

MEMORANDUM

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

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SUBJECT: OPDRA POSTMARKETING SAFETY REVIEW
Consult: HMG-CoA Reductase Inhibitors and Liver Failure
Drugs: Atorvastatin, Cerivastatin, Fluvastatin, Lovastatin, Pravastatin,
and Simvastatin

EXECUTIVE SUMMARY

This memorandum responds to a consult request from Mary Parks, M.D., Medical Officer in the Division of Endocrine and Metabolic Drug Products, regarding liver failure associated with atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin, known collectively as HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors or "statins". This concern was generated due to the desire of Merck Research Laboratories and Bristol Myers Squibb Company to seek nonprescription (over-the-counter, OTC) status for their drugs, despite regulatory guidance (see attachment, *Guidance for Industry: OTC Treatment of Hypercholesterolemia*, September 1997) that these cholesterol-lowering agents should not receive OTC designation.

For each of the aforementioned drugs, an AERS database search was undertaken using the MedDRA High Level Term (HLT), Hepatic failure and associated disorders, and Preferred Term (PT), Hepatic necrosis. A total number of 90 cases were found in AERS. Of the 90 cases found, 62 of them were in accordance with our case definition of liver failure associated with HMG-CoA reductase inhibitor administration. More than half of the 62 patients expired. A significant concern does exist given that liver transplants, and in many instances irreversible and fatal hepatic damage have occurred. The labeling in the package inserts does not currently list liver failure as an adverse reaction to HMG-CoA reductase inhibitor administration. Based on our findings and the severity of liver failure as a clinical diagnosis itself, we recommend that liver failure be included as an adverse event in the labeling of package inserts for this class of cholesterol-lowering agents.

In addition to the analysis presented in this document, an OPDRA epidemiologist also reviewed the AERS data to accomplish two objectives: 1) compare the reported rates of liver failure

among HMG-CoA reductase inhibitors and 2) compare the reporting rates versus the background rates of liver failure. The complete epidemiologic analysis is presented as an attached companion document.

BACKGROUND

This memorandum responds to a consult request from Mary Parks, M.D., Medical Officer in the Division of Endocrine and Metabolic Drug Products, regarding liver failure associated with the HMG-CoA reductase inhibitors. This interest arose from safety concerns regarding particular drugs of this class if they are granted OTC status. Certain pharmaceutical companies have requested a meeting with the Agency to discuss the possibility of nonprescription designation for its HMG-CoA reductase inhibitors, despite reservations from the Agency about the marketing of cholesterol-lowering agents in the OTC setting.

LABELING

Please see attachments 2-7 for labeling (*Warning and Adverse Reactions*) on each of the HMG-CoA reductase inhibitors. None of the product labeling mentions the possibility of liver failure.

METHODS AND RESULTS

Case Criteria

For the purposes of this consult, cases were defined as "liver failure" if the reporter stated a diagnosis of liver failure or if the patient underwent a liver transplantation. Exceptions to this definition were cases that were reported by a consumer in which no confirmatory information was provided in the case. Cases were further reviewed for the presence of confounding factors, defined as follows: (1) serologic markers for current infection with hepatitis A or B, or (2) other causes of liver necrosis such as acute hepatic insult, e.g., shock or sepsis; evidence of chronic liver disease, e.g., cirrhosis; or other drugs considered to be hepatotoxins.

The cases of hepatic failure were further categorized as liver failure with or without transplant. If a patient suffered from hepatic damage resulting in a transplant, the incident was classified as liver failure by default.

Selection of Cases

An AERS database search was undertaken to determine the number of potential cases of HMG-CoA reductase inhibitor-induced liver failure using the following MedDRA High Level Term (HLT), Hepatic failure and associated disorders, and the Preferred Term (PT), Hepatic necrosis. The time period for report extraction is from marketing of these agents until February 25, 2000 for each of the HMG-CoA reductase inhibitors.

Summary of Cases

A total number of 90 unduplicated cases of potential liver failure induced by HMG-CoA reductase inhibitors was found in AERS. The number of cases of hepatic failure for each of the

agents is parsed out below:

<u>Drug</u>	<u>No. of possible cases</u>	<u>No. of liver failure cases</u>
Atorvastatin	15	13
Cerivastatin	4	3
Fluvastatin	4	3
Lovastatin	25	18
Pravastatin	20	13
Simvastatin	22	12
Total	90	62

Of the 90 cases found in AERS, only 62 of them are in accordance with the case definition of liver failure associated with the use of HMG-CoA reductase inhibitors. The remaining 28 cases were not included in this consult as the patients were diagnosed with hepatocellular carcinoma, rhabdomyolysis, cholestatic jaundice, hepatitis, or gallstones.

