Metairie Institute of Comprehensive Health, LLC

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Internal Medicine
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Dear Patient:

The following is what I need you to know before starting Pravachol:

This drug is tolerated by 99% of all patients. There has not been one reported case of true liver damage in the entire United States in ten years of this drug on the market in the United States and in many years of use in Europe prior to approval of the drug in the United States. One percent of people get a mild "liver irritation" which would be similar to someone drinking a few drinks of alcohol a day. The liver irritation is totally reversible when the drug is stopped. Liver biopsy studies have shown no architectural damage at all to the liver and no functional damage at all to the liver after the drug is stopped. Recently, the FDA told us we did not have to check liver function tests every eight weeks for the first year, but could simply get a liver function test in six weeks, three months later, and then once a year after that. We would encourage you to strictly adhere to the protocol for the blood test that we order on Pravachol. This will help us determine if there is a liver irritation and also whether the drug is helping you.

Pravachol is only started after low cholesterol diet therapy has not brought down your cholesterol enough. It is important to realize that two out of three people in this country die of vascular disease, so the benefits of this drug far outweigh the risks. Often diet therapy for cholesterol does not bring the cholesterol down low enough to be acceptable. We need to keep your "bad cholesterol," which is also called LDL or low-density lipoprotein, low enough to prevent cholesterol deposition in the arteries of the heart, brain, kidneys, and peripheral blood vessels. It is known that even small plaques of these arteries can rupture and cause a complete occlusion of the artery, so you do not have to completely occlude an artery with cholesterol to get a heart attack or stroke. The heart attack and the stroke CAN occur

It is known that Pravachol can reverse the process of cholesterol deposition in two ways—one, by decreasing the cholesterol in the artery and keeping the artery from becoming narrower, and two, by stabilizing the cholesterol plaque so that the plaque does not rupture. Sixty-eight percent of heart attacks are caused by plaques that narrow the artery less than 50%. Previous studies have shown that patients who have vascular

disease greatly benefit from "statin" drugs. The 4S study, published in 1994, proved that if I put 100 patients with coronary artery disease on a statin drug I will prevent four of nine fatal heart attacks, six of 19 non-fatal heart attacks, seven of 21 bypass surgeries, and two of five strokes over a period of six years. Other studies in patients without any evidence of coronary artery disease or vascular disease show that I can decrease cardiac events by 41% to 38%. I am referring to the West Scotland Study and the Tex/Caps AF/Caps studies.

Pravachol has been shown to have other beneficial effects such as lowering fibrinogen, raising nitrous oxide, and increasing apoptosis of cancer cells, which allows cancer cells to die quicker. It has also recently been shown to help prevent osteoporosis.

It is important to know that you should never take high doses of niacin, Serzone or the antibiotic erythromycin while you are on Pravachol. There are many trade names for erythromycin such as E.E.S., Eryc, E-Mycin, and Biaxin. Recently, it has been shown that Zithromax, which is an erythromycin, is allowable to take with statin drugs. Also, never take any antifungal drugs or Cyclosporin with Pravachol or other statin drugs. If you need to take erythromycin, Pravachol can be stopped and the erythromycin started and then after this temporary discontinuance of the Pravachol you can restart the Pravachol after the erythromycin is finished.

You need not avoid grapefruit juice on Pravachol, but you should avoid it on the other statin drugs (Zocor etc). Also you can't take statin drugs when on Serzone or HIV drugs.

There is a very rare side effect of Pravachol which can be serious. This is sort of an allergic reaction which involves muscles and occurs in one out of 112,000 patients. Therefore, if you ever get generalized muscle weakness or generalized muscle aching, it is probably the flu, but I need to know this to do a blood test on you as soon as possible to be sure it is not the Pravachol. As I said, the drug benefits far outweigh the risk of this drug as the chances are two out of three that you will die of a cholesterol-related process.

I believe Pravachol is the safest of all cholesterol-lowering drugs as it has the lowest incidence of drug interactions and the lowest incidence of the muscle reaction called rhabdomyolysis.

Other statin drugs, however, also are very safe and effective, however, they do have more drug interactions. So, if you are on a statin drug other than Pravachol it is important to let us know if you are starting any drug from any other

physician. If you have any questions about Pravachol or statin drugs do not hesitate to call.

