Appendix B

Table 5.0 Deaths (Page 1 of 3)

Case #	Country	Origin	Cause Of Death
HEPATO-BILIARY DISORDERS			
M055257	United States	Spontaneous report	Fulminant Drug Induced, Hepatic Necrosis
M055540	United States	Spontaneous report	Hepatic Failure
M074549	United States	Spontaneous report	Liver Failure
M078251	United States	Spontaneous report	Liver Failure
B034237	Germany	Spontaneous report	Hepatic Coma
B044052	Great Britain	Spontaneous report	Cerebral Edema, Hepatorenal Failure, Hepatic Necrosis
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS			
M032103	United States	Spontaneous report	Muscle Weakness
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
B039832	Japan	Spontaneous report	Reactive Hemophagocytotic Syndrome
CARDIAC DISORDERS			
M027048	United States	Spontaneous report	Congestive Heart Failure
M054999	United States	Spontaneous report	Massive Heart Attack
M078780	United States	Spontaneous report	Junctional Bradycardia, Acute Renal Failure, Cardiac Arrest
B007592	France	Phase IV report	Myocardial Infarct Nos
B022493	Belgium	Spontaneous report	Myocardial Infarction
B022651	China	Spontaneous report	Subvalvular Aortic Stenosis
B023217	Belgium	Spontaneous report	Myocardial Infarction, Heart Failure, Mesenteric Infarction
B023218	Belgium	Spontaneous report	Myocardial Infarction
B026805	Great Britain	Spontaneous report	Myocardial Infarction
B027120	Germany	Phase IV report	Cardiogenic Shock, Myocardial Infarction
B027158	Canada	Spontaneous report	Heart Failure
B031907	Japan	Spontaneous report	Renal Failure, Heart Failure
B036596	Italy	Phase IV report	Heart Arrest
B042920	France	Spontaneous report	Cardio-Respiratory Arrest
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
B009359	Portugal	Spontaneous report	Sudden Death
B012190	France	Phase IV report	Sudden Death
GASTROINTESTINAL DISORDERS			
M025584	United States	Spontaneous report	Hemorrhagic Pancreatitis
M026150	United States	Spontaneous report	Multiorgan Failure, Sepsis, Necrotizing Pancreatitis
B027145	Austria	Spontaneous report	Hematemsis, Gastrointestinal Bleeding

Table 5.0 Deaths (Page 2 of 3)

Case #	Country	Origin	Cause Of Death
INJURY AND POISONING			
B008403	Great Britain	Spontaneous report	Injury Nos
METABOLISM AND NUTRITIONAL DISORDERS			
M047449	United States	Spontaneous report	Shock, Acidosis, Respiratory Insufficiency
B015654	Japan	Spontaneous report	Hyperkalemia, Cardiac Failure Aggravated
NEOPLASMS BENIGN AND MALIGNANT			
M026486	United States	Spontaneous report	Metastatic Disease
B022734	Sweden	Phase IV report	Uterine Carcinoma
B025582	Sweden	Phase IV report	Pancreatic Cancer
RENAL AND URINARY DISORDERS			
M042285	United States	Spontaneous report	Hepatorenal Failure
B035960	Japan	Spontaneous report	Renal Failure, Rhabdomyolysis
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
B007485	France	Phase IV report	Acute Lung Edema
B019034	Belgium	Spontaneous report	Respiratory Insufficiency
B019117	China	Phase IV report	Pneumococcal Infection Nos
VASCULAR DISORDERS			
B017160	Germany	Spontaneous report	Circulatory Failure, Cerebral Edema
B019723	Sweden	Phase IV report	Thromboembolism
B022173	Australia	Phase IV report	Stroke
B029367	Great Britain	Spontaneous report	Cardiac, Tampanade, Hypoxic, Brain Damage, Renal Failure
B022767	Belgium	Spontaneous report	Embolus
B026596	France	Spontaneous report	Septic Shock
B043380	France	Spontaneous report	Aortic Dissection
MULTI-ORGAN FAILURE			
M078777	United States	Spontaneous report	Multisystem Organ Failure
B041542	Japan	Spontaneous report	Multiple Organ Failure, Sepsis, Cholecystitis
CAUSE OF DEATH NOT REPORTED			
M027532	United States	Spontaneous report	
M031451	United States	Spontaneous report	
M034994	United States	Phase IV report	
M036469	United States	Spontaneous report	
M047272	United States	Spontaneous report	
M062128	United States	Spontaneous report	

Table 5.0 Deaths (Page 3 of 3)

Case #	Country	Origin	Cause Of Death
M062223	United States	Spontaneous report	
M070944	United States	Spontaneous report	
M081010	United States	Spontaneus report	
M082307	United States	Literature report	
M090294	United States	Phase IV report	
10009074	France	Spontaneous report	
B011696	Sweden	Phase IV report	
B013293	France	Phase IV report	
B018636	Japan	Spontaneous report	
B020117	Germany	Phase IV report	
B020875	Belgium	Spontaneous report	
B026451	France	Phase IV report	
B027531	France	Spontaneous report	
B037646	Italy	Phase IV report	
B039092	Netherlands	Phase IV report	

5.1 Hepato-Biliary Disorders

M055257/US, reported by a pharmacist, describes a 68-year-old male with a history of small cell lung cancer, status-post left lower lobectomy, myocardial infarction (MI), coronary artery bypass graft (CABG), congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), atrial fibrillation, hypertension, peripheral vascular disease, pulmonary embolism, nephrolithiasis, cholecystitis, peptic ulcer disease, gout, irritable bowel syndrome, and allergies to sulfonamides and lidocaine, who developed fulminant hepatic failure with rhabdomyolysis, hepatorenal syndrome, exacerbation of congestive heart failure with hypoxemia, and subsequently expired after approximately nine months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications included digoxin, theophylline, lisinopril, albuterol, furosemide, potassium chloride, calcium carbonate, and cimetidine. Approximately two months prior to his death, the patient was treated for bronchiolitis obliterans with prednisone. Subsequently, the patient developed gastrointestinal distress which was

treated with cimetidine and Percocet® (an acetaminophen + oxycodone hydrochloride combination). Approximately one week later, the patient developed abdominal pain, nausea, and vomiting and was hospitalized with increased transaminases and increased CPK to 13,332 U/L (laboratory normal ranges not given). An ultrasound of the abdomen showed thickened gall bladder, enlarged spleen and an enlarged liver. Pravastatin, cimetidine, and lisinopril were discontinued. Therapy with omeprazole was initiated. Hepatitis screen was negative. The patient developed acute hepatic failure with rhabdomyolysis. Treatment included fluids and fresh frozen plasma. The patient became grossly volume-overloaded secondary to hepatorenal syndrome. He refused intubation and became increasingly hypoxic and subsequently expired. The cause of death was considered to be acute hepatic failure with hepatorenal syndrome resulting in an exacerbation of congestive heart failure and hypoxemia. The results of a post-mortem examination were: 1) fulminant hepatic failure with extensive non-inflammatory hepatocellular necrosis probably secondary to idiosyncratic reaction to therapeutic drug: pravastatin, 2) clinical rhabdomyolysis possibly related to the hepatic failure with no evidence of myofiber degeneration, 3) atherosclerotic coronary artery disease, and 4) multiple pulmonary emboli. The reporting pharmacist suspected a "possible competition by pravastatin and prednisone for isozyme CYP3A4 inhibited by cimetidine."