ATORVASTATIN

Liver failure cases (n=13)		
Unconfounded cases (n=8)		
	Foreign	Domestic
Liver failure-all	3 (1)	10 (7)
Liver transplant	0	1 (0)
Fatal	3 (1)	6 (5)
Nonfatal	0	3 (2)

For the table above and the subsequent ones for the other five HMG-CoA reductase inhibitors, the numbers in parentheses under the subheadings of liver failure indicated how many cases did not have confounding factors (“unconfounded”) for the diagnosis of liver failure. Liver failure reporting rates will be calculated for all and unconfounded cases in the epidemiologist’s analysis.

Sixteen unduplicated cases were retrieved from AERS using the aforementioned search strategy. Of the sixteen cases, only 13 cases were in agreement with the case definition of liver failure as the final outcome of atorvastatin-induced hepatotoxicity. Of the 13 cases, three of them were foreign reports and the remaining ten were domestic. All three patients in the foreign cases expired. Patients in two of these cases had a background of alcoholism as a possible contributory factor to the liver failure. The demographics of these cases are presented below.

Of the ten domestic cases reported, six were fatal. Three of the ten cases were confounded by other drugs which may have contributed the liver failure. In one case, the patient underwent a liver transplant following liver failure from the administration of troglitazone and atorvastatin. In another case that resulted in death, the patient was receiving cyclosporine and gabapentin concomitantly with atorvastatin. No liver enzyme levels were stated in the narrative. In the third case, the patient was taking terbinafine concomitantly with atorvastatin before he went into liver failure.

The demographics of these cases and two index narratives are presented below.

DEMOGRAPHIC DATA

N=13

AGE: range 21-82 years (median 62; mean 64)
SEX: M (4), F(9)
REACTION ONSET (DAYS), n=11: 21-1466 days (median 333, mean 381)
DOSE PER DAY (MG), n=10: 10 (3), 20 (6), 40 (1)
ROUTE: PO
OUTCOME: Dead (8); Alive (4); Transplant, nonfatal (1)

ISR #3072218-4-00, United States

A 72 year old female patient began taking atorvastatin 10 mg daily approximately in Spring 1997 for hyperlipidemia. She was seen by her physician on Sept. 15, 1997 and was determined to be "healthy." On April 9, 1998, the patient returned to her physician jaundiced, but with no fever and eating well. Atorvastatin was discontinued and she was subsequently hospitalized later that day for obstructive jaundice. Liver function tests revealed a bilirubin of 31.6 mg/dl, AST 2210 IU/L, ALT 1080 IU/L. On April 10, 1998, an ultrasound of the gallbladder and a computed tomography (CT) scan of the abdomen revealed no abnormalities, and a hepatitis screen was negative. On April 15, 1998, a liver biopsy revealed "necrosis with unnecrosed cells demonstrating swelling and edema." Reportedly, no improvement was seen in the patient's liver function. Her medical history was remarkable for a stroke at 40 years of age. This might have been secondary to birth control pills. Concomitant medications included a fiber laxative and aspirin.

ISR #3005384-7-00, United States

A 68 year-old female began antihyperlipidemic therapy in Summer 1997 with atorvastatin. She was also receiving oxaprozin for osteoarthritis and atenolol for hypertension. Because of the nausea she was experiencing, she discontinued atorvastatin in late September 1997. On October 6, 1997, she was seen by her primary care provider for sinusitis, with no icterus evident. Total bilirubin was measured at 3.3 mg/dl. About two weeks thereafter, she presented to her physician again with complaints of malaise, weakness, fatigue, and weight loss over a 2-4 week period. During this time, she was noted to be icteric. She was admitted to a local hospital for further work-up and was subsequently transferred to another one. Her liver enzyme panel peaked with a total bilirubin 9.4 mg/dl, AST ~1500 IU/L, and ALT ~2000 IU/L on October 21, 1997. Her condition worsened to a stage IV encephalopathy and progressively deteriorated to fulminant hepatic failure. She expired on November 15, 1997.

CERIVASTATIN

Liver failure cases (n=3)		
Unconfounded cases (n=3)		
	Foreign	Domestic
Liver failure-all	3 (3)	0 (0)
Liver transplant	0	0
Fatal	1 (1)	0
Nonfatal	2 (2)	0

Four unduplicated cases were retrieved from AERS using the aforementioned search strategy, of which three met the case definition of liver failure as the final outcome. No domestic cases of liver failure were reported. One fatality occurred.

