CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-198	SUBMISSION DATE: 12-23-1999
BRAND NAME:	Pravachol® (nonprescription pravastatin)
GENERIC NAME:	Pravastatin 10 mg tablets
REVIEWER:	Xiaoxiong (Jim) Wei, M.D., Ph.D.
SPONSOR:	Bristol-Myers Squibb Company, Hillside, New Jersey
TYPE OF SUBMISSION:	Original NDA for OTC

SYNOPSIS:

On December 23, 1999, BMS submitted NDA21-198 for Pravachol 10-mg tablets (nonprescription pravastatin).

The information presented in this submission for Section 6 (Human Pharmacokinetics) is summary of studies submitted to the original pravastatin NDA and subsequent supplements after approval of the prescription pravastatin NDA. The 10-mg tablet of pravastatin proposed for the OTC product has the same composition as currently marketed prescription pravastatin.

The metabolism of pravastatin is not involved CYP3A4 at a clinically relevant level. The bioavailability is 17%. Pravastatin undergoes extensive first-pass hepatic extraction. The important feature of pravastatin in pharmacokinetics related issues is that pravastatin is a substrate of P-glycoproteins (P-gp). Since most of CYP3A4 drugs share substrates with P-glycoproteins and some of CYP3A4 drugs function as potent inhibitors of P-glycoproteins, P-gp related drug interactions will be major mechanism in pravastatin drug interactions.

Although this NDA does not contain any new information for Section 6 (Human Pharmacokinetics), the following important question is addressed in this review:

Are there any safety concerns about 10 mg-Pravachol® from a clinical pharmacology perspective?

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-198 OTC Pravachol® (nonprescription pravastatin) 10 mg tablets submitted on December 23, 1999. The labeling changes/comments (Page 5) should be sent to the sponsor as appropriate.

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CLINICAL PHARMACOLOGY

Are there any safety concerns about 10 mg-Pravachol® from a clinical pharmacology perspective?

From a clinical pharmacology perspective, the following facts concern us about safety of Pravachol® once it becomes available over the counter.

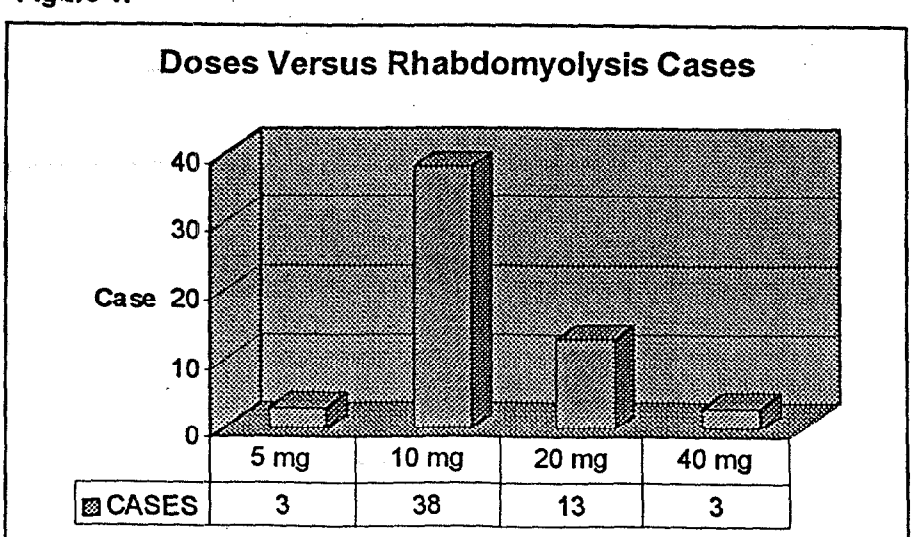
(1) Susceptibility of rhabdomyolysis: This reviewer surveyed MedWatch case reports from 1990– 1999. There are 61 severe myopathy or rhabdomyolysis cases reported to MedWatch related to pravastatin of which 57 cases had specified doses in reports. The percentage of dose distribution is summarized in the following table:

Table 1. Dose versus Rhabdomyolysis

DOSE	CASES	PERCENT
5 mg	3	5.3 %
10 mg	38	66.6 %
20 mg	13	22.8 %
40 mg	3	5.3 %
TOTAL	57	100 %