M055540/US, reported by a physician, describes a 62-year-old female with a history of coronary artery disease (CAD) with recent (date not given) percutaneous transluminal coronary angioplasty (PTCA), hypertension, hiatal hernia with gastroesophageal reflux disease, Type II diabetes mellitus, depression, osteoarthritis, gallstones, blood transfusion, total abdominal hysterectomy, spinal fusion, ventral hernia repair, and multiple drug allergies including aspirin, morphine, meperidine hydrochloride, and codeine, who developed jaundice, liver failure, hepatic encephalopathy, coma, and subsequently expired after approximately one year of therapy with pravastatin for the treatment of hypercholesterolemia. Concomitant medications included ticlopidine hydrochloride, conjugated estrogens, chlorpheniramine maleate, acetaminophen, furosemide, atenolol, diltiazem, nizatidine, and trazodone. All medications were

discontinued when symptoms were initially noted with the exception of nizatidine and trazodone. Hepatitis profile was negative. Abdominal ultrasound a suggested of common bile duct dilatation without a definite obstruction. Liver biopsy showed marked inflammatory infiltration associated with widespread fibrosis, bile duct and ductular proliferation, spotty hepatocellular necrosis, and reactive hepatocellular changes. These findings were considered non-specific, consistent with possible bile duct obstruction and/or sepsis which were not felt to be present clinically. Treatment included sucralfate, lactulose, cholestyramine, vitamin K, furosemide, potassium chloride, and subsequently, hydromorphone hydrochloride and lorazepam. The patient refused a liver transplant or aggressive care and subsequently expired. The reporting physician considered the etiology of the hepatitis unknown but may have been related to drug toxicity, possibly a combination of pravastatin, acetaminophen, and ticlopidine.

M074549/US describes a 58-year-old female with a history of sub-endocardial myocardial infarction, irritable bowel syndrome, gastrointestinal bleed, diverticulosis, sciatica, and asthma, who developed heart failure, liver failure, and subsequently expired after seven months of therapy with pravastatin 20 mg daily. Two months after a subendocardial myocardial infarction and the initiation of pravastatin and nadolol therapies, the patient developed heart failure and exacerbation of asthma requiring hospital admission. Laboratory results at that time included AST 100 U/L (reference range not reported). Nadolol therapy was discontinued and verapamil was initiated. Approximately one month later, the patient was noted to be jaundiced during a follow-up visit to the reporting physician, and bilirubin was 10 mg/dl (reference range not reported). The patient was instructed to discontinue pravastatin therapy at that time, but apparently she did not stop taking it. Approximately two months later during her next office visit, bilirubin was 35. The physician "took the patient's pravastatin tablets away from her." The patient was diagnosed with liver failure and was admitted to the hospital. Hepatitis A antibody was positive; other serology's were negative. The patient expired approximately three weeks later. Additional laboratory results, clinical course, and treatment were not reported. Other suspect drugs included nadolol and omeprazole. Other concomitant

medications included diltiazem, ranitidine, ipatropium, unspecified steroids, and naproxen.

M078251/US, reported by the wife of a consumer, describes a male (age not specified) who developed liver cancer, cancer of the pancreas, liver failure, and expired after approximately five months of therapy with pravastatin (dose not specified) and six weeks of therapy with atorvastatin for the treatment of hypercholesterolemia. Therapy had been changed from pravastatin to atorvastatin after five months because the consumer reportedly "did not feel well," and experienced nausea and pain in his abdomen. Subsequently, he was admitted to the hospital and was diagnosed with cancer of the liver and pancreas. Approximately one to two months later he reportedly expired. The cause of death was reported as liver failure. Additional information was requested from the treating physician but has not been received at the time of this report. Medical history, laboratory results, clinical course, concomitant medications, and treatment were not reported.

B034237/Germany, reported from the Germany Drug Agency, describes a 66-year-old male with a history of lung cancer with liver metastasis, cardiac failure, coronary heart disease and edema. The patient experienced a hepatotoxic effect resulting in fatigue, alcoholic feces, dark urine and abdominal pain after 16 days of therapy with pravastatin 5 mg daily for the treatment of hyperlipidemia. Concomitant medications included captopril, digitoxin, verapamil, and furosemide. The patient was hospitalized and therapy with pravastatin was discontinued. The patient expired 41 days later. The cause of death was reported as hepatic coma. The reporter considered the death not drug-related, but due to the underlying disease of lung cancer with liver metastasis.

B044052/GB describes a 65-year-old male with a history of MI, hypertension, non-insulin-dependent diabetes mellitus, and gout, who developed hepatic necrosis, hepatic failure, renal failure, and subsequently expired after 29 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. There was no

evidence of hepatitis B or C virus infection. Death was attributed to hepatic necrosis and failure. The coroner's post-mortem examination indicated "cerebral edema secondary to hepatorenal failure and secondary hepatic necrosis. A liver biopsy indicated acute hepatocytic degeneration with polymorph infiltrative change. A renal biopsy revealed no glomerular lesion, but "an acute or chronic interstitial infiltrate." Concomitant medications included indapamide, aspirin, metformin, and diclofenac.

5.2 Musculoskeletal, Connective Tissue and Bone Disorders

M032103/US, reported by Merck Worldwide Product Safety and Epidemiology Department, describes an 85-year-old female with a medical history of arteriosclerotic heart disease, hypertension, and degenerative joint disease with compression fracture who developed myositis and digital skin ulcers after three months of therapy with pravastatin, 20 mg daily. She was hospitalized and pravastatin was discontinued. Polymyositis was diagnosed. CPK level continued to rise to 5500 U/L (normal 0-20 U/L), although her condition had begun to improve. A muscle biopsy confirmed inflammatory myopathy, which was diagnosed two months after pravastatin had been stopped. Treatment with prednisone was initiated and the CPK level returned to within normal limits. Subsequently she demonstrated weakness and falling and was readmitted to the hospital. Premature ventricular contractions, vasculitis, as well as colitis were diagnosed. Her medication regimen consisted of enalaprilat, furosemide, methotrexate, isordil, aspirin and prednisone. Two months later she was re-hospitalized for a bleeding gastric ulcer from which she subsequently died. The reporting physician indicates that the cause of death was "unclear", but attributed the course of events to the patient's underlying of muscle weakness.

5.3 Blood and Lymphatic System Disorders

B039832/Japan, reported by a physician, describes a 72-year-old male with a history of diabetes mellitus and a MI who developed generalized fatigue, anorexia, fever, decreased leukocytes, increased CPK, and decreased renal function requiring hospital admission after approximately one year of therapy with pravastatin 10 mg daily and bezafibrate. Concomitant medications included epalrestat, voglibose, and medigoxin. Pravastatin and bezafibrate therapies were discontinued. The patient was discharged from the hospital and initially symptoms were improved, but the decreased leukocytes noted during the hospitalization progressed, and the patient expired approximately one week later. Laboratory results (peak reported values) included serum glutamic oxaloacetic transaminase (SGOT) 282 U/L (normal, 5-37 U/L), serum glutamic pyruvic transaminase (SGPT) 66 U/L (0-35 U/L), lactic dehydrogenase (LDH) 1305 U/L (200-460 U/L), blood urea nitrogen (BUN) 40 mg/dl (8-20 mg/dl), and serum creatinine 2.2 mg/dl (0.3-1.5 mg/dl). Hematology laboratory results (lowest reported values) included white blood cell (WBC) 1700/mm^3 (normal 4000-9000/mm^3), red blood cell (RBC) 359 x 10^4/mm^3 (410-520 x 10^4/mm^3), hemoglobin 10 g/dl (13-18 g/dl), hematocrit 31.2% (40-48%), and platelets 8.8 x 10^4/mm^3 (13-40 x 104/mm^3). An autopsy showed tumors in the liver and spleen, and the diagnosis was hemophagocytic syndrome. The physician noted that "the rise in SGOT, LDH, and CPK noted at the time of hospitalization had been caused by an elevation of bezafibrate concentration in the blood due to liver dysfunction from the complication (tumors)." The physician considered "the fatality as unrelated to the administration of the medication."

