PRODUCT MONOGRAPH

LORELCO®

(probucol)

250 mg tablets

Lipid Metabolism Regulator

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PRODUCT MONOGRAPH

LORELCO®

(probucol)

250 mg tablets

THERAPEUTIC CLASSIFICATION

Lipid Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

Lorelco (probucol) is a cholesterol-lowering agent with antioxidant properties. Its chemical structure does not resemble that of any other available cholesterol-lowering agent. Probucol lowers total serum cholesterol and has relatively little effect on serum triglycerides. Patients responding to probucol exhibit decreases in both low density lipoprotein (LDL) cholesterol, and high density lipoprotein (HDL) cholesterol, with proportionately greater effect on the high density portion. Epidemiologic studies have shown that both low HDL cholesterol and high LDL cholesterol are independent risk factors for coronary heart disease. The risk of lowering HDL cholesterol while lowering LDL cholesterol remains unknown. There is little or no effect on very low density lipoprotein (VLDL).

Studies on the mode of action of probucol suggest that the decrease in HDL cholesterol is due to an increase in the transfer of cholesteryl esters from HDL to lower density lipoproteins (LDL and VLDL). This effect is reflected by an increased plasma concentration of cholesteryl ester transfer protein (CETP). In addition, there is an increased uptake of HDL-cholesterol by the liver. The clinical significance of probucol's effects on HDL cholesterol metabolism is not clear.

Probucol increases the fractional rate of LDL catabolism. This effect may be linked to the observed increased excretion of fecal bile acids, a final metabolic pathway for the elimination of cholesterol from the body. Probucol also exhibits inhibition of early stages of cholesterol biosynthesis and slight inhibition of absorption of dietary cholesterol. There is no increase in the cyclic precursors of cholesterol, namely desmosterol and 7-dehydrocholesterol. On this basis, it is concluded that probucol does not affect the later stages of cholesterol biosynthesis.

Probucol is an antioxidant and inhibits the oxidation of LDL. *In vitro* and *in vivo/ex vivo* studies in animals and man have shown that probucol prevents foam cell formation. **The clinical significance of these actions remains to be established.**

With prolonged treatment, probucol slowly accumulates in the body's fat tissue. Generally, tissue levels are highest in the fat and adrenal glands, although high concentrations have also been

reported in aortic plaques and the bone marrow. The drug is eliminated from the body slowly and is excreted in the feces and to a lesser extent in the urine, mainly as unchanged drug. The biliary system plays a significant role in excretion. Multicompartmental analysis has revealed a series of half-lives of elimination, ranging from 0.5 to 123 days. The longest half-life is most likely associated with elimination from adipose tissue.

INDICATIONS AND CLINICAL USE

Lorelco (probucol) is indicated as an adjunct to diet (at least equivalent to the American Heart Association (AHA) Step 1 Diet) and other measures for the treatment of primary hypercholesterolemia associated with elevated low density lipoproteins (Type IIa hyperlipoproteinemia), and may be useful in lowering elevated cholesterol levels in patients with mixed hyperlipidemia (hypercholesterolemia and hypertriglyceridemia, Type IIb hyperlipoproteinemia), where the hypercholesterolemia is the moiety of most concern.

Before instituting therapy with Lorelco, attempts should be made to control serum cholesterol by appropriate dietary regimes, weight reduction and the treatment of any underlying disorder which might aggravate the hyperlipidemia.

Response to probucol is variable, and it is not always possible to predict from the lipoprotein type which patients will obtain a

favourable response. **Strict attention should be paid to the Indications, Contraindications, Warnings, and Precautions.**

It has not been established at this time whether the drug-induced lowering of serum cholesterol has a beneficial effect, no effect, or a detrimental effect on the morbidity or mortality due to atherosclerosis, including coronary heart disease.