The data is also presented in the following figure:

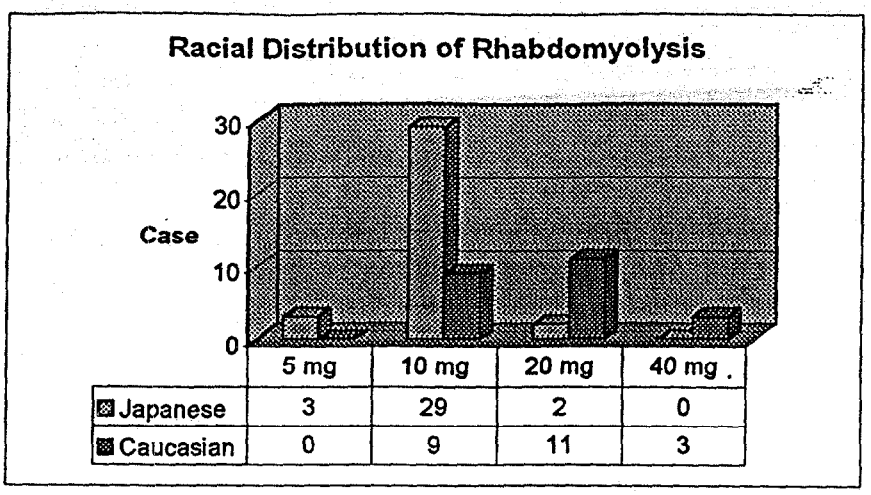
Figure 1.



Two fatalities due to rhabdomyolysis may be related to pravastatin. One case was 84 years old Japanese patient under 10-mg pravastatin therapy, who also suffered from bacterial infection. The other fatality case was 56 years old American patient under 20-mg pravastatin therapy.

From Table 1, it should be noted that the majority of rhabdomyolysis cases occurred in the low dose range between 5 mg to 10 mg per day. This reviewer further analyzed the population distribution of this severe adverse drug event (Figure 2).

Figure 2.



Therefore, the Asian patients may be particularly susceptible to develop rhabdomyolysis although the patients were given less than or equal to the lowest recommended dose, 10 mg. The mechanism is unknown. It may be related to genetic makeup, low body weight, disease status, etc. Since there are most cases related to10-mg dose in Japanese patients, this reviewer also analyzed age and gender distribution as shown in Figure 3 and Figure 4.

Figure 3.

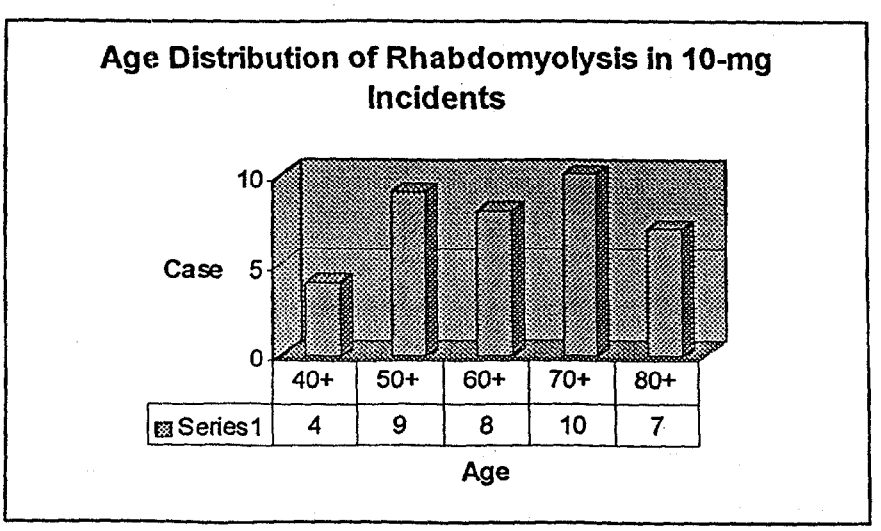
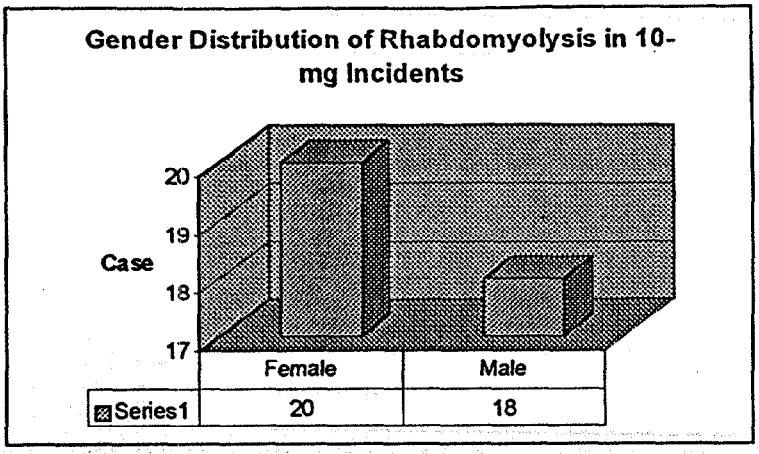


