When the goal is to lower serum cholesterol*

*Please see the last page for Prescribing Information.
For effective reduction of serum cholesterol* and a high degree of patient acceptance, year after year

The response of patients with high serum cholesterol levels to Lorelco (500 mg b.i.d.) has been well documented. For example, mean serum cholesterol was reduced by 27% in one study, by up to 23% in another, and by 26% with diet in a third.

Prescribed in 24 countries... proven in 10 years of use

Long-term efficacy of Lorelco shown in combined studies in 129 patients followed for a ten-year period

Chemically unrelated to any other cholesterol-lowering agent...not an analog of clofibrate

- Documented long-term efficacy for up to ten years
- Effective in three lipoprotein phenotypes—type II, type IV, and unclassified hyperlipoproteinemia
- Side effects (mainly loose stools and other GI disturbances) are usually mild and transient and seldom require discontinuance of therapy
- No observed interactions in concomitant use with oral hypoglycemics and anticoagulants

*As an adjunct to diet

It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis including coronary heart disease. Investigations now in progress may yield an answer to this problem.

Please see the following page for Contraindications, Warnings, Precautions, and Prescribing Information.

Merrell Dow
LORELCO® (probucol) is an agent for the reduction of elevated serum cholesterol.

**CLINICAL PHARMACOLOGY:** Mechanism studies suggest that LORELCO acts by inhibi-
tion of earlier stages of cholesterol synthesis, increased excretion of fecal bile acids, and a slight inhibition of the absorption of dietary cholesterol. The relative role of these mechanisms has not been established. There is indication that LORELCO, namely desmosterol and 7-dehydrocholesterol. On this basis it is concluded that LORELCO does not affect the later stages of cholesterol biosynthesis.

Absorption of LORELCO from the gastrointestinal tract is limited and variable. When it is administered with food, peak blood levels are higher and less variable. With continuous administration in a dosage of 500 mg b.i.d., the blood levels of an individual gradually increase over the first three to four months and thereafter remain fairly constant. In 116 patients treated with 500 mg probucol for two years, the average blood level was 11.7 ± 12.2 mcg/ml (± S.D.) ranging to 73.3 mcg/ml. Levels observed after seven years of treatment in 40 patients revealed an average blood level of 24.5 ± 16.5 mcg/ml (± S.D.) ranging to 62.0 mcg/ml. At the end of 12 months of treatment in eight patients, blood levels averaged 19.0 mcg/ml. Nine weeks after cessation of therapy, the average had fallen by 10 percent. After six months the average had fallen by 20 percent.

**INDICATIONS AND USAGE:** This is not an innocuous drug (see Animal Pharmacology and Toxicology). Slight attention should be paid to the indications, contraindications, warnings and precautions, particularly when selecting drugs for long-term use.

Treatment of primary hyperlipidemia should begin with an appropriate diet. The use of drugs should be reserved only for patients who have not responded adequately to diet. Treatment of such patients should be considered only when every reasonable attempt has been made to obtain satisfactory results with diet alone. Even if the decision ultimately is to use drugs, the patient must understand that this does not reduce the importance of adhering to diet.

The selection of patients for cholesterol-lowering drug therapy should take into account other important cardiovascular risk factors such as hypertension, age, smoking, diabetes mellitus.

Consideration should be given to the efficacy, safety, and compliance factors for each of the cholesterol-lowering drugs prior to selecting the one most appropriate for an individual patient. LORELCO may be indicated as adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low density lipoproteins) who are known to have a hypersensitivity to it. LORELCO may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyce-
diuria is the abnormality.

Response to probucol is variable, and it is not always possible to predict from the lipoprotein type whether the patient will obtain favorable results with diet alone. It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect. No effect, or adverse effect, is attributed to the moderate or mild hypolipidemia should not be considered a primary indication for use of probucol. If moderate or mild hypolipidemia is the primary indication for use of probucol, it should be discontinued.

It is recommended, however, that patients treated with probucol should be monitored for lipid levels following withdrawal of treatment. In patients who have responded adequately to diet, weight reduction, and control of diabetes mellitus, LORELCO may be useful to lower elevated cholesterol that occurs in patients with combined hypercholesterolemia and hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality.