5.4 Cardiac Disorders

M027048/US, reported by a physician, describes a 66-year-old female, with a history of coronary artery disease, coronary artery bypass graft (CABG), MI, congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) who was diagnosed with dermatomyositis and subsequently died after receiving 8 days of therapy with

pravastatin (dosage not reported). The patient was previously treated with lovastatin, and was switched to pravastatin. Concomitant medications included nifedipine and an unknown steroid. Six days after starting pravastatin she complained of muscular weakness, muscle aching, rash, and mouth sores. Nifedipine and the unknown steroid were discontinued at this time. Two days later her symptoms intensified with heartburn, chest pain and weakness. She was hospitalized to rule out MI, the CPK was 2432 U/L and LDH was 952 U/L. Pravastatin was discontinued at this time. The CPK increased to 2900 U/L and the diagnosis of dermatomyositis was made. The patient was treated with prednisone, with resolution of some symptoms. She was then discharged home on decreasing doses of prednisone. Steroidal therapy exacerbated her CHF and COPD and she was subsequently rehospitalized. The patient expired the following week from CHF.

M054999/US, reported by the wife of a consumer, describes a 68-year-old male who experienced a massive heart attack and subsequently expired after twelve days of therapy with pravastatin 10 mg daily for the treatment of hypercholesterolemia. Follow-up information from the treating physician indicated that the patient had a normal cardiac evaluation including treadmill approximately three years prior to the event. The patient experienced a massive MI from an occlusion of the left main coronary artery at the juncture with the aorta resulting in death. An autopsy was not performed.

M078780/US, reported by a physician, describes a 64-year-old male with a history of hypertension who developed shortness of breath, renal failure, and junctional bradycardia, and subsequently expired during therapy with pravastatin and mibefradil dihydrochloride. Prior therapy included "an angiotensin-converting enzyme inhibitor and a beta blocker". Both pravastatin and mibefradil therapies were discontinued upon hospital admission. The patient was transferred to the Intensive Care Unit and was intubated. Over the next five days, the patient continued to decline and the junctional bradycardia worsened. He subsequently went into cardiac arrest and expired. The physician considered the causality probable regarding mibefradil therapy, and possible with regard to pravastatin therapy.

B007592/France, describes a 65-year-old male who expired while participating in a Phase IV open-label pravastatin study. The subject, with a history of atherosclerosis, aorto-iliac-femoral bypass and cerebrovascular disease, developed retinal artery thrombosis two months after starting therapy with pravastatin 40 mg. Pravastatin therapy was continued. One month later the subject had a myocardial infarction and pravastatin was discontinued. Ten months later, the subject had another myocardial infarction and expired. The reporter stated the death was not related to study drug.

B022493/Belgium, reported by a physician, describes a 64-year-old male with a history of MI and peripheral arteriopathy, who experienced a MI and expired after 4 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications were not reported. No additional information is available.

B022651/China, reported by a physician, describes a 61-year-old female with a history of subvalvular aortic stenosis and diabetes mellitus, who suddenly expired after 9 months of therapy with pravastatin 20 mg daily. Concomitant medications included nifedipine, insulin, furosemide, and glyceryl trinitrate. The patient's height and weight were reported to be 161 centimeters and 86 kilograms. The reporting physician did not attribute the cause of death to pravastatin, but to her preexisting disease of subvalvular aortic stenosis.

B023217/Belgium, reported by a physician, describes a 57-year-old male with a history of MI, multiple percutaneous transluminal coronary angioplasties (PTCAs), diabetes, and peripheral arterial disease, who expired after eight months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. The patient was admitted to the hospital for the evaluation of heart failure and increased triglyceride levels to 2453 mg/dL (normal <160 mg/dL). The patient was discharged (no additional information is available). Three months later he was readmitted to the hospital for heart failure and "recidive" MI. One month later the patient expired. The death was attributed to "recidive" MI, heart failure, and mesenteric infarction.

B023218/Belgium, reported by a physician, describes a 75-year-old male with a history of cerebrovascular accident, CAD, and MI, who was found dead in bed after six months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications included molsidomine, dipyridamole, and acetylsalicylic acid. The reporter indicated the patient died due to a "recidive MI". An autopsy was not performed.

B026805/GB, reported from the Medicines Control Agency of the United Kingdom, describes a 68-year-old female with a history of angina pectoris, dyspepsia, and CHF, who experienced an MI and subsequently expired after one day of therapy with pravastatin 10 mg daily, for the treatment of hyperlipidemia. The patient had been taking bezafibrate 400 mg daily for the treatment of hyperlipidemia prior to receiving pravastatin therapy. Concomitant medications included isosorbide dinitrate, nifedipine, thyroxine, cimetidine, amiloride and cyclopenthiazide.

B027120/Germany, describes a 47-year-old male who developed cardiogenic shock after a myocardial infarction and subsequently expired while participating in a captopril/pravastatin study. The subject began the study after his first myocardial infarction, several months prior to the event. Study therapy included captopril 12.5 mg for the treatment of hypertension and pravastatin 20 mg for the treatment of hypercholesterolemia (exact duration unknown). The reporter stated that the events were not related to study therapies.

B027158/Canada, reported by a physician, describes a 54-year-old male with a history of well controlled diabetes mellitus, developed cardiac failure after 6 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia and hypertriglyceridemia. Treatment with pravastatin was discontinued at this time. The patient expired 3 months later. Concomitant medications included glyburide, perindopril, and metformin HCL. The physician reports that the patient's cholesterol and

triglycerides were controlled with pravastatin therapy. The physician did not attribute the event to pravastatin therapy.

B031907/Japan describes an 83-year-old female who experienced rhabdomyolysis and subsequently expired after five months of therapy with pravastatin 10 mg daily for the treatment of hyperlipidemia. The patient had a history of hypertension, cerebral infarction, bacteremia, cardiac dysrhythmia, thrombocytopenia, and neurosis. Concomitant medications included captopril, ticlopidine hydrochloride, nifedipine, disopyramide, and lorazepam. After 4 months of therapy with pravastatin the patient was suspected of having a chronic subdural hemorrhage, because of complaints of sleepiness, urinary incontinence and dull headaches. Cerebral CT scans showed no abnormality. One month later, pravastatin therapy and concomitant medications were discontinued. One day later, the patient vomited and was found lying on the floor. The patient was admitted to the hospital. On admission laboratory values were, BUN 35 mg/dL, creatinine 2.7 mg/dL, CPK 1313 U/L, and WBC 22,500 (normal ranges not reported). A muscle biopsy showed maintenance of muscle fiber structure and no necrotic changes. In addition, Kital- oxytoca was detected in blood and urine cultures. Antibiotic therapy was started. The next day the patient developed acute renal failure and was started on hemo dialysis. She was placed on a ventilator because of worsening heart failure and respiratory insufficiency. Laboratory values increased to BUN 54 mg/dL, creatinine 4.5 mg/dL, CPK 21,092 U/L, and WBC 44,300. Two days later the patient expired due to renal failure and heart failure. The reporter considered that anuria resulting from impaired renal tubules by development of rhabdomyolysis seemed to be a cause of heart failure, which was a cause of death.