Sincerely,

MD

Edward M. Gaber, MD

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TABLE 1. REPORTED CASES OF FATAL RHABDOMYOLYSIS AND NUMBERS OF PRESCRIPTIONS FOR ALL STATINS DISPENSED IN THE UNITED STATES SINCE THESE PRODUCTS WERE LAUNCHED.

VARIABLE	LOVASTATIN	PRAVASTATIN	SIMVASTATIN	FLUVASTATIN	ATORVASTATIN	CERIVASTATIN	TOTAL
Date approved	8/31/87	10/31/91	12/23/91	12/31/93	12/17/96	6/26/97	—
Fatal cases of rhabdomyolysis*	19	3	14	0	6	31	73
No. of prescriptions dispensed since marketing began†	99,197,000	81,364,000	116,145,000	37,392,000	140,360,000	9,815,000	484,273,000
Reporting rate (per 1 million prescriptions)‡	0.19	0.04	0.12	0	0.04	3.16	0.15

*U.S. cases reported to the FDA before June 26, 2001, that met the following criteria were included: the report included a clinical diagnosis of rhabdomyolysis, a temporal association between rhabdomyolysis and the use of a statin could be identified from the report, and death resulted either directly or indirectly from rhabdomyolysis.

†Data are through May 2001 and are from the National Prescription Audit Plus, excluding the Long Term Care Channel.

‡The reporting rate is the number of fatal cases divided by the number of prescriptions dispensed and is a crude measure of the number of reports received by the FDA relative to the extent of the use of an agent in the U.S. population. Rigorous comparisons between drugs that are based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates.

Please read this carefully to understand the rare risk of rhabdomyolysis and death with statin drugs. Weigh this information with the knowledge that 2 out of 3 people in the USA die of preventable vascular disease (strokes AND heart attacks)

E alone or with vitamin C harmful as far as potentially decreasing HDL when used with a statin?

A21: I think the Heart Protection Study is really the stake in the heart of the vitamin E issue. The HOPE and GISSI-2 trials have not shown any benefits of the antioxidant vitamins. The HATS trial actually suggested that patients on vitamin E and a statin did *not* get the HDL-raising benefit from the statin, which raised the idea that you could actually have some detrimental effects from antioxidant vitamins. The Heart Protection Study showed no effect whatsoever for vitamin E with or without a statin. Having this 20,000-person study with 10,000 patients of every description on antioxidant vitamins showing no evidence whatsoever for efficacy provides the answer. I think the state of the art for vitamin E is no benefit, with a few studies actually showing some detriment. I think that's enough for us to act clinically not to recommend vitamin E or C in our patients.

Patients Worry About Statin Side Effects

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group, urged the Food and Drug Administration to strengthen warnings on the remaining cholesterol-lowering drugs, saying that it had documented evidence that all five of them were associated with some cases of rhabdomyolysis, though comparatively much fewer than for those taking the Bayer drug. Sidney Wolfe, director of Public Citizen Health Research Group, called for a so-called black box warning, the agency's strongest, on the label governing use of the drug.

Doctors who have handled inquiries from patients during the past two weeks say that in addition to switching Baycol patients to other statins, they are counseling those taking the other drugs not to worry.

"The vast majority of people who have been on these drugs for years and years—that's millions of patients—have done extremely well," says Paul Ridker, a cardiologist at Boston's Brigham and Women's Hospital and Harvard Medical School. "I've been spending a fair amount of time reassuring patients who are on them" to stay on them.

The telltale signs of the culprit side effect are muscle aches and pains not associated with rigorous physical activity. Doctors say generally that any patients on a statin who experience such pain should stop taking their drug and call their doctor.

The new attention to the problem also calls on both patients and doctors to be more vigilant about getting regular blood tests to check not only for signs of the muscle problem but for elevated liver enzymes that could be a sign of liver inflammation.

Both the muscle and liver side effects, though potentially serious if left unchecked, are nearly always reversible if caught early and the use of the medication is stopped, doctors say. Moreover, oftentimes, after a brief period off the drug, patients can try again with a different statin without experiencing any side effects.

Marc Pfeffer, professor of medicine at Harvard Medical School, says a recent analysis of three major studies involving Bristol-Myers' Pravachol didn't turn up any differences of muscle or liver side effects for those taking the drug compared with those who were taking a placebo. The analysis covered the equivalent of 112,000 patients taking the drug for a year. Rare events happen, says Dr. Pfeffer, also a cardiologist at Brigham and Women's Hospital, and "you can never have too much safety." But "these are very safe drugs."