Response to probucol is variable, and it is not always possible to predict from the lipoprotein type whether the patient will obtain favorable results with diet alone. It has not been established whether the drug-induced lowering of serum cholesterol or triglyceride levels has a beneficial effect. No effect, or adverse effect, is attributed to the moderate or mild hypolipidemia should not be considered a primary indication for use of probucol. If moderate or mild hypolipidemia is the primary indication for use of probucol, it should be discontinued.

**CONTRAINDICATIONS** (see Also Precautions): LORELCO is contraindicated in patients who are known to have a hypersensitivity to it.

**WARNINGS:** SERIOUS AND POTENTIAL LIFE-ThREATENING TOXICITY HAS BEEN ENCOUNTERED WITH PROBUCOL IN RHEUS MONKEYS FED AN Atherosclerotic DIET AND IN BEAGLE DOGS (SEE ANIMAL PHARMACOLOGY AND TOXICOLOGY SECTION OF THIS INSERT)

Proper monitoring of patients on LORELCO to determine the appropriate drug therapy is required. At the start of treatment with LORELCO, injections of epinephrine to probucol-treated dogs and control dogs demonstrated no difference in their responses.

Myocardial injury was produced in various groups of rats by one of the following procedures:

- Ischemic injury produced in some groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

- In rats, dogs, and monkeys it is known that probucol accumulates slowly in adipose tissue. Approximately 90% of probucol administered orally is unabsorbed. For that which is absorbed, the biliary tract is the major pathway for clearance from the body and very little is excreted by way of the kidneys.

Myocardial injury was produced in various groups of rats by one of the following procedures: aortic coarctation, coronary ligation, or cobalt or isoproterenol injection. After probucol administration no deleterious effects related to treatment occurred as measured by survival and microscopic examination of myocardial damage.

- Probucol was administered to minipigs beginning 10 days before ligation of a coronary artery and continued for 60 days post-surgery. Challenge with epinephrine at the end of 60 days caused ventricular fibrillation in some of the rats that were treated with probucol. In the other rats, no toxicity or cardiogenicity was observed.

References:
1. Data on file, Merrell Dow Pharmaceuticals Inc.
Guidelines for Authors

Manuscripts for publication and authors' correspondence should be sent to the Editor, Arteriosclerosis, 1107 N.E. 45th Street, Room 316, Seattle, WA 98105, telephone (206) 545-1609. Articles are accepted for consideration only if they are submitted solely to this journal. Except for reviews, the editors will not publish articles in which a significant portion of the data has been published or submitted for publication elsewhere. If any form of prior publication, other than a short abstract, has occurred or is contemplated, a reprint or a copy of the manuscript must accompany the article. If in the editors' judgment prior publication renders the submitted article not original, the manuscript will be returned promptly without review.

Manuscript Form
Manuscripts, tables, and illustrations must be submitted in triplicate and should conform to the specifications in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (Ann Intern Med 1982; 96:766-771). Manuscripts should be double-spaced throughout, on good quality, nonerasable paper. A separate title page should be provided. Summary, text, acknowledgments, references, tables, legends, and figures should begin on separate sheets and follow in that order. Consult the Council on Biology Editors Style Manual for recommended abbreviations (American Institute of Biological Sciences, 1401 Wilson Boulevard, Arlington, VA 22209). Abbreviations should be defined at first appearance, but should be avoided in the title and the summary. Use generic names of drugs. References should be cited by number (e.g., (3)) in the text.

Title Page
Titles should be brief and specific. Include full name, address, academic affiliation, and highest degree(s) for each author; acknowledgment of grant support where appropriate; address for galley proofs and reprint requests; a short title (40 characters or less) to be used as a running head; and 3-10 key words or phrases for indexing.

Abstract
A concise description (not more than 200 words) of the purpose, methods, results, and conclusion of the study is required.

Text
The text of experimental articles should usually be divided into sections with the headings: Introduction, Methods, Results, and Discussion. Other types of articles may conform to other formats.