B036596/Italy describes a 69-year-old female who experienced "probably heart arrest" and subsequently expired while participating in a clinical study. The patient was randomized to receive treatment with either pravastatin, fosinopril, hydrochlorthiazide (HCTZ), or placebo. No autopsy was performed. Concomitant medications included

nimesulide for the treatment of coxo/femoral arthrosis. The investigator considered the causality of the event to be unassessable.

B042920/France, reported by a physician from an antipoisoning center, describes a 59-year-old male with a history of depression, angina pectoris, and myocardial infarction who overdosed on multiple medications including, pravastatin, captopril, amlodipine, verapamil, and alcohol. The patient was taking pravastatin 30 mg daily (duration not reported). Upon arrival to the hospital, the patient was still conscious and his arterial pressure was "still alright". His systolic blood pressure fell to 5 mmHg and his heart rate fell to 20 bpm. He received inotropic medications, gastric lavage with activated charcoal and glucagon. He died of cardio-respiratory arrest 4 hours after his arrival and during input of a pacemaker.

5.5 Gastrointestinal Disorders

M025584/US, reported by a physician via a sales representative describes a 93-year-old female with a medical history of hypertension, non-insulin dependent diabetes, CAD, renal calculi, cholelithiasis and angina. The patient started concomitant treatment with both lovastatin, 20 mg daily, and pravastatin, 20 mg daily. The duration of treatment with either drug was not reported to us. Concomitant medications also included, digoxin, trichlorpheniramine, nitroglycerin, diphenhydramine HCl, nadolol, dicyclomine HCl and acetaminophen. She was reported to have experienced abdominal pain and was hospitalized. She had ascites, pleural effusion and hypercalcemia. Hemorrhagic pancreatitis was diagnosed and she died 2 days after being admitted. Autopsy revealed arteriosclerosis, renal calculi, cholelithiasis and cause of death of hemorrhagic pancreatitis was confirmed.

M026150/US, reported by a pharmacist, describes a 66-year-old male with a medical history peptic ulcer disease, CABG for CAD, cholecystectomy for cholelithiasis, diverticulosis and polyps of the large bowel, and macular degeneration who was

hospitalized for acute severe abdominal pain approximately 6 months after starting therapy with pravastatin, 10mg daily. Concomitant medications included aspirin, niacin, psyllium, omeprazole, and diltiazem. Upon hospital admission, pravastatin and niacin were discontinued. A laparotomy revealed a large pancreatic pseudocyst and a large mesenteric abscess. Bilateral renal cysts were also seen. The pancreas was found to be mostly necrotic requiring surgical removal of most of the organ. The clinical course of this patient continued to worsen and he died from sepsis, necrotizing pancreatitis and multiple organ failure. The gastrointestinal intensive care physician thought this event may be related to pravastatin therapy.

B027145/Austria, reported by a physician, describes an 83-year-old male with a history of hypertension and myocardial infarction, who developed hematemesis and hypovolemic shock, and subsequently expired one day later. The patient received 5 weeks of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications included captopril, acetylsalicylic acid and furosemide. No laboratory data was reported. The reporting physician judged causality to aspirin as "most probable."

5.6 General Disorders And Administration Site Conditions

B009359/Portugal, a spontaneous report describes a 65-year-old male, with a history of myocardial infarction and hypertension, who experienced sudden death after two weeks of therapy with pravastatin 20 mg daily for the treatment of hyperlipidemia. Concomitant medications included captopril 50 mg. Family history included two male siblings who had also experienced sudden death. An autopsy was not performed, therefore no additional information is expected.

B012190/France, describes a 67-year-old male who expired suddenly after 14 months of double-blind therapy while participating in a pravastatin/placebo trial. The subject had a history of cerebellar hematoma, cerebrovascular accident, hypertension, abdominal aortic aneurysm, and myocardial infarction. Concomitant medications included nifedipine,

furosemide, enalapril, and aspirin. The investigator stated the adverse event was related to the subject's underlying disease.

5.7 Injury and Poisoning

B008403/Great Britain, a spontaneous report from the March, April and May 1991 listings of the Committee on Safety of Medicines via the U.K. affiliate, describes a 66-year-old male who committed suicide after 4 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. The patient had no medical history of psychiatric illness. He was not taking any other concomitant medications. No further information is available. The reporting physician states pravastatin therapy is not related to this event.

5.8 Metabolism and Nutritional Disorders

M047449/US, reported by a physician, describes a 65-year-old female with a history of hypothyroidism, premature ventricular contractions, supraventricular tachycardia, myalgia, muscle weakness, angina pectoris, and coronary artery disease. The patient was admitted to the hospital for the evaluation of muscle weakness and myalgia while taking pravastatin 20 mg daily for 8 days for the treatment of hyperlipidemia. The patient had previously been treated for 6 months with cholestyramine and diet. Concomitant medications included levothyroxine mononitrate, isosorbide mononitrate, verapamil, aspirin and ibuprofen. The patient started to complain of muscle weakness and myalgia while on therapy with cholestyramine. Five months later the patient experienced diffuse chest pain, tightness, and heaviness. She was admitted to the hospital for evaluation. A coronary angiogram showed 50% plaque deposit in the right anterior coronary and right circumflex arteries. The patient was then switched to pravastatin therapy and discharged from the hospital. Three days later the patient had a worsening of the myalgia and muscle weakness in her right arm and leg. She presented in the emergency room for evaluation. Her CPK level was noted to be 360 U/L (normal 0-150 U/L) at that time.

Pravastatin therapy was continued and she was discharged. The next day she experienced these same symptoms with greater severity and was admitted to the hospital. Her CPK level was noted to be 8000 U/L. A muscle biopsy of the right thigh was done. The results and possible diagnoses were 1) excessive steroid usage, noted in the tissue, and 2) upper motor neuron disease. The reporter stated that these results were incorrect as the patient had not been taking steroids and a neurologist ruled out upper motor neuron disease. Four days after this admission her CPK level had increased to 12,000 U/L. On the fifth day the patient experienced diaphragmatic failure and was intubated. She experienced acidosis, shock, and lapsed into a coma. Her CPK level was noted to be 94,000 U/L and increased to 191,000 U/L by the sixth day. She also experienced renal failure and her hemoglobin level fell from 10-11 mg/dL to under 6 mg/dL (normal range not reported). On the sixth hospital day she was diagnosed with rhabdomyolysis. She was treated with hemodialysis and expired on the sixth hospital day. Preliminary results from the post-mortem revealed an infarct of the small intestine and a hemorrhage in the abdominal cavity. The reporting physician stated that some type of vasculitis may have been the underlying condition. The patient's occupational history is significant for having worked in a factory on circuit boards for several years. A metal screen was done. The results of the metal screen are not available. A definitive diagnosis cannot be made until the final results of the post-mortem examination become available. However, the physician attributed these events as being possible related to environmental exposure or pravastatin therapy. The physician attributed the death to shock, acidosis, respiratory insufficiency and renal failure.