The demographics of these cases are presented below. Due to insufficient information provided in the cases, only one foreign narrative is documented.

DEMOGRAPHIC DATA

N=3
 AGE: range 49-65 years (median 60, mean 58)
 SEX: M (2), F(1)
 REACTION ONSET (DAYS): not available
 DOSE PER DAY (MG), n=1: 0.3 mg
 ROUTE: PO
 OUTCOME: Dead (1), Alive (2)

ISR #3358045-9-00-01, France

A 49 year old male started treatment with cerivastatin on December 1998. On May 22, 1999, the patient presented with liver dysfunction, thrombocytopenia, and asthenia. Labs at time of presentation included an ALT of 68 IU/L, AST 132 IU/L, total bilirubin 201 µmol/l, alkaline phosphatase 233 IU/L, creatine kinase 382 U/L, and platelet count 38,000/mm³. Patient also had a background history of alcohol abuse consisting of “four pints of beer and two drinks a day”. Follow-up on June 23, 1999 revealed “liver biology and platelet count unchanged.” The patient died on August 7, 1999 of liver failure, as stated per reporter.

FLUVASTATIN

Liver failure cases (n=3) Unconfounded cases (n=3)		
	Foreign	Domestic
Liver failure-all	2 (2)	1 (1)
Liver transplant	0	0
Fatal	2 (2)	1 (1)
Nonfatal	0	0

Of the four unduplicated cases retrieved from AERS using the aforementioned search strategy, three of them described liver failure as the outcome associated with fluvastatin use. Two cases were foreign reports; both succumbed to death from liver failure in these cases.

The demographics of these cases and two narratives are presented below.

DEMOGRAPHIC DATA

N=3
 AGE: range 63-70 years (median 67; mean 70)
 SEX: M (0), F(3)
 REACTION ONSET (DAYS) not available
 DOSE PER DAY (MG), n=1: 20
 ROUTE: PO
 OUTCOME: Dead (2), Alive (1)

ISR #314909-9-00-01, United States

A 66 year old female developed acute liver failure after two months of treatment on fluvastatin 20 mg daily on October 1996. All liver function enzymes were normal at the time she initiated therapy. On December 10, 1996, she was seen in the office ten days prior to admission complaining of dark urine, but no fever or chills, dysuria, nausea, vomiting, or abdominal pain. Lab studies revealed a markedly elevated liver enzymes at this time. Repeat labs revealed a bilirubin of 7.3 mg/dl, AST 950 IU/L and ALT 1009 IU/L. The patient had a medical history of insulin-dependent diabetes and thrombocytopenia, in addition to her hyperlipidemia. Subsequently, she was hospitalized and the attending physician determined her hepatitis to be drug-induced. Her hepatitis panel was negative. Another differential diagnosis of lupus erythematosus was also ruled out by negative serology. Fluvastatin was then discontinued. She also had high serum iron levels, which were thought to be caused by hematochromatosis, but magnetic resonance imaging (MRI) disproved this observation. The patient was hospitalized and placed on prednisone. Liver biopsy was not conducted secondary to prolonged thromboplastin time. With continual improvement in her liver function, she was discharged to home. Three to four months later, repeat blood tests showed normalized levels of her liver enzymes.

ISR #3385635-X-00-01, Japan

A 63 year old female experienced malaise 11 days after starting treatment with fluvastatin. She was hospitalized after her liver function tests revealed acute hepatitis. Peak AST was 1850 IU/L, ALT 2340 IU/L, and total bilirubin 7.6 mg/dl. Echography of the liver demonstrated marked liver atrophy. The patient had persistent ascites, jaundice, and asterixis throughout her hospital course. Her condition worsened with encephalopathy and pneumonia, and finally she succumbed to death one month later. The cause of death was reported as "liver atrophy following liver deficiency."

LOVASTATIN

Liver failure cases (n=18)		
Unconfounded cases (n=15)		
	Foreign	Domestic
Liver failure-all	4 (4)	14 (11)
Liver transplant, nonfatal	1 (1)	0
Liver transplant, fatal	1 (1)	0
Fatal	1 (1)	7 (5)
Nonfatal	1 (1)	7 (6)

From AERS using the aforementioned search strategy, 25 non-duplicated cases were retrieved and 18 of them described liver failure associated with lovastatin use. Four of the cases found in AERS were foreign, 14 domestic. Of the four foreign cases reported, two patients received liver transplants following irreversible hepatic damage, one survived.