References
Number references consecutively in the order cited in the text, not alphabetically. All references must be cited. Accuracy of reference data is the author's responsibility. Reference style and journal abbreviations follow the Uniform Requirements. Personal communications and unpublished data should be cited in parentheses in the text. If such a citation is from someone other than the authors, a letter should be submitted in which the direct quotation is given with the author's signature. Provide inclusive page numbers for all references. Provide all authors' names when six or fewer; when seven or more, list the first three and add et al.

Tables
Tables should be cited in the text. Each table should be given a number and a brief informative title, and should appear on a separate page. Omit vertical or horizontal rules and use extra space to delineate sections of a table. Explain in footnotes all abbreviations used in the table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‡†, ‡‡, §§, ‡§, ‡‡‡, ‡‡‡‡.

Illustrations
Enclose figures in a separate envelope; use no clips. Each figure should have a label pasted on its back indicating the figure number and the top of the figure. Legends should be on a separate sheet. They should be brief but should provide sufficient description to interpret the figure and be numbered to correspond with figure numbers.

To insure clear reproduction, all illustrations should be submitted as 5 x 7 inch (11 x 17 cm) glossy prints, unmounted and untrimmed. Original drawings and graphs should be prepared with black India ink on white background; no typewriting or computer printing should be used. Letters, numbers, and symbols should be clear and even throughout and of sufficient size that when reduced for publication each item will still be legible. Photographs of the original drawings should be submitted. Photomicrographs must have internal scale markers. Specific permission for facial photographs of patients is required.

Copyright Information
In accordance with journal implementation of the 1976 U.S. Copyright Law, authors must release first and subsidiary rights to their manuscript at submission. A dated cover letter, containing signatures of all authors, should state: "We, the authors, assign first and subsidiary rights to the American Heart Association in the event that our manuscript (title) is published by Arteriosclerosis." The journal, in turn, grants authors the right to use portions of their manuscripts, without charge, in books or articles of which they are authors or editors.

Reprints
Reprints of articles will be furnished to authors when ordered in advance of publication. An order form, including cost of reprints, will be sent to the author with galley proof.

Costs to Author
A charge of $25 per printed page will be made. The cost of color reproductions will be borne by the author.

Business Communications
Send all communications regarding advertising, subscriptions, change of address, reprints, and permissions to the American Heart Association at the address listed below. Remittance for subscriptions should be made by check, draft, or money order payable to: American Heart Association, 7320 Greenville Avenue, Dallas, TX 75231. The Publishing Director should be advised of change of address 30 days before date of issue, with the subscriber's old and new addresses given. Advertising space is given only to copy approved by an American Heart Association committee. Deadline is the first day of the month preceding the date of issue. Advertising rates appear on the application.
STATEMENT OF OWNERSHIP, MANAGEMENT AND CIRCULATION  
(Required by 39 U.S.C. 3689)

1. TITLE OF PUBLICATION: ARTERIOSCLEROSIS

2. DATE OF ISSUE: 9/16/82

3. FREQUENCY OF ISSUE: BI-MONTHLY

4. COMPLETE MAILING ADDRESS OF KNOWN OFFICE OF PUBLICATION: AMERICAN HEART ASSOCIATION 7320 GREENVILLE AVENUE, DALLAS TX 75231

5. COMPLETE MAILING ADDRESS OF THE HEADQUARTERS OR GENERAL BUSINESS OFFICES OF THE PUBLISHERS: SAME

6. FULL NAMES AND COMPLETE MAILING ADDRESS OF PUBLISHER, EDITOR, AND MANAGING EDITOR: (This item MUST NOT be blank)

   PUBLISHER: AMERICAN HEART ASSOCIATION, 7320 GREENVILLE, DALLAS TX 75231
   EDITOR: EDWIN L. BIERMAN, M.D. 1107 N.E. 45TH ST., ROOM 316, SEATTLE WASHINGTON 98105
   MANAGING EDITOR: ALAYNE VANDYCK, SAME AS ABOVE

7. OWNER: (If owned by a corporation, its name and address must be stated and also immediately thereunder the names and addresses of stockholders owning or holding 1 percent or more of total amount of stock. If not owned by a corporation, the names and addresses of the individual owners must be given. If owned by a partnership or other unincorporated firm, its name and address, as well as that of each individual must be given. If the publication is published by a nonprofit organization, its name and address must be stated. (Item must be completed)