B015654/Japan, reported by the Sankyo Company of Japan, describes a 56-year-old female with a medical history of cardiac failure, renal failure, peptic ulcer, diabetes mellitus, MI and diabetic nephropathy, who experienced rhabdomyolysis and expired after greater than two years of therapy with pravastatin 10 mg for the treatment of hypercholesterolemia. Concomitant medications included isosorbide dinitrate, nifedipine, cimetidine, multiple vitamin, bumetanide ascorbic acid, vitamin B complex, nicorandil and gefarnate. Four months prior to the patient's death, she had an exacerbation of renal

failure, treated with hemodialysis. At this time, the patient also experienced hyperkalemia secondary to rhabdomyolysis, nausea, facial edema, tachycardia and weight gain. Laboratory values at this time were, SGOT 16 U/L (normal 8-40 U/L), SGPT 8 U/L (normal 5-35 U/L), ALP 95 U/L (normal 30-120 U/L). At the time of hospital admission, one day prior to her death, laboratory values included, SGOT 162 U/L, SGPT 106 U/L, ALP 155 U/L, serum myoglobin 4450 ng/ml (normal 30-90 ng/ml), LDH 1126 U/L (normal 100-220 U/L), CPK 881 U/L (normal 0-150 U/L), and potassium 7.1 meq/L (normal 3.5-5.0 meq/L). On the day of her death, hemodialysis was performed five times to decrease the potassium level. Following the fifth treatment, the patient's clinical course deteriorated resulting in an exacerbation of heart failure and multiple organ failure, leading to cardiac arrest. Cardiopulmonary resuscitation was unsuccessful. The reporting physician attributed the hyperkalemia to the rhabdomyolysis. The death was attributed to hyperkalemia and an exacerbation of heart failure secondary to hemodialysis.

5.9 Neoplasms Benign and Malignant

M026486/US, reported by a physician, describes a 64-year-old male with a medical history was of femoral aneurysm that had been surgically repaired, who was diagnosed with metastatic carcinoma to the liver and subsequently died after 3 months of therapy with pravastatin, 20 mg daily for hyperlipidemia. Concomitant medications included famotidine, metoprolol tartrate and lisinopril. One month after starting pravastatin, results of liver function tests were within normal ranges; however, approximately 1.5 months later, he experienced general weakness so the patient, on his own, stopped taking pravastatin. He was hospitalized within a week and a preliminary diagnosis of liver toxicity was confirmed. A liver biopsy revealed small cell carcinoma of the liver with the suspected primary site identified as the lung. He died 8 days later due to complications from metastatic disease to the liver.

B022734/Sweden, describes a 59-year-old female who was participating in a study, "Pravastatin and Cholestyramine (PACT)". The subject was treated with pravastatin 20 mg daily for eight months. Approximately one month later the subject was diagnosed with uterine carcinoma and expired twenty-two days later. The cause of death was listed as carcinoma of the uterus. The investigator did not attribute the event to pravastatin therapy.

B025582/Sweden, describes a 52-year-old male who was participating in a study, "Pravastatin and Cholestyramine (PACT)". The subject was treated with pravastatin 20 mg daily for 9 weeks. Nine months later the subject expired due to pancreatic cancer. The reporting physician stated that the event was not related to pravastatin therapy. Although the subject was not receiving pravastatin therapy at the time of his death, he was still enrolled in the study for follow-up visits two years after randomization. No further information is available.

5.10 Renal and Urinary Disorders

M042285/US, reported by a pathologist, describes an 81-year-old male, with a medical history of ventricular extrasystoles, atypical chest pain, COPD, and self medication with large doses of acetaminophen for long periods of time, who was hospitalized with complaints of nausea and feeling ill who subsequently died. The patient had taken pravastatin 40 mg/day for two years for the treatment of hypercholesterolemia. Concomitant medications included verapamil, triamterene hydroclorothiazide acetaminophen, lovastatin and nitroglycerin. Liver enzyme profile was within normal limits. At the time of admission, liver enzymes, bilirubin, LDH and CPK were dramatically elevated, AST 7,400 U/L (normal 0-40 U/L), ALT 2000 U/L (normal <56 U/L), bilirubin 2.2 mg/dL (normal 0.1-1.0 mg/dL), LDH 27,000 U/L (normal <600 U/L) and CPK 230 U/L (normal <170 U/L). The patient died shortly after. An autopsy revealed confluent hepatocellular necrosis, acute tubular necrosis, renal cell carcinoma (diameter-1.0 cm), chronic interstitial nephritis, and arterionephrosclerosis. The acetaminophen

blood level was 9 mcg/ml (therapeutic range 10-25 mcg/ml). The combination of acute tubular necrosis in the kidney and hepatocellular necrosis were most compatible with a toxic agent, therefore, the reporter did not exclude acetaminophen as the responsible agent. Considering that the half-life of acetaminophen is 2-4 hours, the possibility was considered that the patient had taken massive doses of acetaminophen between 10-14 days preceding death. The reporter also considered the role pravastatin may have played in explaining that other HMG-CoA reductase inhibitors have been implicated in fulminant hepatocellular necrosis; however, the reporter had also noted that toxicology, laboratory and animal tests with pravastatin failed to produce hepatocellular damage.

B035960/Japan describes an 85-year-old male with a history of renal failure, diabetes mellitus, myocardial infarction, and angina pectoris. After five years of therapy with pravastatin 10 mg daily and eight years of therapy with clinofibrate the patient developed acute renal failure secondary to rhabdomyolysis, characterized by dyspnea, back pain, pulmonary edema, and anuria, and subsequently expired. Laboratory results included myoglobin 8623 ng/mL and CPK 701 IU/L (laboratory normal ranges not reported). Treatment included unspecified diuretics and dialysis. Concomitant medications included diltiazem, isosorbide dinitrate, dipyridamole, and gliclazide.

5.11 Respiratory, Thoracic and Mediastinal Disorders

B007485/France, describes a 66-year-old who expired while participating in a clinical study. The subject, with history of hypertension, ischemic heart disease, respiratory abnormality, and an unspecified allergy, suffered an acute myocardial infarction with ventricular arrhythmias and cardiac failure after taking pravastatin 20 mg daily for 6 months for the treatment of hypercholesterolemia. Concomitant medications included captopril and HCTZ and isosorbide dinitrate. The subject expired the next day due to acute pulmonary edema.

B019034/Belgium, reported by a physician, describes a 70-year-old female, with a medical history of COPD and cerebrovascular accident (CVA), who developed a lung abscess while taking pravastatin 20 mg daily. Pravastatin was continued until death, a total duration of 23 days. No concomitant drugs were taken. The reporter attributed the death to respiratory insufficiency caused by the lung abscess. No further information was reported.

B019117/China, describes a 53-year-old male who experienced pneumonia, septic shock and subsequently expired after approximately 2 months of pravastatin therapy while participating in a BMS sponsored study. The subject had a history of coronary heart disease, diabetes mellitus, obesity and tobacco abuse. Concomitant medications included atenolol. The investigator attributed the death to "fulminant pneumococcus" and not to study medication.

5.12 Vascular Disorders

B017160/BGA/Germany, reported by the German Regulatory Agency, describes a 77-year-old female with a medical history of cardiac pathology that included CHF, hypertension, generalized arteriosclerosis, cardiac hypertrophy, CABG, myocardial scarring in addition to necrotizing pseudomembranous colitis, who started therapy with pravastatin, 40 mg daily, for mixed hyperlipidemia. Concomitant medications included digoxin and nifedipine. Pravastatin was withdrawn 12 weeks later. Two days later, liver function tests showed increases in lactic dehydrogenase (LDH), transaminases, and serum creatinine. Results of laboratory tests for platelet count, leukocyte count and erythrocyte count were indicative of pancytopenia. The patient had become comatose and E. coli septic shock was diagnosed. The patient died that day of toxic cardiovascular failure and cerebral edema with compression. It was noted that although the patients blood count was normal she had conspicuous pancytopenia which was possibly related to hypolipidemic drugs.

