Probucol (Systemic)

VA CLASSIFICATION
Primary: CV359

Commonly used brand name(s): *Lorelco.*

Note: For a listing of dosage forms and brand names by country availability, see *Dosage Forms* section(s).

*Not commercially available in the U.S.

Category:

Antihyperlipidemic—

Indications

Accepted

Hyperlipidemia (treatment)—Probucol is recommended for use as an adjunct to dietary measures in patients with primary hypercholesterolemia {19} (type IIa {12} hyperlipoproteinemia) and a significant risk of coronary artery disease, who have not responded to diet or other measures alone. Probucol reduces plasma cholesterol concentrations, but has a variable effect on serum triglyceride concentrations, and so is not useful in patients with elevated triglyceride concentrations alone. Its use is limited in other types of hyperlipidemia (including type IIb) because it may cause further elevation of triglycerides. Its main advantage over the anion exchange resins is its ease of administration and better acceptance and tolerance by the patient. {01}
—For additional information on initial therapeutic guidelines related to the treatment of hyperlipidemia, see Appendix III.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:
Molecular weight—
516.84

Mechanism of action/Effect:

Probucol lowers serum cholesterol by increasing the fractional rate of low-density lipoprotein (LDL) catabolism in the final metabolic pathway for cholesterol elimination from the body. {19} Additionally, probucol may inhibit early stages of cholesterol biosynthesis and slightly inhibit dietary cholesterol absorption. {19} Recent information suggests that probucol may inhibit the oxidation and tissue deposition of LDL cholesterol, thereby inhibiting atherogenesis. {12} {16}

Absorption:

Absorption from the gastrointestinal tract is limited and variable {19} (about 7%).

Distribution:

Accumulates in fat tissue with prolonged treatment.

Half-life:

Ranges from 12 hours to more than 500 hours, the longest half-life probably being in adipose tissue.

Time to peak plasma concentration

Plasma concentrations increase slowly and reach steady state after 3 to 4 months; they also decline slowly after withdrawal, by 60% after 6 weeks and by 80% after 6 months. {01}

Time to peak effect:

Maximal reduction in plasma cholesterol concentrations usually occurs within 20 to 50 days after initiation of probucol therapy, although a further decrease may occur gradually over several months. A clinical response usually occurs within 1 to 3 months.

Elimination:

Biliary (slowly in the feces).
Renal, very little (mainly as unchanged drug).

Precautions to Consider

Carcinogenicity

Two-year studies in rats did not reveal carcinogenicity. {19}

Mutagenicity

Mutagenic studies were negative. {19}

Pregnancy/Reproduction

Fertility—
Studies in rats and rabbits did not reveal adverse effects on fertility. {19}

Pregnancy—
Studies in humans have not been done. {19}

Studies in rats and rabbits at doses up to 50 times the human dose have not shown that probucol causes adverse effects on the fetus. {19}

FDA Pregnancy Category B. {19}

Breast-feeding

It is not known whether probucol is distributed into human breast milk. However, it is distributed into the milk of animals. Use of probucol while breast-feeding is not recommended, because of potentially serious adverse effects on nursing infants. {01} {19}

Pediatrics

Appropriate studies on the relationship of age to the effects of probucol have not been performed in the pediatric population. However, use in children under 2 years of age is not recommended since cholesterol is required for normal development. {14}

Geriatrics

No information is available on the relationship of age to the effects of probucol in geriatric patients.

Drug interactions and/or related problems
The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive (**»** = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.

