

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

PID # 99085

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THROUGH ~~Evelyn Rodriguez, M.D., M.P.H., Director~~ 15/01/00  
Division of Drug Risk Evaluation II, HFD-440  
Office of Postmarketing Drug Risk Assessment (OPDRA)

TO John Jenkins, M.D., Acting Division Director  
Division of Endocrine & Metabolic Drug Products, HFD-510

SUBJECT OPDRA SAFETY REVIEW  
Consult: Statins and Hepatotoxicity  
Drugs: Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin,  
and Simvastatin

**Confidential: Contains IMS data; Do not use outside FDA without IMS clearance**

**Background**

This memorandum is in response to a request for consult from Mary Parks, M.D., Medical Officer in the Division of Endocrine and Metabolic Drug Products to search the FDA's Adverse Event Reporting System (AERS) database to find out cases of serious liver disease (hepatitis, and liver failure) associated with atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors have been associated with transaminases elevations. LFTs (Liver Function Tests) monitoring is recommended for all these statins. Typical labeling of these drugs states that:

"It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation of dose, and periodically thereafter (e.g. semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality (ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with the x drug is recommended."

Recently sponsors have proposed cutting back on LFTs monitoring, and some sponsors are actively pursuing OTC (over-the-counter) switch of their drugs.

## Methods

Lanh Green/Jennie Chang searched the FDA's postmarketing AERS database to identify all reports of liver failure associated with atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. The search strategies, case definitions and results are summarized in a companion document.

IMS Health's National Prescription Audit (NPA) Plus, and National Disease and Therapeutic Index (NDTI) databases were used to obtain estimates of drug use for all the six drugs. An estimate of person-years of exposure for all the drugs was calculated by using the formula: (total number of prescriptions for each drug X average days of therapy for each drug) / 365 days. Estimates of reporting rates of liver failure were calculated using the formula: number of cases/estimated person-years of exposure with each drug.

## Results

A search in the AERS database through February 25, 2000 generated 62 reports of liver failure associated with lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin respectively. Table 1 lists the annual projected total number of prescriptions dispensed by retail pharmacies (chain, independent, food stores and mail order) since each drug was first marketed in the U.S. and the number of yearly reported cases of liver failure associated with each of the statins.

Table 1: Annual Projected Total Prescriptions\* of Statins Dispensed by Retail Pharmacies & Yearly Reported Domestic Cases of Liver Failure associated with these Statins

Year	Lovastatin		Pravastatin		Simvastatin		Fluvastatin		Atorvastatin		Cerivastatin	
	Rxs*	Cases LF/U	Rxs*	Cases LF/U	Rxs*	Case LF/U	Rxs*	Cases LF/U	Rxs*	Cases LF/U	Rxs*	Cases LF/U
1987		0/0	---		---		---		---		---	
1988		1/0	---		---		---		---		---	
1989		1/1	---		---		---		---		---	
1990		1/1	---		---		---		---		---	
1991		1/1		0/0	---		---		---		---	
1992		1/1		0/0		1/1	---		---		---	
1993		4/2		0/0		0/0	---		---		---	
1994		1/1		1/0		1/1		0/0	---		---	
1995		2/2		0/0		0/0		0/0	---		---	
1996		0/0		1/2		0/0		0/0	---		---	
1997		0/0		2/1		1/1		1/1		1/1	---	
1998		1/2		2/1		2/2		0/0		4/4		0/0
1999		1/0		1/1		1/1		0/0		5/2		0/0
Total		14/11		7/5		6/6		1/1		10/7		0/0

(in thousands; add three 0's to each figure).

LF = Liver Failure, total cases. U = Liver failure, unconfounded cases.

A possible case of pravastatin-associated liver failure was reported in 1/2000.

Table 2 summarizes the estimated person-year of exposure and four-year (where applicable) reporting rates of liver failure (total and unconfounded) associated with the statins. In computing reporting rates we limited our analysis to domestic reports.