Pertaining to the 14 domestic cases, seven were fatal. Three of the 14 cases had confounding factors. One patient experienced liver failure while taking atorvastatin concomitantly with acetaminophen and niacin. Another patient experienced a drug interaction consisting of lovastatin and ketoconazole which led to death, despite a liver transplant. The last case consisted of a patient who had a cardiac arrest following attempted exploratory laparotomy to rule out acalculus cholecystitis versus occult intra-abdominal sepsis. Autopsy revealed hepatomegaly with prominent granulomatous hepatitis of unknown etiology and moderate fatty changes of the liver.

The demographics of these cases and two index narratives are presented below.

DEMOGRAPHIC DATA

N=18	
AGE:	range 28-77 years (median 63; mean 61)
SEX:	M (6), F (10), Unk (2)
REACTION ONSET (DAYS), n=12:	14-2190 days (median 210; mean 398)
DOSE PER DAY (MG), n=12:	20 (9), 40 (3)
ROUTE:	PO
OUTCOME:	Dead (8); Alive (8); Transplant, nonfatal (1), fatal (1)

ISR #749543, United States

A 73 year-old male was placed on lovastatin therapy in April 1989 to manage his hypercholesterolemia. His medical history included pancreatitis, nephrosclerosis, arteriosclerotic disease, hypertension, and angina pectoris. His concomitant medications were furosemide, multivitamins, propranolol, and diltiazem. In April 1990 he was hospitalized for right middle lobe pneumonia. He was placed on antibiotics and improved, but on May 24, 1990, he progressively became weaker and fatigued. In addition, he had malaise, palpitations, vitiligo of the arms, severe inanition, and cough. On May 31, 1990, he developed a fever of 100.8°F and confusion. He became jaundiced and was rehospitalized on June 6, 1990. During his hospitalization, his total serum bilirubin peaked at 17.5mg/dl, AST 304 IU/L, ALT 224 IU/L. An abdominal CT scan did not reveal any common bile duct or hepatic obstruction, hepatomegaly or extrinsic compression of the biliary tract. All viral hepatitis serologies were negative. Infectious disease specialists felt that the patient's progressive hepatic failure and renal failure with pancytopenia were of unclear etiology. *Leptospirosis*, *Brucella*, and *Legionella* serologies were negative. The patient's condition worsened to multisystem organ failure of unknown etiology. By June 23, 1990, the patient had no urine output of significance, most likely representing hepatorenal syndrome. He developed hypoxemia and difficulty with ventilation, which required intubation, and mechanical ventilation on June 24, 1990. He remained in a comatose state until he expired on June 26, 1990. An autopsy showed hepatomegaly with massive hepatic necrosis, in addition to atherosclerotic heart disease involving the right and left coronary arteries, pulmonary edema, superficial colonic ulcerations, chronic pancreatitis, peripancreatic adenopathy, and arterial and arteriolar nephrosclerosis bilaterally.

ISR #3109077-7-00, United States

A 75 year-old male initiated therapy with lovastatin 20 mg daily on May 1992 for treatment of his hypercholesterolemia. The patient was also receiving metoprolol simultaneously and received the influenza vaccine on November 16, 1992. His medical history also included an enlarged prostate with nocturia. He consumed alcohol on occasion and was physically fit. Around mid to late December 1992, he developed malaise, nausea, jaundice, dark urine, lighter stools than usual, and chills in the evening with no pain, fever, or pruritis. The patient noted that symptoms may have started earlier in the fall. Lovastatin was discontinued on December 30, 1992 and he was subsequently diagnosed with hepatitis the following day. He had traveled to Denver, Colorado recently during a hepatitis A outbreak, but had no clear exposure to either hepatitis A or B. Labs revealed an AST 1497 IU/L, ALT 2321 IU/L, and a total bilirubin 6.2 mg/dl. He was hospitalized on February 1, 1993 after a 10-12 lb weight loss. An HIV test was ordered and results showed "confusing results". Abdominal ultrasound was normal except for a gallstone. His condition then deteriorated from subfulminant to fulminant hepatic failure complicated by renal failure. A liver biopsy on February 9, 1993 showed "submassive collapse with little evidence of regenerative activity and no etiologic clues." Patient died of liver failure on February 13, 1993. Autopsy demonstrated jaundice and ascites and confirmed massive and submassive hepatic necrosis with no definitive etiology.

