. It contains facts about smokeless tobacco, suggested classroom activities, and selected educational resources.

INSTITUTE MANUAL FOR PHYSICIANS (92-3064). This is a step-by-step handbook for instituting smoking cessation techniques in medical practices. The manual, with resource lists and tear-out materials, is based on the results of NCI clinical trials. 75 pages.

This is a handbook for dentists, dental hygienists, and dental assistants. It complements the physicians' manual and includes additional information on smoking prevention and on smokeless tobacco use. 58 pages.

PHARMACISTS HELPING SMOKERS QUIT KIT. A packet of materials to help pharmacists encourage their smoking patients to quit. Contains a pharmacist's guide and self-help materials for 25 patients.

INSTITUTE GUIDE TO STRATEGIES THAT SUCCEED (90-500). This guide outlines eight essential elements of a successful school-based smoking prevention program based on NCI research. It includes a list of available curriculum resources and selected references. 24 pages.

PLANNER'S GUIDE (91-3104). This booklet outlines key characteristics of successful self-help materials and programs based on NCI collaborative research. It lists additional resources and references. 36 pages.

SMOKING POLICY: QUESTIONS AND ANSWERS. These ten fact sheets

provide basic information about the establishment of worksite smoking policies. Topics range from the health effects of environmental tobacco smoke to legal issues concerning policy implementation.

Smoking and Control Monograph No. 1). This volume provides a summary of what has been learned from 40 years of a public health effort against smoking, from the early trial-and-error health information campaigns of the 1960s to the NCI's science-based project, American Stop Smoking Intervention Study for Cancer Prevention, which began in 1991. It offers reasons why comprehensive smoking control strategies are now needed to address the smoker's total environment and to reduce smoking prevalence significantly over the next decade.

Three kits are available for community program planners and health professionals to set up local cancer prevention and early detection education projects:

CANCER COMMUNITY OUTREACH PROGRAM. This community outreach kit targets Black American audiences. It contains materials to help health professionals conduct community education programs for black audiences. The kit emphasizes the early detection of breast cancer by mammography and of cervical cancer by the Pap test. It also discusses smoking and

nutrition. The kit includes helpful program guidance, facts, news articles, visuals, and brochures.

HAGALO HOY COMMUNITY OUTREACH PROGRAM. This community outreach kit targets Hispanic audiences. It contains bilingual and Spanish language materials to help health professionals conduct community education programs. The materials educate Hispanic audiences about early detection of breast cancer by mammography



and of cervical cancer by Pap tests. The kit also discusses smoking and related issues. The kit includes helpful guidance, facts, news articles, visuals and brochures.

MAMMOGRAPHY PROGRAM. This community outreach kit targets all women age 40 or over. It supplies community program planners and health professionals with planning guidance, facts about mammography, news articles, visuals and brochures.

(92-1493). This handbook presents key principles and steps in developing and evaluating health communications programs for the public, patients, and health professionals. It expands upon and replaces "Pretesting in Health Communications" and "Making PSAs Work." 131 pages.

The video and slide presentations listed below support the mammography outreach programs.

ONCE A YEAR...FOR A LIFETIME VIDEOTAPE. This 5-minute VHS videotape uses a dramatic format to highlight the important facts about the early detection of breast cancer by mammography.

UNA VEZ AL ANO...PARA TODA UNA VIDA VIDEOTAPE. This 27-minute Spanish videotape informs Spanish-speaking women of the need for medical screening, particularly mammography. It explains commonly misunderstood facts about breast cancer and early detection. The program, in a dramatic format, features Edward James Olmos and Cristina Saralegui.

This kit includes 66 full-color slides and a number-coded, ready-to-read script suitable for a mammography presentation to a large group. It addresses the misconceptions prevalent about mammography and urges women age 40 and older to get regular mammograms so that breast cancer can be detected as early as possible. Kit



includes a guide, poster, media announcement, news feature, flyer, and pamphlets on mammography. This kit is available directly by writing to: Modern, 5000 Park Street North, St. Petersburg, FL 33709-9989.

--------- end of part 2 ----------

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