CONTRAINDICATIONS

Lorelco (probucol) is contraindicated in patients known to be hypersensitive to the drug. The safety of Lorelco has not been established in pregnancy and, therefore, it should not be used in these circumstances. It should not be used in nursing mothers either, since animal studies have shown that the drug is excreted in milk. **Lorelco should not be used in patients with uncontrolled congestive cardiac failure, or in patients with electrocardiographic anomalies consisting of significantly prolonged QT interval, conduction defects or ventricular arrhythmias, or in patients with evidence of recent or progressive myocardial damage.**

WARNINGS

IN RHESUS MONKEYS FED HIGH DOSES OF LORELCO (PROBUCOL) ADMIXED TO AN ATHEROGENIC DIET, CARDIAC TOXICITY HAS BEEN ENCOUNTERED. CARDIAC TOXICITY WAS ALSO ENCOUNTERED IN BEAGLE DOGS FED HIGH DOSES

OF LORELCO AND A NORMAL DIET. (See ANIMAL PHARMACOLOGY and TOXICOLOGY).

Because probucol may cause prolongation of the QT interval, caution should be exercised in administering probucol to patients with evidence of recent or progressive myocardial damage or findings suggestive of serious ventricular arrhythmias or cardiovascular-associated syncope.

Serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco alone and in patients on Lorelco and a concomitant antiarrhythmic drug (see SELECTED BIBLIOGRAPHY).

The effect of probucol-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality, or total mortality has not been established.

Strict birth control procedures must be exercised by women of child bearing potential. Since there are no adequate studies in pregnant women, use of this drug in pregnancy is not recommended. In women who plan to become pregnant, it is recommended that Lorelco be withdrawn and birth control procedures be continued for at least six months, because of the prolonged persistence of the drug in the body.

In the event a patient shows a marked and sustained elevation in the serum triglyceride level that is not related to diet, consideration should be given to discontinuing treatment with Lorelco.

PRECAUTIONS

Lorelco (probucol) should not be prescribed indiscriminantly. Before instituting therapy with Lorelco, attempts should be made to control serum cholesterol by appropriate dietary regimes, weight reduction, and the treatment of any underlying disorder which might aggravate the hyperlipidemia.

Since Lorelco is intended for long-term administration, adequate baseline studies should be performed to establish that the patient has elevated serum cholesterol levels of clinical significance. Serum cholesterol levels should be determined frequently during the first few months of treatment and periodically thereafter. A favourable trend in cholesterol reduction should be evident during the first two months of Lorelco administration. This regimen should be followed as long as the trend continues and a decision should be made by the fourth month as to whether adequate reduction is being maintained.

A baseline for serum triglycerides should also be established and serum triglyceride levels should be determined periodically. If a marked sustained rise in serum triglycerides is observed during

probucol therapy, consideration should be given to improved diet compliance, alcohol abstinence, further caloric restriction or adjustment of carbohydrate intake. Probucol should not be continued if this hypertriglyceridemia persists.

The following precautions are deemed prudent when prescribing Lorelco:

(1) Patients should be advised to adhere to a low cholesterol, low fat diet at the start of treatment with Lorelco and throughout the treatment period.

(2) An ECG should be done prior to starting treatment and repeated at appropriate intervals during treatment. If an abnormally long QT interval is observed, the possible benefits and risks should be carefully considered before making a decision to continue Lorelco.

(3) Patients developing unexplained syncope or syncope of cardiovascular origin should have Lorelco therapy discontinued and should have ECG surveillance.

(4) Drugs that prolong the QT interval are more likely to be associated with ventricular tachycardia after:

a. Increase in the dose of the drug.

b. Addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, phenothiazines and certain antihistamines, e.g. terfenadine, astemizole).

c. Hypokalemia or hypomagnesemia.

d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).

e. Development of recent or acute myocardial infarction, ischemia, or inflammation.

The use of Lorelco in patients receiving any of these drugs should be based on the conclusion that alternate methods of hypocholesterolemic therapy are either ineffective or not tolerated, and the potential benefits of cholesterol lowering outweigh the risk of serious arrhythmia.

The following conditions should be resolved or corrected prior to initiation of therapy with Lorelco:

a. Hypokalemia

b. Hypomagnesemia

c. Hypoalbuminemia

d. Severe bradycardia due to intrinsic heart disease or drug effects on the atrial rate (beta-blockers) or AV block (digoxin).

e. Recent or acute myocardial infarction, ischemia, or inflammation.

Effect on Lipoprotein (A) [Lp(a)]

Limited clinical experience indicates that although Lorelco has no significant effect on circulating Lp(a) levels, it may have a potent antioxidant activity in both LDL and Lp(a). Further studies, however, are needed to establish if its antioxidant property may prevent or reduce the progression of atherosclerosis in humans (see SELECTED BIBLIOGRAPHY).