PRAVASTATIN

Liver failure cases (n=13) Unconfounded cases (n=10)		
	Foreign	Domestic
Liver failure-all	5 (5)	8 (5)
Liver transplant, nonfatal	1 (1)	0
Fatal	3 (3)	5 (3)
Nonfatal	1 (1)	3 (2)

Twenty cases were retrieved from AERS using the aforementioned search strategy. Of the 20 cases, 13 reports were in agreement with the case definition of hepatic failure associated with pravastatin use. Five foreign cases were reported, three fatal and two nonfatal. In one of the nonfatal hepatic failure cases, the patient received a liver transplant.

Eight domestic cases were reported, five of them resulting in death. Three of the eight cases had confounders which may have also contributed to the liver failure. Two complicated cases listed thiazolidinedione antidiabetic agents (troglitazone and rosiglitazone) as a concomitant medication, thus making the association of liver failure and pravastatin indeterminate. Another case of fatal liver failure mentioned possible acetaminophen toxicity.

The demographics of these cases and two case histories are presented below.

DEMOGRAPHIC DATA

N=13

AGE: range 21-81 years (median 62; mean 64)
SEX: M (4), F (9)
REACTION ONSET (DAYS), n=8: 21-1466 days (median 333, mean 381)
DOSE PER DAY (MG), n=10: 10 (3), 20 (6), 40 (1)
ROUTE: PO
OUTCOME: Died (8), Alive (4), Transplant, nonfatal (1)

ISR #2044333, United States

A 62 year-old female began pravastatin therapy for hypercholesterolemia on December 26, 1995. The patient had a background history of coronary artery disease, hypertension, hiatal hernia with gastroesophageal reflux disease, type II diabetes mellitus, depression, osteoarthritis, and gallstones. Treatment for these medical conditions included ticlopidine, conjugated estrogens, chlorpheniramine, acetaminophen, furosemide, atenolol, nizatidine, trazodone, and diltiazem. One month after initiation of therapy, she developed jaundice and subsequently discontinued all her medications. Hepatitis serology, cytomegalovirus testing, and IgM titer were all negative. IgG titer was positive. On January 30, 1996, the patient was admitted for hospitalization. The patient's bilirubin had risen to a high of 20 mg/dl, AST 81 IU/L, and ALT 549 IU/L, with symptoms such as severe jaundice and pruritis evident. Liver biopsy results showed "marked inflammatory infiltration associated with widespread fibrosis, bile duct and ductular proliferation." In addition, spotty hepatocellular necrosis and reactive hepatocellular changes were noted. Liver impairment worsened over the next two weeks, progressing from hepatic encephalopathy to coma, then eventually death. The patient refused a liver transplant, and thus, only comfort care was provided. She died on February 21, 1996, secondary to liver failure while taking pravastatin.

ISR #186726, United States

A 68 year-old male started on anti-hyperlipidemic therapy on February, 1995, consisting of pravastatin 20 mg daily. The patient also had a history of congestive heart failure. In addition to pravastatin, the patient was on long-term therapy with digoxin and theophylline. These three medications were given concomitantly for about ten months with no reported problems. On November 16, 1995, the patient started on prednisone for *bronchiolitis obliterans* and cimetidine for peptic ulcer disease. Acetaminophen with oxycodone was also initiated at that time. On November 25, 1995, the patient was admitted to the hospital for abdominal pains that persisted for three weeks. Liver function tests done at baseline were normal, but now were elevated, with a bilirubin of 20.1 mg/dl, AST 1324 IU/L, and ALT 960 IU/L on November 25, 1995. Toxicology, *Leptospira*, enteroviral, and hepatitis screen were all negative. Progressively worsening, the patient expired five days later on December 6, 1995. Autopsy findings showed fulminant hepatic failure with extensive non-inflammatory hepatocellular necrosis probably secondary to an idiosyncratic reaction to pravastatin.

SIMVASTATIN

Liver failure cases (n=12) Unconfounded cases (n=12)		
	Foreign	Domestic
Liver failure-all	6 (6)	6 (6)
Liver transplant, nonfatal	0	1 (1)
Fatal	6 (6)	4 (4)
Nonfatal	0	1 (1)

Twenty-two cases were retrieved from AERS using the aforementioned search strategy. Of the 22 cases that were found, 12 of them met the definition of liver failure associated with simvastatin use. All of the foreign cases reported death as the outcome.

Regarding the six cases that occurred in the U.S., four of them resulted in death, though one patient survived liver failure following a transplant.