B019723/Sweden, describes a 64-year-old female who expired while participating in a study, "Pravastatin and Cholestyramine (PACT)". The subject received treatment with pravastatin 40 mg daily for 10 months for the treatment of hypercholesterolemia. The subject, with an unknown medical history, experienced a thromboembolism on the right side of the middle cerebral artery and expired one day later. The investigator attributed causality of the event as "possibly" related to pravastatin therapy.

B022173/Australia, describes a 74-year-old female who was admitted to the hospital and underwent a triple bypass graft after 5 months of participation in a double-blind study with pravastatin 40 mg daily and/or placebo and/or fish oil to prevent restenosis following surgical intervention in peripheral arterial occlusive disease. The subject had a history of peripheral vascular disease, cardiac failure and hypertension. Concomitant medications included imipramine hydrochloride, enalapril maleate, furosemide, and perhexiline maleate. The subject never recovered from the triple bypass graft and expired two months later. The cause of death was reported as a stroke. The investigator did not attribute the event to study medication.

B022767/Belgium, reported by a physician, describes a 66-year-old male with a history of peripheral vascular disease, who suddenly expired after 11 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications included diazepam, acetylsalicylic acid, terazosin HCL, buflomedil and trazodone. The patient was admitted to the hospital for angioplasty and died suddenly. The reporting physician stated that the death was "probably" due to an embolus.

B026596/France describes a 64-year-old male who developed septic shock, jaundice, subfulminant hepatitis, hepatic encephalopathy (grade 4), and subsequently expired after nine weeks of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Other suspect medications included acetylsalicylic acid and diltiazem. Medical history, laboratory values, concomitant medications, clinical course

and treatment were not reported. The reporter considered the event to be of unknown causality. This report was received from the French Drug Agency (#ST9600249).

B029367/GB (MCA #343739) describes a 51-year-old male with a history of renal transplant, aortic valve disease, dyspepsia, lower respiratory tract infection, and angina pectoris who developed an increased international normalized ratio (INR) of 9 (baseline not reported), hemorrhagic pericardial effusion, cardiac tamponade, renal failure, cardiac arrest, hypoxic brain damage, and subsequently expired after 18 days of therapy with pravastatin 10 mg daily for the treatment of hypercholesterolemia. Concomitant medications included warfarin, ranitidine, cyclosporin, prednisolone, amoxicillin+clavulanic acid, and glyceryl trinitrate.

B043380/France, reported by a physician, describes a 61-year-old male with a history of a herniated disc who experienced severe back pain, was hospitalized and subsequently expired of an aortic dissection. The patient was taking pravastatin 20 mg once daily (duration and indication not reported). Upon hospitalization, a physical examination was normal, as were an electrocardiogram, a chest x-ray and a spine x-ray. The patient was treated symptomatically with propacetamol and the pain nearly resolved. On this same day, the patient experienced an aortic dissection secondary to an aortic aneurysm rupture and expired. The physician attributed the dorsalgia to the aortic dissection, unrelated to drug.

5.13 Multi-Organ Failure

M078777/US, reported by a physician, describes a 64-year-old female with a history of diabetes, diabetic retinopathy, eye surgery, hypertension, and total hysterectomy for fibroids, who developed acute liver failure, hepatic coma, multisystem organ failure, and subsequently expired, after four months of therapy with pravastatin 40 mg daily for the treatment of hypercholesterolemia, and troglitazone 400 mg daily for the treatment of Type II diabetes mellitus. Death was attributed to liver failure and multisystem organ

failure. Liver function tests were reportedly normal at the time of initiation of the therapies. After four months of therapy, the patient's brother noticed that she was yellow. She was seen by her physician and all medications were discontinued. Her bilirubin kept increasing even after pravastatin and troglitazone therapies were discontinued. The patient was admitted to the hospital with elevated transaminases, drowsiness, and change in mental status, and was diagnosed to have fulminant liver failure. She was transferred to another hospital to await a liver transplant and developed hepatic coma. Laboratory results (peak reported values) included SGOT 3640, SGPT 3340, bilirubin of 30 mg/dL, and international normalized ratio (INR) 5 (normal ranges not reported). Supplemental information indicated that an abdominal ultrasound showed cirrhotic liver without focal mass, patent hepatic vessels, moderate abdominal and pelvic ascites, contracted gallbladder limits assessments of the gallbladder, no bile duct obstruction, 6 mm echogenic focus within lower pole of kidney likely represents an incidental angiomyolipoma, and right pleural effusion. The patient reportedly refused any blood or blood products. She continued to receive medical management, including ventilator support, dialysis, and antibiotics, which consisted of ticarcillin/clavulanate and fluconazole, and she was also given lactulose, neomycin and Vitamin K. The patient died of multi-system organ failure approximately one month after discontinuation of pravastatin and troglitazone therapies. Concomitant medications included glipizide, amlodipine besylate + benazepril, famotidine, lisinopril/HCTZ, and verapamil. Supplemental information received from a pharmacist indicated that "the patient was a Jehovah's Witness and refused blood products which could have corrected the coagulopathy and enabled a liver transplant." The reporting physician considered that the fulminant liver failure was most likely due to troglitazone therapy.

B041542/Japan, reported by a physician, describes a 69-year-old female with a history of idiopathic thrombocytopenic purpura (ITP), diabetes mellitus, rheumatoid arthritis, hypertension, cholelithiasis, and convulsions, who developed pancytopenia, cholecystitis, sepsis, multiple organ failure, and subsequently expired after six weeks of therapy with pravastatin 10 mg daily for the treatment of hyperlipidemia. Therapy with pravastatin

and temocapril hydrochloride was initiated approximately two weeks after the patient had been admitted to the hospital and diagnosed to have ITP, along with diabetes mellitus and hypertension. Laboratory results (normal ranges not reported) included SGOT 105 IU/L, SGPT 125 IU/L, ALP 1351 IU/L, GGTP 426 IU/L, and BUN 39.6 mg/dL. Hematology laboratory results included WBC 700/mm^3, RBC 360 x $10^4/mm^3$, and platelets 1.8 x $10^4/mm^3$. Concomitant medications included ranitidine, human insulin, "stronger neo-minophagen C" (medication for hepatic dysfunction), cefozopran hydrochloride, imipenem/cilastatin, nilvadipine, Gastron (aluminum hydroxide + bicarbonate + magnesium + alginic), Globenin-I, (polyethylene glycol treated human normal immunoglobulin), "Syakuyakukanzoutou", a Chinese herbal medicine used to treat chronic neuralgia and arthritis, and prednisolone. The reporting physician stated "this patient developed cholecystitis during treatment of ITP." The uncontrolled cholecystitis led to sepsis, multiple organ failure, and eventually death. Causality assessment between pancytopenia and pravastatin and temocapril hydrochloride cannot be excluded because pancytopenia progressed after starting pravastatin and temocapril hydrochloride. At the time of onset of cholecystitis, WBC was 1900/mm^3, but granulocytes were 97%. Therefore, leukopenia is unlikely the cause of cholecystitis. Immunosuppression induced by diabetes mellitus, rheumatoid arthritis, and prednisolone administration is likely the cause of cholecystitis.

5.14 Cause of Death Not Reported

M027532/US, reported by a physician describes a 21-year-old female with a history of congestive heart failure, ischemic bowel, lung mass, and renal failure secondary to vasculitis secondary to anistreplase plasminogen-streptokinase activator complex therapy. The patient developed hypotension and liver failure while taking pravastatin 20 mg daily for 3 weeks for the treatment of hyperlipidemia. Concomitant medications included furosemide, potassium chloride, digoxin and prednisone. The patient was hospitalized and then transferred to another facility where she expired. Laboratory results included SGOT 5428 U/L, LDH 5728 U/L, creatinine 3.9 mg/dL, and potassium 6.1 meq/L

(laboratory normal ranges not reported). An autopsy was not performed. In the opinion of the reporting physician, the events were not related to pravastatin therapy.