Antiarrhythmics with QT interval prolongation, such as:{15}
Amiodarone
Bretylium
Disopyramide
Encainide
Flecainide
Lidocaine
Mexiletine
Moricizine
Procainamide
Propafenone
Quinidine
Sotalol
Tocainide or{11}
Antidepressants, tricyclic or
Phenothiazines (additive QT interval prolongation may increase risk of ventricular tachycardia {01} {05} {10})

Beta-adrenergic blocking agents or
Digoxin (the effect of beta-adrenergic blocking agents on the atrial rate and the effect of digoxin on AV block can cause bradycardia; when these medications are given in conjunction with a medication that prolongs the QT interval [i.e. probucol], the risk of ventricular tachycardia may be increased {01})

Chenodiol or{17}
Ursodiol{18} (effect may be decreased when chenodiol or ursodiol is used concurrently with antihyperlipidemics since they tend to increase cholesterol saturation of bile)

Laboratory value alterations
The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)—not necessarily inclusive (**»** = major clinical significance):

With physiology/laboratory test values
Alanine aminotransferase (ALT [SGPT]), serum and
Alkaline phosphatase, serum and
Aspartate aminotransferase (AST [SGOT]), serum and
Bilirubin and
Blood urea nitrogen (BUN) and
Creatine kinase (CK) and
Glucose, blood, and
Uric acid, serum (concentrations may be slightly increased {01})

Electrocardiogram (ECG) (QT interval prolongation may occur {19})

Eosinophil concentrations in blood and
Hematocrit and
Hemoglobin concentrations (may be decreased {01})

Medical considerations/Contraindications
The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)— not necessarily inclusive (**»** = major clinical significance).

Except under special circumstances, this medication should not be used when the following medical problems exist:
» Primary biliary cirrhosis (may further raise the cholesterol concentration)

» QT interval prolongation{01}{15} (probucol may prolong QT interval)

Risk-benefit should be considered when the following medical problems exist
Bradycardia, intrinsic, severe or
Hypokalemia or
Hypomagnesemia (the risk of ventricular tachycardia may be increased because probucol prolongs the QT interval {01} {10} {19})

» Cardiac arrhythmias or evidence of recent or progressive myocardial damage{19} (condition may be exacerbated; probucol should be used only with periodic electrocardiogram [ECG] monitoring {01} {19})

» Congestive heart failure, unresponsive or
Gallstones (conditions may be exacerbated {01})

Hepatic function impairment (higher blood levels of probucol may result {01})

Sensitivity to probucol{01}

Patient monitoring
*The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; **»** = major clinical significance):*

» Cholesterol, serum and
» Triglycerides, serum (determinations recommended prior to initiation of therapy and every 3 to 4 months during therapy to confirm efficacy; {19} if an increase in serum triglyceride concentrations occurs, adjustment of the diet is recommended; if the increase persists, it is recommended that probucol therapy be withdrawn {01})

ECG (recommended at periodic intervals in patients with a history of cardiac arrhythmias; probucol therapy should be withdrawn if cardiac arrhythmias or a prolonged QT interval occurs {01})

Side/Adverse Effects

Note: Prolongation of QT interval associated with serious arrhythmias has been reported in patients treated with

probucol {01}.

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention
Incidence more frequent

Eosinophilia *{01}{19}*

QT interval prolongation and ventricular arrhythmias (dizziness or fainting; pounding heartbeat; fast or irregular heartbeat){01}{10}{19}

Incidence rare

Anemia (unusual tiredness or weakness){01}

angioneurotic edema (swellings on face, hands, or feet, or in mouth){01}

thrombocytopenia (unusual bleeding or bruising){01}{19}

Those indicating need for medical attention only if they continue or are bothersome
Incidence more frequent

Gastrointestinal irritation (bloating; diarrhea; nausea and vomiting; stomach pain){01}

Note: *Gastrointestinal irritation* is usually transient and mild.

Incidence less frequent

Dizziness *{01}{19}*

headache *{01}{19}*

paresthesia (numbness or tingling of fingers, toes, or face)

Patient Consultation
As an aid to patient consultation, refer to Advice for the Patient, Probucol (Systemic) .