The demographics of these cases and two representative narratives are presented below.

DEMOGRAPHIC DATA

N=12

AGE: range 45-79 (median 65 years; mean 63 years)
SEX: M (3), F (8), Unk (1)
REACTION ONSET (DAYS), n=9: 7-1311 days (median 308, mean 144)
DOSE PER DAY (MG), n=8: 5 (1), 10 (3), 20 (2), 30 (1), 40 (1)
ROUTE: PO
OUTCOME: Died (10), Alive (1), Transplant, nonfatal (1)

ISR #3286623-4-00-01, United States

A 77 year-old male was placed on simvastatin on February 1999 for treatment of hypercholesterolemia. Concomitant medication included aspirin. Two months later on April 12, 1999, routine liver function tests were elevated with an AST of 780 IU/L, ALT 734 IU/L, and bilirubin 21.2 mg/dl. His medications were discontinued. The patient then began to notice jaundice, darker urine, lighter stools, and abdominal discomfort. Subsequently, he was hospitalized. Liver enzyme levels started to improve slightly. Symptomatically, he experienced nausea, vomiting, anorexia, confusion, lethargy, and became unresponsive. A liver biopsy from June 1, 1999 showed 50% centrilobular hepatic necrosis with no underlying cirrhosis and cholestasis with polymorphonuclear infiltrates. Biopsy was suggestive of a drug reaction. On June 4, 1999, the patient died of fulminant liver failure.

ISR #1343734, Japan

A 79 year-old with angina, hypertension, and ischemic heart disease was placed on therapy with simvastatin 20 mg daily on October 1992 for treatment of hypercholesterolemia. Concomitant medications included nifedipine, atenolol, aspirin, isosorbide dinitrate and glyceryl trinitrate (topical ointment). On October 8, 1993, the patient experienced fulminant hepatitis, with an AST 705 IU/L, and ALT 1450 IU/L. Simvastatin therapy was discontinued on October 20, 1993 and

the patient subsequently died. The cause of death was hepatitis. A liver biopsy revealed severe hepatitis with lobular and portal activity progressing toward necrosis.

LITERATURE SEARCH

A literature search on hepatotoxicity and HMG-CoA reductase inhibitors revealed a small number of cases in which the patients suffered from drug-induced hepatitis or liver failure. In the various studies, the range of patients having a diagnosis of hepatitis or liver failure was 0.4-5%.¹⁻⁴ The total number of patients treated with atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin in these studies was 5,479. Only one fatal case of liver failure, while a patient was receiving lovastatin, was reported.⁴ Though the case was suggestive of drug-induced toxicity, the patient had a history of non-A/non-B hepatitis.

DISCUSSION

A total of 90 cases of potential liver failure induced by HMG-CoA reductase inhibitors were found in AERS. Of the 90 cases that were reported, 62 (69%) cases were in concordance with the case definition of liver failure. In the subset of the 62 cases, 38 (61%) cases resulted in death. Six patients received liver transplants following a diagnosis of fulminant liver failure. Five of the six transplant patients survived.

Most of the literature describe asymptomatic elevations in liver function tests secondary to statin administration.⁵⁻¹⁵ One possible explanation for this observation is the inherent controlled environment of clinical studies. In clinical trials, patients underwent frequent and close monitoring of their liver enzymes and had their statin discontinued or suspended if transaminase elevations occurred. Another reason may be the natural underreporting of this occurrence in the literature. Despite the underreporting of cases in the literature, the cases of liver failure associated with the use of HMG-CoA reductase inhibitors, as documented by AERS, underscore the seriousness of the issue.

Upon reviewing the package inserts for each of the HMG-CoA reductase inhibitors, no description of the occurrence of liver failure was evident anywhere in the labeling, although all describe liver dysfunction in both the "Warning" and "Adverse Reactions" sections (see attachments 2-7).

In addition to the analysis presented in this document, an epidemiologist also reviewed the AERS data to accomplish two objectives: 1) compare the reported rates of liver failure among HMG-CoA reductase inhibitors and 2) compare the reporting rates versus the background rates of liver failure. The full epidemiologic analysis is presented in an attached companion document.