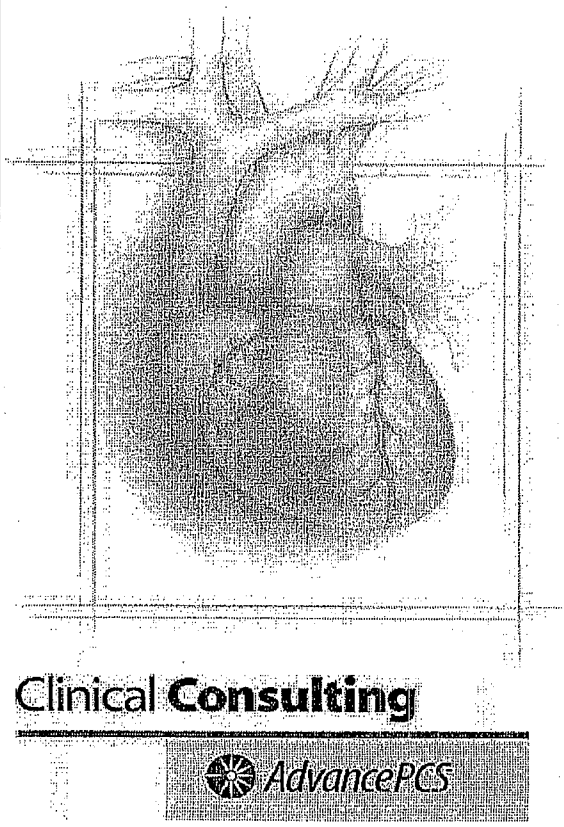
Michael Lauer, director of clinical cardiology research at the Cleveland Clinic, has been prescribing statins for his patients since the late 1980s, when they first reached the market, and says he hasn't seen a case of rhabdomyolysis. Indeed, he has encountered relatively few cases where a patient had to stop taking the drugs because of muscle or liver irregularities.

Doctors have known about the potentially serious muscle problems since shortly after statins came on the market, but they were preoccupied with other worries: cataracts, birth defects and cancer. The drug isn't recommended for pregnant women. The cataract problem, which showed up in some early animal studies, never materialized, says Donald Black, a former Warner Lambert executive who helped develop Lipitor, now marketed by Pfizer. Large-scale studies haven't turned up any increased incidence of cancer among those who take the drugs.

Comparison of Pravachol Studies

	WOSCOPS	CARE	LIPID
	PRIMARY PREVENTION - HIGH CHOLESTEROL	SECONDARY PREVENTION - AVERAGE CHOLESTEROL	SECONDARY PREVENTION - MODERATE CHOLESTEROL
Study Design	Double-Blind, Placebo Based, Randomized	Double-Blind, Placebo Based, Randomized	Double-Blind, Placebo Based, Randomized
Length of Study and Timing	4.9 years - 2/89 through 5/95	5 years - 12/89 through 2/96	6.1 years - 6/90 through 9/97
Patient Information	6595 Men, ages 45-64 years old	3583 Men & 576 postmenopausal Women, ages 21-75 years old	7498 men & 1516 women, ages 31-75 years old
Baseline Cholesterol Levels	Total Cholesterol 272 +/- 23 mg/dL	Total Cholesterol of < 240 mg/dL	Total Cholesterol between 196-241 mg/dl
	LDL-C 192 +/- 17 mg/dL	LDL-C of 115 to 174 mg/dL	LDL-C between 131-170 mg/dl
Medical History	No History of Myocardial Infarction (MI)	Experienced MI 3-20 months before Study	Experienced Non-fatal MI or Angina 1-6 months before
Drug / Strength	Pravachol 40mg QPM and Dietary Information vs. Placebo	Pravachol 40mg QD and Dietary Information vs. Placebo	Pravachol 40mg QD and Dietary Information vs. Placebo
Primary Endpoint	Combined Incidence of Non-fatal MI and Death from CHD	Incidence of Non-fatal MI or Death from CHD	Death from CHD
Secondary Endpoints	Death from Coronary Heart Disease (CHD) Incidence of Non-fatal MI Death From Any Cause Frequency of Coronary Revascularization	Death from CHD Incidence of Non-fatal MI Incidence of Stroke Coronary-Artery Bypass	Death from CHD or Non-fatal MI Incidence of Non-fatal MI Incidence of Stroke Incidence of Revascularizations
Results	31% Reduction in Combined Incidence of Non-fatal MI and Death 26% Reduction in Risk of Death from CHD Alone	24% Reduction in combined incidence of MI and Death 20% Reduction in Risk of Death from CHD 31% Reduction in Frequency of Stroke	25% Reduction in Incidence of Non-fatal MI and Death 24% Reduction in Risk of Death from CHD 19% Reduction in Stroke
	Actual Incidence of Death + Non-fatal MI & Death from CHD in Pravachol Group vs Placebo - 6.8% vs 9.3%; 1.9% vs 1.9%	Incidence of Death + Non-fatal MI; Death from CHD; Stroke in Pravachol Group vs Placebo - 10.2% vs 13.2%; 4.6% vs 5.7%; 2.6% vs 3.8%	Actual Incidence of Death + MI; Death from CHD; Stroke in Pravachol Group vs Placebo - 12.3% vs 15.0%; 6.4% vs 8.3%; 3.7% vs 4.5%
Effect of Pravachol on Lipid Levels	20% Reduction in Total Cholesterol 26% Reduction in LDL-C 12% Reduction in TG 5% Increase in HDL-C levels	20 % Reduction in Total Cholesterol 28 % Reduction in LDL-C 14 % Reduction in TG 5% Increase in HDL-C	18% Reduction in Total Cholesterol 25% Reduction in LDL-C 11% Reduction in TG 5% Increase in HDL-C