In providing consultation, consider emphasizing the following selected information (**»** = major clinical significance):

Before using this medication
Diet as preferred therapy; importance of following prescribed diet
» Conditions affecting use, especially:
Sensitivity to probucol

Breast-feeding—Use not recommended because of potentially serious adverse effects on nursing infants {01}

Use in children—Not recommended in children under 2 years of age since cholesterol is required for normal development

Other medical problems, especially primary biliary cirrhosis, and cardiac abnormalities including congestive heart failure and QT interval prolongation

Proper use of this medication
» Importance of not taking more or less medication than the amount prescribed

This medication does not cure the condition but rather helps control it

» Compliance with prescribed diet

Taking with meals, since medication is more effective with food

» Proper dosing
Missed dose: Taking as soon as possible; not taking if almost time for next dose; not doubling doses

» Proper storage

Precautions while using this medication
» Importance of close monitoring by the physician

» Checking with physician before discontinuing medication; blood lipid concentrations may increase significantly

Side/adverse effects
Signs of potential side effects, especially angioneurotic edema, blood dyscrasias, QT interval prolongation, and tachycardia

General Dosing Information
See also Patient Monitoring .

If unexplained or cardiovascular-related syncope occurs, probucol therapy should be withdrawn and ECG monitored {01} {19}.

If response is inadequate after 4 months of treatment, probucol therapy should be re-evaluated and possibly withdrawn, {19} except in the case of xanthoma tuberosum, which may require up to 1 year of treatment as long as reduction in size and/or number of xanthomata occurs.

When probucol is discontinued, an appropriate hypolipidemic diet and monitoring of serum lipids are recommended until the patient stabilizes, since a rise in serum cholesterol concentrations to or above the original base may occur.

Diet/Nutrition
It is recommended that probucol be taken with food to maximize absorption.

Oral Dosage Forms

PROBUCOL TABLETS

Usual adult dose
Antihyperlipidemic
Oral, 500 mg two times a day with the morning and evening meals. {01} {19}

Usual pediatric dose
Dosage has not been established.

Strength(s) usually available
U.S.—
Not commercially available.

Canada—

250 mg (Rx) [*Lorelco*]

Packaging and storage:
Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed, light-resistant container, unless otherwise specified by manufacturer.

Auxiliary labeling:
- Take with meals.

Revised: 08/24/1998

References

1. Probucol package insert (Lorelco, Merrell Dow—US), Rec 2/89.
2. USAN and the USP dictionary of drug names 1990. The United States Pharmacopeial Convention, Inc. Rockville, Maryland.
3. USP NF, 1990. The United States Pharmacopeial Convention, Inc. Rockville, Maryland.
4. Martindale's the extra pharmacopeia. 29th ed. 1989. Reynolds JE, editor; p 1203.
5. Applied therapeutics, the clinical use of drugs. 4th ed. 1988; Young LY, Koda-Kimble MA, editors. p 229-30.
6. The Expert Panel. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988; 148: 36-69.
7. Carew T. Role of biologically modified low-density lipoprotein in atherosclerosis. Am J Cardiol 1989; 64(13): 18G-22G.
8. Meyler's side effects of drugs. 10th ed. 1984; p 825-6.
9. Howard P. Probucol in hypercholesterolemia. Ann Pharmacother 1989; 23: 880-1.
10. Dujovne C, et al. Electrocardiographic effects of probucol. A controlled prospective clinical trial. Eur J Clin Pharmacol 1984; 26: 735-9.
11. Applied therapeutics, the clinical use of drugs. 4th ed. 1988; Young LY, Koda-Kimble MA, editors. p 229-30.
12. Manufacturer comment, 1991.
13. National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation 1994; 89(3): 1329-445.
14. Panel comment, 1991.
15. Fish F, Roden D. A prolonged QT interval. Med Toxicol Adverse Drug Exp 1989; 4(6): 400-11.

16. Parthasarathy P, Young S, Witztum J, Pittman R, Steinberg D. Probucol inhibits oxidative modification of low density lipoprotein. J Clin Invest; 77: 641-4.

17. Chenodiol product information (Chenix, Reid-Rowell—US), Rec 10/88.

18. Ursodiol product information (Actigall, Ciba—US), Rev 6/88, Rec 1989.

19. Probucol package insert (Lorelco, Merrell Dow—US), Rev 6/88, Rec 1/93.

20. Knodel LC, Talbert RL. Adverse effects of hypolipidaemic drugs. Med Toxicol 1987; 2: 10-32.