Figure 4.



MedWatch case reports reveal that rhabdomyolysis can occur in very low dose of pravastatin such as 5mg daily doses. The 10-mg use of pravastatin was related to one fatal rhabdomyolysis case. After reviewing these post market reports, this reviewer found that rhabdomyolysis does not seem to have gender-related preference. However, it can not be determined if the advanced age is related to increase incidents since this reviewer did not have a complete prescription information for all ages of patients.

(2) Multiple drug interactions: Pravastatin is a substrate of P-glycoproteins. From original NDA, supplements and publications, we know that many potent inhibitors of P-glycoproteins can significantly increase the pharmacokinetic parameters of pravastatin. The following table summarizes the outcomes of drug-drug interactions with these inhibitors.

Table 2. Pravastatin Interactions with Inhibitors of P-Glycoproteins.

Drug	Study design	Pravastatin Dose	Ratio of Means	
			AUC	Cmax
Itraconazole	200 mg, single dose	40 mg, single dose	1.7	2.5
Erythromycin	0.5gQID X 7 days	40 mg, single dose	1.7	2.2
Clarithromycin	0.5 g BID X 7 days	40 mg qd X 7 days	2.0	UD
Cyclosporin A	2-6mg/kg/day X 28 days	20 mg, single & multiple doses	5.0	UD
Verapamil	120 mg(IR) on day 1 & 480 mg(MR) qd on days 2-4	40 mg, single dose	1.3	1.42

Furthermore, the patients who need to take lipid-lowering drugs are likely in advanced age. They often have multiple medical problems and are often under multiple drug therapies. Different categories of drugs such as calcium channel blockers, macrolide antibiotics, etc. can be prescribed to a patient at the same time. These inhibitory drugs of p-glycoproteins can act on additive manner to exhibit inhibitory additive effect on pravastatin. The Table 3 shows some representative of some categories of drugs that function as inhibitors of P-glycoproteins.

Table 3. Inhibitors of P-glycoproteins

Azole antifungal	Steroid	Miscellaneous
Ketoconazole	Progesterone	Quinidine
Itraconazole	Tamoxifen	Chloroquine
	Cortisol	Reserpine
Macrolide Antibiotics	**Cyclic Peptides**	Amiodarone
Erythromycin	Cyclosporin A	Terfenadine
Clarithromycin	Valinomycin	Dipyridamole
Calcium Channel Blockers	**Calmodulin antagonists**	
Verapamil	Trifluoperazine	
Nifedipine	Chlorpromazine	
Azidopine		

One important fact should be emphasized here that most CYP3A4 drugs share substrates with P-glycoproteins. Some of them also function as inhibitors of P-glycoproteins. Since 55% to 70% of marketed drugs are CYP3A4 drugs, the potential for P-glycoprotein related drug interactions is conceivable,

(3) Pravastatin interaction with fibrates. Both categories of drugs, statins and fibrates can cause rhabdomyolysis during monotherapy. Since they share a common severe adverse drug event, the combination therapy of both classes should generally be avoided. All statins but pravastatin don't interact with fibrates in pharmacokinetic profiles. However, gemfibrozil can decrease urinary excretion and protein binding of pravastatin and significantly increase the pharmacokinetic parameters such as AUC, Cmax, and Tmax. The other fibrates such as fenofibrate etc. can have similar PK related interactions with pravastatin.