CONCLUSION

This document describes the cases of liver failure associated with HMG-CoA reductase inhibitors. A significant concern does exist on this issue given that liver transplants, and in many instances, irreversible and fatal hepatic damage, have occurred. Of the liver failure cases, more than 50% of the patients expired while on lipid-lowering therapy consisting of an HMG-CoA reductase inhibitor. Despite this fatal consequence, the labeling in package inserts does not mention liver failure as an adverse reaction to HMG-CoA reductase inhibitor administration. In

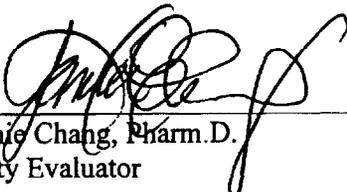
addition, OPDRA's epidemiologist's analysis indicated that the reporting rate of liver failure for the HMG-CoA reductase inhibitors exceeds the background rate for liver failure. As evident by our discussion on this issue and the severity of liver failure as a clinical diagnosis itself, we recommend that liver failure be included as an adverse event in the labeling of package inserts for these cholesterol-lowering agents.

REFERENCES

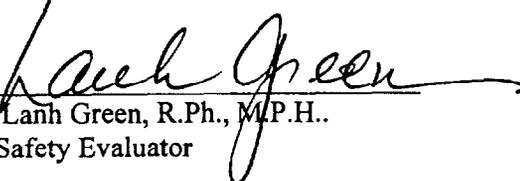
1. Ballare M, Campanini M, Airoidi G, et al. Hepatotoxicity of hydroxy-methyl-glutaryl-conenzyme A reductase inhibitors. *Minerva Gastroenterol Dietol* 1992;38:41-4.
2. Jacotot B, Banga JD, Waite R, Peters TK. Long-term efficacy with fluvastatin as monotherapy and combined with cholestyramine (a 156-week multi-center study). *Am J Cardiol* 1995;76:41A-46A.
3. Black DM, Bakker-Arkerma RG, Nawrocki JW. An overview of the clinical safety profile of atorvastatin (Lipitor), a new HMG-CoA reductase inhibitor. *Arch Intern Med*. 1998;158:577-84.
4. Tobert JA, Shear CL, Chremos AN, Mantell GE. Clinical experience with lovastatin. *Am J Cardiol* 1990;65:23F-26F.
5. Boccuzzi SJ, Bocanegra TS, Walker JF, et al. Long-term safety and efficacy profile of simvastatin. *Am J Cardiol* 1991;68:1127-31.
6. Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;156:2085-92.
7. Betteridge DJ. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolaemia. International Cerivastatin Study Group. *Int J Clin Pract* 1999;53:243-50.
8. Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 300 micrograms and 400 micrograms cerivastatin once daily in patients with primary hypercholesterolaemia: a multicentre, randomized, double-blind, placebo-controlled study. *J Int Med Res* 1999;27:115-29. Stein E. Cerivastatin in primary hyperlipidemia—a multicenter analysis of efficacy and safety. *Atherosclerosis* 1998;139:S15-22.
9. Farnier M. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT study. The Cerivastatin Study Group. Cerivastatin Gemfibrozil Hyperlipidemia Treatment. *Am J Cardiol* 1998;82:47J-51J.
10. Davidson MH. Fluvastatin long-term extension trial (FLUENT): Summary of efficacy and safety. *Am J Med* 1994;96:21S-44S.
11. Peters TK. Safety profile of fluvastatin. *Br J Clin Pract Suppl* 1996;77A:20-3.
12. Molgaard J, Lundh BL, von Schenck H, et al. Long-term efficacy and safety of simvastatin alone and in combination therapy in treatment of hypercholesterolaemia. *Atherosclerosis*

1991;91 Suppl:S21-8.

13. Hunninghake DB, Mellies MJ, Goldberg AC, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. II. Once-daily versus twice-daily dosing. *Atherosclerosis* 1990;85:219-27.
14. Hunninghake DB, Knopp RH, Schonfeld G, et al. Efficacy and safety of pravastatin in patients with primary hypercholesterolemia. I. A dose-response study. *Atherosclerosis* 1990;85:81-9.
15. Lambrecht LF, Malini PL. Efficacy and tolerability of simvastatin 20 mg vs pravastatin 20 mg in patients with primary hypercholesterolemia. European Study Group. *Acta Cardiol* 1993;48:541-54.



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HFD-400

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HFD-440

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HFD-002

Lumpkin

ATTACHMENT 1

Guidance for Industry

OTC Treatment of Hypercholesterolemia

Additional copies are available from:

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U.S. Department of Health and Human Services
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Cltn 5

GUIDANCE FOR INDUSTRY¹

OTC Treatment of Hypercholesterolemia

I. INTRODUCTION

Recent interest expressed in marketing cholesterol-lowering agents as over-the-counter (OTC) drug products has raised several regulatory policy and medical therapy issues. Because of the interest in this subject on the part of individuals, professional groups, and drug manufacturers, the Center for Drug Evaluation and Research (CDER) has decided to state publicly its current view on this matter.