Table 2: Estimated Person-Years of Exposure with the Six Statins and 4-year Reporting Rate of Liver Failure with these drugs

Drug	Estimated Person-Years of Exposure (PYE)	4-Yr Liver Failure (total cases) Reporting Rate Per One Million PYE*	4-Year Liver Failure (unconfounded) Reporting Rate Per One Million PYE*
Lovastatin (1987-1990)			
Pravastatin (1991-1994)			
Simvastatin (1992-1995)			
Fluvastatin (1994-1997)			
Atorvastatin (1997-1999)			
Cerivastatin (1998-1999)			

\*Three years in the case of atorvastatin

The estimated four-year reporting rates of liver failure ranged from about \_\_\_\_\_ in both categories (total cases and nonconfounded). The highest reporting rate for liver failure was for lovastatin, and fluvastatin had the lowest rate. The FDA has not received any report of liver failure associated with the use of cerivastatin.

## Discussion

Spontaneous reporting systems are the most common method used in pharmacovigilance to generate signals on new or rare adverse events.<sup>1</sup> However, because of the problem of underreporting of adverse events, it is difficult to quantify the risks associated with a given drug on the basis of spontaneously reported data alone. It is estimated that the magnitude of underreporting varies from 1% to 10% but this is based on data that are more than a decade old. Spontaneously reported information is subject to influence of a number of biases that include the length of time a product has been on the market, country, reporting environment, detailing time, the quality of the data, and the effects of media.<sup>2,3,4</sup> In addition, it has been observed that the peak of spontaneous reporting of adverse events for a drug is at the end of the second year of marketing and reporting declines later (the Weber effect).<sup>5</sup>

Because of the limitations of spontaneously reported data as enumerated above, we focused our analysis to the first 4 years of marketing of the statins (where applicable) because reporting is generally more intense during the first few years of product launch. Our analysis was restricted to cases of liver failure reported from within the U.S.

A review of AERS identified 3, 1, 2, and 1 case(s) of liver failure associated with lovastatin, pravastatin, simvastatin, and fluvastatin respectively and the estimated four-year reporting rate of liver failure based on these cases were \_\_\_\_\_ respectively. The estimated three-year reporting rate of liver failure based on the 10 liver failure cases reported with atorvastatin

was \_\_\_\_ The estimated baseline rate of drug-related liver failure is approximately \_\_\_\_  
On this basis, there appears to be an increased risk of liver failure with the use of the statin drugs. Because of underreporting, the actual incidence rate for liver failure is probably much higher than shown here.

Spontaneous reporting systems are an excellent means to detect the occurrence of rare events, but are extremely inadequate when it comes to estimating incidence. Underreporting is extensive. As a result, incidence rates for liver failure are undoubtedly substantially greater than shown above.

### **Regulatory considerations**

Liver injury (hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and fulminant hepatic necrosis) is stated in the current labeling of all statins except atorvastatin which only mentions hepatitis. In controlled clinical trials marked increase in serum transaminases (> 3 times upper limit of normal) was observed in approximately 1% of patients who received these drugs. It is recommended in the labeling that liver function tests be performed before or after initiation of therapy and periodically with the different statins.

Statin are metabolized in the liver via the cytochrome P450 enzyme system and hence have the potential to interact with drugs which are metabolized by the same metabolic pathway. Atorvastatin, cerivastatin, lovastatin and simvastatin are all substrates of CYP3A4 and would be subject to marked inhibition of metabolism by azole antifungal agents (ketoconazole), macrolides (erythromycin), selective serotonin reuptake inhibitors (fluoxetine), cyclosporine, diltiazem and grapefruit juice. Fluvastatin is metabolized by CYP2C9 and therefore is not expected to interact with CYP3A4 inhibitors. Pravastatin is not significantly metabolized by CYP3A4.<sup>6</sup>

Statin are normally used on a long-term basis. In the non-controlled over-the-counter (OTC) environment, it is possible that these drugs will be used by individuals who are already on other medications. Given the fact that there is very little compliance with liver function test monitoring,<sup>7</sup> and this class of drugs have been associated with other potentially serious adverse events (including rhabdomyolysis), and have the potential to cause dangerous drug and drug-food (grapefruit) interactions, it is prudent to defer any decision on the OTC switch of these drugs.

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