Use in Children

Only limited experience with the use of Lorelco is available in children. Its safety and effectiveness have not been fully established (see SELECTED BIBLIOGRAPHY).

Drug Interactions

Concomitant therapy with other lipid-lowering agents should be approached with caution as insufficient information exists on the effects of combined therapy.

Fibric Acid Derivatives: The addition of clofibrate to Lorelco is not recommended, since the lowering effect on mean serum levels of either LDL or total cholesterol is generally not significantly additive and, in some patients, there may be a pronounced lowering of HDL cholesterol. Since gemfibrozil and other fibric acid derivatives are clinically and pharmacologically similar to clofibrate, caution should be exercised when administering them with Lorelco.

Bile Acid Binding Resins: Limited clinical evidence suggests that the cholesterol-lowering effects of probucol and the bile acid sequestrants cholestyramine and colestipol are additive. Combination treatment with probucol and bile acid binding resins appears to reduce LDL cholesterol levels beyond those attained with either drug alone, while the lowering effect of probucol on HDL cholesterol appears to be partially mitigated.

HMG CoA Reductase Inhibitors: There is insufficient data on the effect of coadministration of probucol and HMG CoA reductase inhibitors on lipid metabolism. Limited clinical evidence suggests that the addition of probucol to HMG CoA reductase inhibitor therapy results in pronounced decreases in both LDL and HDL cholesterol.

Niacin: There is insufficient data on the combined effect of probucol and niacin on lipid metabolism.

Oral Hypoglycemics and Anticoagulants: Neither oral hypoglycemic agents nor oral anticoagulants alter the effect of Lorelco on serum cholesterol. The dosage of these agents is not usually modified when given with Lorelco.

Drugs Which Prolong the QT Interval: Prolongation of the QT interval can occur in patients on Lorelco and serious arrhythmias have been seen in association with an abnormally long QT interval in patients on Lorelco. The addition of a second drug that prolongs the QT interval (including tricyclic antidepressants, class I and III antiarrhythmics, phenothiazines and certain antihistamines, e.g. terfenadine, astemizole) may increase the risk of serious arrhythmia (see PRECAUTIONS and WARNINGS).

ADVERSE REACTIONS

The adverse reactions associated with Lorelco (probucol) are generally mild to moderate and of short duration. In some patients, however, probucol is also known to induce QT prolongation, which may lead to life-threatening arrhythmias. The most commonly affected system is the gastrointestinal tract. Diarrhea occurs in about 10% of patients. Other adverse gastrointestinal reactions in descending order of frequency are flatulence, abdominal pain, nausea and vomiting. These reactions are usually transient and seldom require the drug to be discontinued. Lorelco has been discontinued in about 2% of

patients in clinical studies because of adverse gastrointestinal reactions.

An idiosyncratic reaction characterized by dizziness, palpitations, syncope, nausea, vomiting, and chest pain has been reported.

The following adverse events, divided by system, have also been reported. Incidence rates of 1% or greater are given in parenthesis:

Cardiovascular: Prolongation of the QT interval on ECG, syncope, ventricular arrhythmias (ventricular tachycardia, torsades de pointes, ventricular fibrillation), sudden death.

Gastrointestinal: Indigestion, gastrointestinal bleeding, heartburn.

Neurologic: Headache (2%); dizziness (2%); paresthesia (2%); insomnia, tinnitus, peripheral neuritis.

Haematologic: Eosinophilia (2%); low haemoglobin and/or haematocrit (1%); thrombocytopenia.

Dermatologic: Rash, pruritus, ecchymosis, petechiae, hyperhidrosis, fetid sweat.

Genitourinary: Impotency, nocturia.

Ophthalmic: Conjunctivitis, tearing, blurred vision.

Endocrine: Enlargement of multinodular goiter.

Other: Diminished sense of taste and smell, anorexia, angioneurotic edema.