II. DISCUSSION

OTC drugs generally are used for self-recognizable conditions that are symptomatic, require treatment of short duration, and can be treated without the oversight and intervention of a health care practitioner.

Hypercholesterolemia, in contrast, is a chronic, unremitting, asymptomatic condition with life-threatening consequences that can be reduced by some interventions. Based on the available evidence reviewed at a May 13, 1997, meeting of an advisory committee involving the Non-Prescription Drugs Advisory Committee and the Endocrine and Metabolic Drugs Advisory Committee, the advisory committee concluded that the treatment of hypercholesterolemia requires both (a) accurate diagnosis and clinical testing and (b) careful health care practitioner-directed medical management, including the choice of appropriate drug(s) for the individual patient based on the patient's specific clinical condition. Because of this conclusion, the advisory committee recommended, in general, that drug treatments for hypercholesterolemia not be sold OTC in the United States.

At this time, CDER concurs with the conclusion of the advisory committee. It is CDER's view that (a) health care practitioner supervision in the diagnosis and ongoing management of hypercholesterolemia is essential for safe and effective use of drug products to treat this condition and (b) this supervision is assured within the context of prescription access to the appropriate drug(s) for the individual patient. CDER therefore believes that drugs for the treatment of hypercholesterolemia should not be sold OTC in the United States.

¹This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on the OTC treatment of hypercholesterolemia. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both.

ATTACHMENT 2

Lipitor

WARNINGS

Liver Dysfunction: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended.

Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS).

ADVERSE REACTIONS

Digestive System: Nausea, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice.

ATTACHMENT 3

Baycol

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. Persistent increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal (occurring on two or more not necessarily sequential occasions, regardless of baseline status) have been reported in less than 0.5% of patients treated with cerivastatin sodium in the US over an average period of 14 months. The incidence of these abnormalities was 0.2%, 0.3%, and 0.4% for BAYCOL® 0.2, 0.3, and 0.4 mg, respectively. These abnormalities usually occurred within the first 6 months of treatment, usually resolved after discontinuation of the drug, and were not associated with cholestasis. In most cases, these biochemical abnormalities were asymptomatic.

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 in 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 cerivastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of BAYCOL® (cerivastatin sodium tablets) (see **CONTRAINDICATIONS**). Caution should be exercised when cerivastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY : Pharmacokinetics / Metabolism**). Such patients should be started at the low end of the recommended dosing range and closely monitored.

ADVERSE REACTIONS

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

ATTACHMENT 4

Lescol

WARNINGS

Liver Enzymes: Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. A small number of patients treated with Lescol® (fluvastatin sodium) in worldwide controlled trials (N=25, 1.1%) developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

In a pooled analysis of all Lescol® (fluvastatin sodium) placebo-controlled studies persistent transaminase elevations (>3 times the upper limit of normal [ULN] on two consecutive weekly measurements) occurred in 0.2%, 1.5%, and 2.7% of patients treated with 20, 40, and 80 mg (40 mg b.i.d.) Lescol® (fluvastatin sodium), respectively. Ninety-one percent of the cases of persistent liver function test abnormalities (20 of 22 patients) occurred within 12 weeks of therapy and in all patients with persistent liver function test abnormalities there was an abnormal liver function test present at baseline or by week 8.

It is recommended that liver function tests be performed before initiation of therapy and at 12 weeks following initiation of treatment or elevation in dose. Patients who develop transaminase elevations or signs and symptoms of liver disease should be monitored to confirm the finding and should be followed thereafter with frequent liver function tests until the levels return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist (found on two consecutive occasions), withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol® (fluvastatin sodium) (see CONTRAINDICATIONS). Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored.

ADVERSE REACTIONS

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

ATTACHMENT 5

Mevacor

WARNINGS

Liver Dysfunction: Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS). In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

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 MEVACOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

ADVERSE REACTIONS

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

ATTACHMENT 7

Zocor

WARNINGS

Liver Dysfunction: Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical trials. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In 4S (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, only 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and periodically thereafter (e.g., semiannually) for the first year of treatment or until one year after the last elevation in dose. Patients titrated to the 80-mg dose should receive an additional test at 3 months. 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 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended. The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

ADVERSE REACTIONS

Gastrointestinal: Pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.