	PROSPER	ALLHAT-LLT
	PRIMARY & SECONDARY PREVENTION - MODERATE CHOLESTEROL	PRIMARY & SECONDARY PREVENTION LOW TO MODERATE CHOLESTEROL
Study Design	Placebo Based, Randomized	Non-Blinded, Randomized
Length of Study and Timing	3.2 years - beginning in 12/97	4.8 years - 2/94 through 8/02
Patient Information	2804 Men & 3000 Women, ages 70-82 years old	5285 Men & 5074 Women, Mean Ages of 66 Years
Baseline Cholesterol Levels	Total Cholesterol of 220 mg/dL	Total Cholesterol - Mean of 224 mg/dL
	LDL-C of 147 mg/dL	LDL-C Mean of 146 mg/dL
Medical History	Vascular disease or increased risk; HTN, Diabetes, Smoking	Hypercholesterolemia with a Minimum of One Additional CHD Risk
Drug / Strength	Pravachol 40mg QD	Pravachol 40mg QD vs. Usual Care
Primary Endpoint	Combination of Coronary Death, non-fatal MI & all strokes	All Cause Mortality
Secondary Endpoints	Transient Ischemic Attack (TIA) Cognitive Function Disability Coronary and Cerebrovascular Components Examined	Death from CHD or Non-fatal MI Incidence of MI Cause-Specific Mortality Incidence of Cancer
Results	15% Reduction in Incidence of Death, Non-fatal MI and Stroke 24% Reduction in Risk of Death from CHD 25% Reduction in Transient Ischemic Attack	9% Reduction in Incidence of Non-fatal MI and Death No Difference in All Cause Mortality 9% Reduction in Stroke
	Incidence of Death + Non-fatal MI; Death from CHD; & TIA in Pravachol Group vs Placebo - (10.1% vs 12.2%); (3.3% vs 4.2%); (2.7% vs 3.5%)	Incidence of Death + Non-fatal MI; Death from CHD; Stroke in Pravachol Group vs Usual Care - (9.9% vs 10.4%); (3.7% vs 3.9%); (5.0% vs 5.4%)
Effect of Pravachol on Lipid Levels	34% Reduction in LDL-C 13% Reduction in TG 5% Increase in HDL-C	17% Reduction in Total Cholesterol - 9.6% Difference from Usual Care 28% Reduction in LDL-C 3% Increase in HDL-C



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Abbreviations

QPM=Once in the evening;QD=Once daily; MI=myocardial infarction; CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides; HDL-C=high-density lipoprotein cholesterol; HTN=Hypertension; TIA =Transient Ischemic Attack

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