Laboratory Tests: Elevations of serum transaminases (glutamic-oxalacetic and glutamic-pyruvic), bilirubin, alkaline phosphatase, creatine phosphokinase, uric acid, blood urea nitrogen and blood glucose above the normal range were observed on one or more occasions in various patients treated with probucol. Most often these were transient in nature and/or could have been related to the patient's clinical state or other modes of therapy. Although the basis for the relationship between probucol and these abnormalities is not firm, the possibility that some of these are drug-related cannot be excluded. In the controlled trials, the incidence of abnormal laboratory values was not higher in the patients treated with probucol than in the patients who received placebo.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Because of its very high margin of safety, fatal overdose with Lorelco (probucol) is extremely unlikely. Gastrointestinal upset characterized by abdominal pain, vomiting, diarrhea, and flatulence, are the symptoms to be expected. Treatment is

symptomatic. Gastric lavage, because of the inherent dangers of the procedure, is not recommended as a routine, although it may sometimes be considered necessary to induce vomiting. **Cases of overdose should be investigated for possible ventricular arrhythmias.**

DOSAGE AND ADMINISTRATION

The recommended adult dose is 500 mg (two 250 mg tablets), twice daily, with morning and evening meals.

Cholesterol levels should be monitored periodically and consideration should be given to stopping the drug therapy if cholesterol levels fall below the targeted range, such as that recommended by the Second Report of the U.S. National Cholesterol Education Program (NCEP) (see SELECTED BIBLIOGRAPHY).

PHARMACEUTICAL INFORMATION

Brand Name: LORELCO®

Proper Name: probucol

Chemical Name: 4,4'-[(1-methylethylidene)bis(thio)]-bis[2,6-bis(1,1-dimethylethyl)phenol]

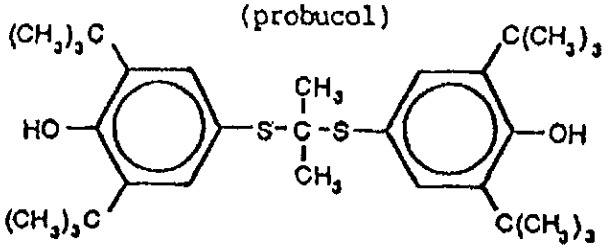
Molecular Formula: $C_{31}H_{48}O_2S_2$

Molecular Weight: 516.84

Structural Formula:

LORELCO

(probucol)



Description:

Probucol is a white, crystalline powder with a melting range of 124°C-127°C. It is practically insoluble in water and dilute aqueous sodium hydroxide, soluble in ethanol and very soluble in chloroform and benzene.

Composition:

Lorelco film-coated tablets for oral administration contain 250 mg of probucol. Each tablet also contains lactose and cornstarch.

Stability and Storage Recommendations:

Store tablets in a well-closed container in a dry place. Avoid excess heat. Dispense in light-resistant containers.

AVAILABILITY

Each round, white, film-coated tablet, imprinted with LORELCO 250 on one side, contains 250 mg probucol. Lorelco tablets are available in bottles of 120.

INFORMATION FOR THE CONSUMER

Please read this leaflet carefully before you start to take your medicine, even if you have taken this medicine before. It contains a brief description and summary of information needed for the proper use of Lorelco. If you have any questions or are not sure about anything, ask your doctor or pharmacist. Please do not throw this leaflet away until you have finished all the medication prescribed by your doctor. You may need to read it again.

1. The Name of Your Medicine

Your medicine is called Lorelco (probucol). Lorelco can only be obtained with a prescription from your doctor.

2. The Purpose of Your Medicine

Lorelco is used to lower levels of cholesterol (a fat-like substance) in the blood. This may help prevent medical problems caused by cholesterol clogging the blood vessels.

3. How Your Medicine Works

Lorelco lowers cholesterol by increasing the rate at which cholesterol is broken down by the body. Lorelco also plays a role in slowing down the formation of cholesterol by the body.

4. Important Points to Note Before Taking this Medicine

Like all medicines, there are important things to consider before taking Lorelco:

Allergies: Tell your doctor if you have ever had any unusual or allergic reaction to Lorelco. Also tell your doctor and pharmacist if you are allergic to any other substances, such as foods, preservatives, or dyes.

Diet: Before prescribing medicine for your condition, your doctor will probably try to control your condition by prescribing a diet for you which may be low in fats, sugars and/or cholesterol. Many people are able to control their condition by carefully following their doctor's orders for proper diet and exercise. Medicine is prescribed only when additional help is needed and is effective only when a schedule of diet and exercise is properly followed.