This PK related drug interactions between pravastatin and fibrates increase the potential to develop rhabdomyolysis. The cases reported to MedWatch support the increased risk.

The reviewer's general comments:

Pravastatin is a relatively safe prescription drug. However, if it becomes an OTC product, we would have safety concerns about racial difference in susceptibility of rhabdomyolysis, additive inhibitory effects of multiple P-gp inhibitory drugs to increase the bioavailability of pravastatin, and the PK and PD related interactions with fibrates to increase the risk of rhabdomyolysis.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☛ indicates an explanation only and is not intended to be included in the labeling)

WARNINGS!

Do not use if you are:

Already taking prescription medication to lower your cholesterol or are taking erythromycin, clarithromycin, ketoconazole, itraconazole, cyclosporin A ~~(an antibiotic)~~.

☛ These drugs have shown that they can significantly increase pharmacokinetic parameters of pravastatin, which may increase the risk to develop severe adverse drug event, rhabdomyolysis.

5/24/00

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Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 5/25/00

CPB Briefing (May 23, 2000): Shiew-Mei Huang, John Hunt, Hae-Young Ahn, Suliman Al-Fayoumi, Margaret Simoneau, and Jim Wei

CC: NDA 21-198 (orig., 1 copy), HFD-510 (Simoneau), HFD-850 (Lesko), HFD-870 (Wei, Ahn, Huang), CDR.

Attached: proposed OTC labeling.

CHOLESTEROL REDUCER

PRAVACHOL 10

Before You Start: SEE YOUR DOCTOR to check your cholesterol levels and discuss your risk factors for heart disease.

FREE ENROLLMENT in *PravaCare*. A consumer support and newsletter program. Call 1-888-200-4758.

ACTIVE INGREDIENT Pravastatin sodium, 10 mg per tablet **PURPOSE** Cholesterol reducer

USE

See Your Dr. Before Use

To lower choelsterol if it is still high after a program of diet and exercise **AND**

For Men:	For Women:
• Your Total Cholesterol number is between 200-240 mg/dL AND • You are35 years of age or older.	• Your Total Cholesterol number is between 200-240 mg/dL AND • You are55 years of age or olderFor women, the risk of heart disease increases after menopause.

WARNINGS

Do Not Use If You Are

- Pregnant, nursing or still able to become pregnant.
- Known to have certain diseases (unless told to do so by a doctor): Heart disease, Diabetes, Liver disease
- Already taking prescription medication to lower your cholesterol or are taking erythromycin (an antibiotic).
- Someone who drinks 3 or more alcoholic beverages daily.
- Under the age of 18 years of age.
- Allergic to pravastatin or any of the inactive ingredients.

Keep this and all drugs out of the reach of children. In case of accidental overdose, get medical help right away or contact a poison control center immediately

Ask Your Doctor Before Use If:

- Your Total Cholesterol is more than 240 mg/dL and/or your Good Cholesterol (HDL) is very low.
- You have more than one of these risk factors for heart disease: Smoking, High blood pressure, Family history of heart disease

If any of the above describe you, you are at increased risk for cholesterol damage and may need prescription strength Pravachol. See your doctor for more advice.

When Using This Product See Your Doctor

- If you have any unusual muscle pain or tenderness, that is not caused by a cold, flu, recent injury or sprain. This is very important if you also feel weak or have a fever.

DIRECTIONS

- Take 1 tablet every day, at bed time.
- 6 weeks later consult your doctoronce more to find out if you have reached a healthy cholesterol level.
  - *If you have reached* a healthy cholesterol levelkeep taking Pravachol 10. to stay at a healthy level.
  - If you haven't reached a healthy cholesterol level, you may need a prescription dose of Pravachol
- Once a year have your cholesterol level checked.
- Continue to exercise and stay on a low-fat diet.

Tamper Resistant Inner Unit. Do not use if foil seal is torn or broken. This package for households without young children.