M031451/US, reported by a physician, describes a 68-year-old female with a medical history of CAD, renal insufficiency, diabetes mellitus, peripheral vascular disease, and rash during treatment with triamterene and hydrochlorthiazide (Dyazide®), who developed avascular necrosis of the left femoral head while receiving therapy with pravastatin, 10 mg daily for 3 months. Concomitant medications included methyldopa, clonidine, guanfacine HCl, nicardipine HCl, theophylline, isosorbide dinitrate, nitroglycerin, human insulin, and psyllium. The patient was admitted to the hospital following a fall that resulted in a fracture of the left femoral head. A bone scan confirmed the diagnosis of avascular necrosis. A total hip replacement was planned. Follow-up information received reported that the patient expired. No cause of death was reported.

M034994/US, describes a 46-year-old male who was involved in an automobile accident and subsequently expired while participating in a pravastatin/placebo coded study. The subject had a history of myocardial infarction and hypertension. Concomitant medications included nitroglycerin, metaproterenol sulfate and verapamil. The investigator attributed the cause of death to the automobile accident and not to study medication.

M036469/US, reported by a physician, describes a female (age was not provided) with a history of congestive heart failure and hepatomegaly, who expired after 2 months of therapy with pravastatin 20 mg daily. Concomitant medications were not reported. The patient was admitted to a hospital for "adjustment and evaluation of her arrhythmia (ventricular tachycardia)." She was then diagnosed with CHF and an elevated CPK to 2000 U/L (normal 0-130 U/L). Myocardial infarction was ruled out and the CPK level returned to within normal limits. The patient's myoglobulin was reported to be negative. The patient's health continued to decline as she experienced renal failure, respiratory

failure, and a GI bleed. She became ventilator dependent and began renal dialysis. The patient was also treated with furosemide and digitalis. While receiving a dialysis treatment the patient experienced a loss of consciousness. She became hypotensive after the dialysis treatment, went into an agonal rhythm and expired.

M047272/US, a report received through the FDA Med Watch program, describes a 47-year-old male with a history of severe ischemic cardiomyopathy, coronary artery disease, s/p 2 myocardial infarctions (MIs), non-insulin dependent diabetes and paroxysmal atrial fibrillation, experienced an MI while receiving therapy with pravastatin, 20mg daily for the treatment of hypercholesterolemia (duration of treatment not reported). Concomitant medications included warfarin, isosorbide dinitrate, lisinopril, furosemide, and digoxin. The patient experienced severe back and neck pain and was admitted to a hospital for mild congestive heart failure and suspected pneumonia. On admission to the hospital the CPK was 632 U/L (normal 0-232 U/L) and CPK-MB 6.5% (normal 0-7.5%). The following day his CPK increased to 1672 U/L and CPK-MB 8.9%. An ECG showed evidence of inferior and anterior wall infarction with ST abnormalities. Three days post-admission the patient expired.

M062128/US, reported by a physician, describes a 56-year-old female who developed rhabdomyolysis characterized by myalgia and markedly elevated CPK of 74,000 IU/L, (reference range not provided), and subsequently expired after seven days of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Past medical history included granuloma, menopause and obesity. Concomitant medications included conjugated estrogens. Treatment included diuresis with mannitol, and discontinuation of pravastatin and estrogen. The patient's condition deteriorated with respiratory distress and fatal cardiopulmonary arrest. Autopsy showed final anatomic and clinical diagnosis of rhabdomyolysis, based on serum CPK levels; possible renal tubular injury; fatty change in liver; cerebral edema, terminal and extensive venous vascular congestion. The sampled skeletal muscle had no diagnostic change. Some fibers, although swollen and hypereosinophilic, did retain their Z band configuration. Internally displaced nuclei

and/or fiber necrosis were not identified. Myocardial fibers were markedly diminished in size but did have some cross striations. No definite myocardial fiber necrosis was identified; the cause of the decreased caliber was therefore difficult to determine with accuracy. No inflammatory reaction was associated. Kidneys had proximal tubular changes which could be due to post-mortem autolysis. Moderately prominent fatty change was present in the liver. Lungs and other organs all had marked venous congestion. After a review of the slides, a second physician concurred that the changes in skeletal and cardiac muscle were non-diagnostic.

M062223/US, reported by the son of a consumer, describes a 77-year-old female with a history of MI and multiple drug intolerance who was diagnosed with amyotrophic lateral sclerosis and subsequently expired. Amyotrophic lateral sclerosis, characterized by taste changes, fading memory, and incapacitating muscle weakness, was diagnosed after approximately nine months of therapy with pravastatin (dose and indication not reported). Pravastatin was discontinued at this time. Two months later, the patient expired. Concomitant medications included an unspecified beta-blocker, an unspecified calcium channel blocker, an unspecified pain medication, an unspecified sleeping medication, and buspirone hydrochloride.

M070944/US, reported by a "distant cousin" of a consumer, describes a 67-year-old female with a history of an unspecified heart condition who expired (cause of death was unknown by the reporter) six months after discontinuation of pravastatin therapy (dose, duration of therapy, indication, and reason for discontinuation were unknown by the reporter). The reporter indicated that the patient had a long-standing history of unspecified heart problems and was taking many unspecified medications.

M081010/US, reported by a physician, describes a 66-year-old female with a history of arteriosclerotic heart disease, hypertension, asthma, smoking, allergy to aspirin, lumbar disc surgery, cervical fusion, abdominal hysterectomy with bilateral salpingo-oophorectomy, and cholecystectomy, who developed bronchitis, flu with generalized

aches and difficulty walking, myopathy, rhabdomyolysis, atrial fibrillation and flutter, respiratory distress, and subsequently expired, after three or four years of therapy with pravastatin 40 mg daily for the treatment of hyperlipidemia. Initially, the patient was seen in the office for chest congestion and bronchitis of approximately one month's duration which was treated with trimethoprim + sulfamethoxazole and hydrocodone bitartrate, both of which were discontinued after several doses when the patient developed nausea and vomiting. Amoxicillin therapy was initiated. The patient developed generalized aches (flu-like) and amantadine hydrochloride therapy was initiated. The patient had difficulty moving around, lost her appetite and had difficulty drinking. She was admitted to the hospital with acute myalgia and possible polymyositis. Treatment included intravenous fluids, mannitol, and unspecified steroids. Biopsy of the anterior thigh muscle showed denervation and type II myofiber atrophy. There was no evidence of an active inflammatory process in the biopsied tissue. Laboratory results included erythrocyte sedimentation rate 74, CPK 63,580, 24-hour urinary protein 2511 mg, creatinine clearance 80mL/min, urine myoglobin 1754 mcg/L (reference ranges not reported). Prothrombin time (PT) and partial thromboplastin time (PTT) were normal. ANA was negative. A sonogram showed "a 14 cm mass in the pelvis located anteriorly to the urinary bladder consistent with a retroperitoneal bleed." The patient developed some left arm weakness. A CT scan of the head showed a stroke in the posterior limb of the right internal capsule. The patient had evidence of rhabdomyolysis and was treated with high-dose steroids. She developed increasing respiratory difficulty and bilateral pneumonia with methicillin-resistant *S. aureus*. Despite antibiotics, the patient became weaker, had difficulty swallowing and speaking. The family elected not to put the patient on a ventilator. The patient subsequently expired approximately three weeks after hospital admission. No autopsy was done. Concomitant medications included nifedipine, triamterene, isosorbide dinitrate, acetazolamide, sublingual nitroglycerin, estradiol + methyltestosterone, quinine sulfate, and diphenhydramine. Final diagnoses included rhabdomyolysis, hypertension, emphysema, bilateral pneumonia secondary to methicillin resistance *S. aureus*, respiratory failure, arteriosclerotic heart disease, proximal atrial flutter and fibrillation, retroperitoneal bleed and hyperlipidemia.