This medicine is less effective if you are very overweight. It may be very important for you to go on a reducing diet. However, check with your doctor before going on any diet.

Make certain your doctor and pharmacist know if you are on a low-sodium, low-sugar, or any other special diet.

Older Adults: Many medicines have not been studied specifically in older people. Therefore, it may not be known whether they work exactly the same way they do in younger adults or if they cause different side effects or problems in older people. There is no specific information comparing use of Lorelco in the elderly with use in other age groups.

Other Medicines: Tell your doctor and pharmacist if you are currently taking any other prescription or nonprescription (over-the-counter) medicine. Check with your doctor before you begin using any new medicine.

Other Medical Problems: The presence of other medical problems may affect the use of Lorelco. Be sure to tell your doctor if you have any other medical problems, especially:

- gallbladder disease or gallstones
- heart disease - probucol may make these conditions worse
- liver disease - higher blood levels of probucol may result, which may increase the chance of side effects.

If you develop any new medical problems while you are using this medicine, tell your doctor.

5. The Use of This Medicine During Pregnancy and Breast-Feeding

Lorelco should not be used if you are pregnant or breast-feeding. Before you use this medicine, tell your doctor if you are pregnant, are likely to become pregnant, or are planning to become pregnant. Tell your doctor immediately if you become pregnant, or suspect that you may be pregnant, during your treatment.

6. How to Take Your Medicine

Many patients who have high cholesterol levels will feel normal. Take this medicine exactly as directed by your doctor, even though you may feel well. Try not to miss any doses, and do not take more

medicine than your doctor instructed. This medicine works better when taken with meals.

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

Do not stop taking this medicine without first checking with your doctor. Remember that this medicine will not cure your condition, but it does help control it. When you stop taking this medicine, your blood fat levels may increase again.

Carefully follow the special diet your doctor gave you. This is the most important part of controlling your condition, and is necessary if the medicine is to work properly.

It is very important that you visit your doctor regularly. This will allow your doctor to see if the medicine is working properly to lower your cholesterol levels and to decide if you should continue taking it.

7. After Taking Your Medicine

This medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur they may need medical attention.

Let your doctor know as soon as possible if any of the following side effects occur:

More common: dizziness or fainting; fast or irregular heartbeat

Rare: swelling of the face, hands or feet, or in the mouth; unusual bleeding or bruising; unusual tiredness or weakness

Other side effects may occur that usually do not need medical attention. These side effects may go away during treatment as your body adjusts to the medicine. However, let your doctor know if any of the following side effects continue or are bothersome:

More common: bloating; diarrhea; nausea and vomiting; stomach pain

Less common: headache; numbness or tingling of fingers, toes or face

Other side effects not listed above may also occur in some patients. If you feel unwell in any other way or have any symptoms that you don't understand, tell your doctor immediately.

8. What to Do if an Overdose is Taken

If you accidentally take an overdose of your medicine, tell your doctor immediately or, if necessary, go to the nearest hospital.

9. Storing Your Medicine

Leave your tablets in their original packaging and keep them in a safe place out of the reach of children. Keep your medicine in a

cool dry place (15-30°C) away from direct light. If your doctor decides to stop your treatment, throw away your medicine as instructed. Be sure that any discarded medicine is out of the reach of children.

10. What is in Your Medicine

Lorelco tablets contain 250 mg probucol. The tablets also contain cornstarch and lactose, in addition to other non-medicinal ingredients.

11. The Class of Your Medicine

This medicine is one of a group of drugs called lipid metabolism regulators.

12. Who Produces Your Medicine

Manufacturer: sanofi-aventis Canada Inc., Laval, Quebec
H7L 4A8

13. A Reminder

REMEMBER this medicine has been prescribed only for you. Never give it to anyone else.

14. Further Information

This leaflet is a brief description and summary of information about your medicine. If you have any questions or if you want more information about this medicine or your medical problem, ask your doctor or pharmacist.