   AMERICAN HEART ASSOCIATION

8. KNOWN BONDHOLDERS, MORTGAGEES, AND OTHER SECURITY HOLDERS OWNING OR HOLDING 1 PERCENT OR MORE OF TOTAL AMOUNT OF BONDS, MORTGAGES OR OTHER SECURITIES: (If there are none, state)

   FULL NAME: AMERICAN HEART ASSOCIATION
   COMPLETE MAILING ADDRESS: 7320 GREENVILLE AVE., DALLAS TX 75231

9. FOR COMPLETION BY NONPROFIT ORGANIZATIONS AUTHORIZED TO MAIL AT SPECIAL RATES (Section 411.3, DMM only)

   The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes (Check one)
   □ HAS NOT CHANGED DURING PRECEDING 12 MONTHS
   ☑ HAS CHANGED DURING PRECEDING 12 MONTHS

   (If changed, publisher must submit explanation of change with this statement)

10. EXTENT AND NATURE OF CIRCULATION

   A. TOTAL NO. COPIES (Net Press Run)
   B. PAID CIRCULATION
      1. SALES THROUGH DEALERS AND CARRIERS, STREET VENDORS AND COUNTER SALES
      2. MAIL SUBSCRIPTION
   C. TOTAL PAID CIRCULATION (Sum of 10A1 and 10B2)
   D. FREE DISTRIBUTION BY MAIL, CARRIER OR OTHER MEANS:
      B. SAMPLES, COMPLIMENTARY, AND OTHER FREE COPIES
   E. TOTAL DISTRIBUTION (Sum of C and D)
   F. COPIES NOT DISTRIBUTED
      1. OFFICE USE, LEFT OVER, UNACCOUNTED, SPOILED AFTER PRINTING
      2. RETURN FROM NEWS AGENTS
   G. TOTAL (Sum of E, F1 and 2 - should equal net press run shown in A)

   AVERAGE NO. COPIES EACH ISSUE DURING PRECEDING 12 MONTHS:
   ACTUAL NO. COPIES OF SINGLE ISSUE PUBLISHED NEAREST TO FILING DATE:

   2,440  2,240
   1,249  1,089
   1,249  1,089
   70  76
   1,319  1,165
   1,121  1,105
   2,440  2,270

11. I certify that the statements made by me above are correct and complete

   SIGNATURE AND TITLE OF EDITOR, PUBLISHER, BUSINESS MANAGER, OR OWNER: Chief Publications
Arteriosclerosis
A Journal of Vascular Biology and Disease

Scope and Purpose

Arteriosclerosis provides a forum for the publication of high quality research from a variety of disciplines bearing on the biology, prevention, and impact of vascular diseases relating to arteriosclerosis. The following are the major research areas and topics from which manuscripts and state of the art reviews are drawn. This list is not meant to be all-inclusive, but is intended as a guide for the submission and selection of manuscripts for publication.

- Studies of the biology and pathology of vascular lesions related to arteriosclerosis, including the disciplines of biochemistry, biophysics, cell and molecular biology, genetics, and metabolism.
- Studies of platelets and thrombogenesis as they relate to arteriosclerosis.
- Aspects of lipid and lipoprotein metabolism and transport related to vascular biology and disease.
- Studies of the metabolism of other formed blood elements and plasma constituents as they relate to vascular biology and disease.
- Connective tissue biochemistry and metabolism related to vascular biology and arteriosclerosis.
- Epidemiologic, population, and genetic studies of arteriosclerosis, including studies of the interplay of risk factors (e.g., diabetes, nutritional factors, hyperlipidemia, and hypertension).
- Studies of arteriosclerosis and its precursors in the young.
- Animal models of arteriosclerosis.
- Research on the detection and quantification of arterial lesions in vivo in humans and animals.
- Evaluation of the effects of prevention and treatment affecting, for example, plasma lipoproteins, thrombogenesis, and/or intimal injury on the established lesions of arteriosclerosis.