It was reported that the exact cause of the rhabdomyolysis and the relationship to pravastatin therapy were both considered unclear.

M082307/USA, a report initially summarized and conveyed to the public in the Wall Street Journal (June 10, 1998, Page B1), from the FDA internet home page, and was received via the BMS Public Affairs Department, describes a 67-year-old male with a history of cardiac disease, hypertension and hypercholesterolemia. Concomitant medications included pravastatin (dosage and duration not reported), captopril, atenolol, and aspirin. Approximately 1 to 1½ hours after taking sildenafil, and engaging in sexual activity, the patient turned gray color, had breathing problems and expired. The patient was dead on arrival at the hospital. The cause of death was not listed.

M090294/US, reported by a physician participating the Pravastatin First MI Risk Reduction Registry describes a female (age not specified) with a history of Lyme disease who expired after therapy with pravastatin (dose and duration of therapy not reported). The death was reported by the family, with no other information, via a six-month patient query. The physician stated that he was unable to confirm the death or the cause of death, and therefore was unable to assess the causality of the event due to his lack of knowledge of the details.

10009074/France, reported by a physician, describes a 73-year-old male with a history of hyperlipidemia, deafness, hypertension, cardiac failure, confusion and falls. The patient developed rhabdomyolysis, acute renal failure, hepatic failure, confusion, falling, left sided hemiparesis, and right sided facial hemiparesis, and subsequently expired after therapy with pravastatin 10 mg daily (duration of therapy not reported). Concomitant medications included lisinopril, allopurinol, benfluorex HCl, bumetanide, and acetylsalicylic acid. The patient was confused and had experienced repetitive falls for several months prior to this hospitalization. The patient fell and could not get up from the floor. On admission to the hospital, the patient was noted to have left sided hemiparesis. Laboratory assessments on admission were ASAT 2000, ALAT 2000, total

protein 40%, creatinine 238 umol/L, creatine kinase 15,080, and myoglobin 20,000 (laboratory normal ranges not reported).. During the first week of admission, the patient developed metabolic acidosis and ionic deficit. A renal echography revealed "only a left kidney." Six days after admission, he was transferred for dialysis, still confused and was noted to have a right facial deficit. The CPK was normalized by hospital day 12, but the patient expired on hospital day 14.

B011696/Sweden, describes a 61-year-old male who suddenly expired while participating in a blinded pravastatin study for hypercholesterolemia. The subject, with a history of myocardial infarction, ischemic heart disease and angina pectoris, was admitted to the hospital with heart failure 4 months after starting therapy with pravastatin 20 mg. Study medication was interrupted while he was hospitalized. The investigator stated that study medication was not related to this adverse event. He was discharged from the hospital and continued on study medication. Twelve months later the subject expired suddenly. Concomitant medications included impugan, imdur, allopurinol, and nitroglycerin.

B013293/France, describes a 71-year-old male who expired suddenly after 4 months of blinded therapy while participating in a Phase IV pravastatin/placebo clinical trial. The subject had a history of angina pectoris and inguinal hernia. Concomitant medications included aspirin, diltiazem, allopurinol, and trimethoprim. The subject is reported to have experienced a recurrence of angina 24-hours prior to death, which was managed by a medical consultation at home. The investigator reports that this event is not related to study medication.

B018636/Japan, reported by the Sankyo Company of Japan via a physician, describes a 56-year-old male, with a medical history of angina pectoris, hypertension, fever, valvular disease resulting in double valve replacement, and CABG who experienced anorexia, nausea, generalized fatigue and fever after 20 months of therapy with pravastatin 10 mg daily for hypercholesterolemia. Concomitant medications included nifedipine, captopril, ticlopidine and warfarin. Treatment for infection with levofloxacin was started and

pravastatin was discontinued. Fulminant hepatitis was later diagnosed. Within a week he was admitted to a hospital in a semiconscious state that progressed to 4th degree hepatic coma with anuria. He was placed on mechanical ventilation. Treatments were unsuccessful and he expired. The reporter stated that the true cause of hepatitis is unknown because of the rapid progression from fulminant hepatitis to death. Results of drug lymphocyte stimulating test (DLST) for pravastatin was positive; therefore, the reporter suggested that if hepatitis was drug induced, pravastatin would be a suspected cause. Levofloxacin was suspected as well because it was introduced just before the onset of fulmination. All tests for viral hepatitis were negative.

B020117/Germany, describes a 54-year-old male who suddenly expired while participating in a clinical study to influence maximal antilipidemic therapy of progression and regression of coronary atherosclerosis. Prior to study drug therapy, the subject experienced a myocardial infarction (MI) and was admitted to the hospital. He was then started on pravastatin 20 mg daily for the treatment of hyperlipidemia. Concomitant medications included aspirin, metoprolol tartrate, molsidomine, and isosorbide dinitrate. Twelve days after experiencing the MI, he was found lying in bed unconscious. Four days later the subject expired due to ventricular fibrillation (sudden death). The BMS medical monitor did not attribute the events to study drug therapy.

B020875/Belgium, reported by a physician, describes an 86-year-old male with a history of cardiomyopathy and diabetes mellitus who experienced a myocardial infarction and died after 2 months of therapy with pravastatin, 20 mg daily for the treatment of hypercholesterolemia. Concomitant medications were not reported. The patient was admitted to a hospital for heart decompensation and precordial pain. The patient subsequently experienced cardiac shock and a MI, which resulted in his death.

B026451/France, describes a 39-year-old male who had participated in a clinical study entitled, "Study of Safety of Pravastatin Administration following Heart Transplantation". The subject completed the study and continued on pravastatin therapy

10 mg daily, for a total of 15 months of duration. Two months after completion of the study, he expired suddenly at his home. Concomitant medications included cyclosporine, azathioprine, prednisolone, calcium and calcifediol. The investigator attributed the death to underlying disease, and not to study medication.

B027531/France describes a 61-year-old male who suddenly expired after participating in a clinical study entitled, "Study of Safety of Pravastatin Administration following Heart Transplantation." The patient received blinded therapy with pravastatin or placebo for approximately one year, and subsequently received therapy with pravastatin (dose not specified) during an open-label phase for six weeks. The patient continued to receive pravastatin therapy after completion of the study (dose not specified) until his death approximately two months later. Concomitant medications included cyclosporine, prednisolone, furosemide, isradipine, calcifediol, phenobarbital with amphetamine, calcium, and azathioprine. The investigator considered the relationship of the event to pravastatin to be unassessable.

B037646/Italy describes a 50-year-old male with a history of carotid artery disease who died suddenly while participating in a study. The patient was randomized to receive treatment with either pravastatin, fosinopril, or placebo. Concomitant medications included nifedipine. The investigator reported that the causality of the event could not be determined.

B039092/Netherlands, reported by a physician participating in a Phase IV marketing study, describes a 63-year-old male who lost consciousness and subsequently expired after 7.5 months of therapy with pravastatin 20 mg daily for the treatment of hypercholesterolemia. Medical history was not reported. Concomitant medications included plantago ovata and carbasalate calcium. The reporter considered the causality was "unassessable but unlikely" with regard to pravastatin therapy.