PHARMACOLOGY

Animal Pharmacology

An effect in lowering the serum cholesterol has been demonstrated in the normal mouse, rat and mini pig, and in dogs and monkeys in which the serum cholesterol has been raised artificially by diet. This effect is not influenced by previous adrenalectomy or oophorectomy. With the exception of one study carried out in mice, an effect on the serum triglyceride level was not demonstrated. In the rat, probucol has been reported to protect and possibly contribute to the healing of the myocardium damaged chemically by isoproterenol or surgically through ligation of the descending branch of the anterior coronary artery. No such effect could be demonstrated in monkeys or mini pigs subjected to this surgical procedure.

In Rhesus monkeys, administration of probucol in diets containing unusually high amounts of cholesterol and saturated fat resulted in the death of 4 to 8 animals after several weeks. Premonitory syncope was frequently observed and was associated with a pronounced prolongation of the QT interval (30-50% longer than that observed in untreated monkeys). Serum levels of probucol greater than 20 μg/mL were generally associated with some prolongation in the QT interval in the cholesterol-fed monkey. A 75 msec or greater prolongation in QT interval from control values was usually seen at 40 μg/mL and above. Blood levels in humans receiving probucol average approximately 20 μg/mL and not uncommonly reach levels of 40 μg/mL and higher. Rhesus monkeys fed normal (low fat)

chow and receiving probucol three to thirty times the human dose equivalent, achieved blood levels only one-third those of many human subjects. No adverse effects were detected in these monkeys over an eight-year period of continuous drug administration.

During the performance of a two-year chronic study involving 32 probucol-treated dogs (beagles), there were 12 fatalities. Subsequent experiments have indicated that probucol sensitizes the canine myocardium to epinephrine, resulting in ventricular fibrillation in many dogs. Among the animal species in which probucol has been studied, the dog is peculiar with respect to the phenomenon of sudden death due to the sensitization of the myocardium to epinephrine. In contrast to findings in the dog, injections of epinephrine to probucol-treated monkeys did not induce ventricular fibrillation.

In other studies, monkeys were given probucol either before and after, or only after, myocardial infarction induced by coronary artery ligation. In these studies, there was no difference between probucol and placebo-treated groups with respect to either survival or detailed blind quantitation of gross or histopathologic myocardial changes. Studies have failed to reveal probucol as having any estrogenic or androgenic properties. Investigations have failed to reveal the drug as having any other pharmacological activity.

From studies 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.

Human Pharmacology

The only consistent pharmacological effect probucol demonstrates in humans is upon serum cholesterol. It is not possible to predict which patient will or will not show a response to the drug. The degree of response is not generally increased when doses higher than those recommended are employed, although it is related in general terms to the initial serum cholesterol level.

Neither race, age, nor sex appear to influence the cholesterol-lowering activity of probucol, and there is no evidence of a "rebound phenomenon" occurring. A favourable trend to treatment in terms of a cholesterol-lowering effect is usually seen within the first 4-8 weeks of treatment. A consistent effect on the serum triglyceride or phospholipid level has not been demonstrated. Prolonged administration failed to affect serum enzymes, hepatic indices, tests of thyroid function, urinary creatinine clearance, glucose tolerance tests, insulin and growth hormone response to oral carbohydrates, hematological parameters, or adrenal cortical function in humans. However, a decrease in the 24-hour urinary excretion of 17 ketosteroid and 11 desoxycortisol metabolites was

observed in some patients receiving long-term treatment with probucol.

No clinical significance has been attached to this finding. An apparent reversal in the normal diurnal variation in the 11 (OH) corticosteroid plasma level was reported by one investigator, who attributed this finding to interference in adrenal cortex function by a concomitant 5-hour glucose tolerance test procedure. Probucol does not interfere with the therapeutic effectiveness or dosage of anticoagulants or hypoglycemic drugs. An increase in the serum triglyceride level can sometimes occur when probucol is given to patients already receiving treatment with clofibrate, and limited clinical experience indicates that the two drugs do not usually display an additive effect in lowering the serum cholesterol. (See Drug Interactions).

Short-term (3 months) double-blind, placebo-controlled studies have shown probucol to lower the serum cholesterol by 10% or more from baseline in 58% of patients; only 16% of placebo-treated patients included in these studies showed this reduction. In similar but longer-term studies (12 months), 67% of probucol-treated, compared with 32% of placebo-treated patients, showed at the twelve-month period, serum cholesterol levels 10% or more below baseline.

Seventy percent of 700 patients studied in open, long-term clinical trials conducted without a placebo control have shown a reduction in the serum cholesterol of at least 10% by the twelfth month.

Three hundred and fifteen of the original 700 patients continued under treatment for at least four years, at which time a mean reduction of 20% in the serum cholesterol from baseline was demonstrated.

An analysis of the effect of probucol on patients categorized according to their Frederickson type showed the drug to lower the serum cholesterol in group II, III, and IV. In all studies with probucol, responding patients have shown a decrease in the atherogenic low density lipoprotein cholesterol.

Probucol lowers levels of HDL cholesterol. In 17 patients who were treated with probucol for two to six months, LDL and HDL cholesterol levels decreased by an average of 11% and 9%, respectively, with total plasma cholesterol decreasing by an average of 12%.

In a primary prevention trial conducted in over 1200 middle-aged men with at least one risk factor but no apparent vascular disease, a total of 252 men received probucol alone or in combination with one or more of the following: clofibrate, beta-blockers, and diuretics. Decreases in mean serum cholesterol in probucol-treated subjects ranged from 15% in those who received probucol alone, to 10% in those who received probucol in combinations including beta-blockers. Compared to subjects treated with other regimens, HDL cholesterol levels and HDL/total cholesterol ratios were observed to be markedly lower in probucol-treated subjects, especially in

those subjects treated with combinations of probucol and clofibrate. Decreases in HDL cholesterol levels were strongly correlated with duration of treatment and serum concentrations of probucol. Despite lowering of HDL, probucol-treated subjects were reported to have the lowest 5-year incidence of sudden death and myocardial infarction, when compared to those who did not receive probucol. **However, it remains to be established to what extent these findings can be extrapolated to other segments of the hypercholesterolemic population not studied.**

Absorption of probucol 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 probucol for periods of three months to one year, the mean blood level was 23.6 ± 17.2 μg/mL (± S.D.) ranging to 78.3 μg/mL. Levels observed after seven years of treatment in 40 patients yielded an average value of 21.5 ± 16.5 μg/mL (± S.D.) ranging to 62.0 μg/mL. In a separate study in eight patients who received probucol 500 mg b.i.d., blood levels averaged 19.0 μg/mL and ranged from 7.3 to 29.8 μg/mL, at the end of 12 months of treatment. Six weeks after cessation of therapy, the average had fallen 60 percent to 7.9 μg/mL (range 3.2 to 16.3

μg/mL). After six months, the average had fallen 80 percent to 3.6 μg/mL (range 1.5 to 6.0 μg/mL).

TOXICOLOGY

Acute and Long-Term Toxicity Studies

Extensive toxicity studies on probucol have been carried out in mice, rats, rabbits, mini pigs, dogs and monkeys. It has not, for reasons of bulk, been possible to establish an accurate oral LD_{50} in the rat or mouse. Single oral doses of 5280 mg/kg body weight failed to produce death or clinical signs of toxicity in these two species. Rats are able to tolerate oral doses of 3852 mg/kg for fourteen consecutive days and average daily dietary levels of 3196 mg/kg body weight for 91 days without untoward effects being apparent. Biochemical tests of liver function, with the exception of glutamic dehydrogenase, remained within normal range. Doses of 800 mg/kg/day of probucol when fed to rats for 24 months failed to produce clinical or pathological changes.

Cardiotoxicity has been observed in beagle dogs fed probucol with a normal diet. Probucol appears to sensitize the canine myocardium to epinephrine-induced ventricular fibrillation, on a species-specific basis. Similar cardiotoxicity studies in monkeys and mini pigs produced no evidence of a similar effect.

The phenomenon of marked QT interval prolongation followed by ventricular ectopy and death was observed in monkeys fed probucol

mixed in a high-cholesterol, high-fat chow. Rhesus monkeys on a regular diet receiving up to 30 times the equivalent human dose of probucol showed no evident cardiac toxicity after 8 years of continuous administration.

Carcinogenicity and Mutagenicity Studies

In chronic studies of two years' duration in rats, no toxicity or carcinogenicity was observed. These results are consistent with the negative findings in tests for mutagenic activity in rats.

Teratology and Reproductive Studies

Reproduction studies have been performed in rats and rabbits at doses up to 50 times the human dose, and have revealed no evidence of impaired fertility or harm to the fetus due to probucol.

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