

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: 2006 Update: Post-Pediatric Exclusivity Postmarketing Adverse Event Review  
Drug: Simvastatin (Zocor®), NDA# 019766  
Pediatric Exclusivity Approval Date: February 22, 2002

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## 1. EXECUTIVE SUMMARY

This document updates a previous Office of Surveillance and Epidemiology consult from 2003 that assessed simvastatin pediatric reports during the one-year post-pediatric exclusivity period (2/22/02-3/22/03).<sup>1</sup> During this period, the AERS database contained four simvastatin pediatric reports so the participants at the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (held June 12, 2003) requested additional follow up.<sup>2</sup>

Simvastatin was approved in 1991, and granted pediatric exclusivity on February 22, 2002. In pediatric patients (adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age) simvastatin is indicated as adjunct to diet to manage heterozygous familial hypercholesterolemia. Simvastatin is classified as Pregnancy Class X, and the recommended pediatric starting dose is 10 mg once daily in the evening and a maximum daily dose of 40 mg.

A search of the AERS database since the last OSE consult (March 22, 2003 through August 22, 2006) identified 4,534 simvastatin reports (crude counts), of which 6 (2 from the United States) were reported in children less than 17 years of age. In three reports, simvastatin was indicated for management of dyslipidemia in children. The remaining three reports were associated with in utero exposures.

Of the three reports where simvastatin was indicated for management of dyslipidemia, two reports were of increased creatine phosphokinase (CK). The first was a foreign report of a 6-year-old female with nephrotic syndrome who developed increased CK levels about a month after starting simvastatin. No muscle symptoms were reported, and the increased CK level was found on a "routine screen." The child was also taking cyclosporine and corticosteroids. The CK continued to rise, and simvastatin and cyclosporine were both discontinued. Eventually the CK decreased, but treatment measures were not reported. The simvastatin labeling notes cyclosporine can increase the area under the curve of statins such as simvastatin (presumably through inhibition of CYP3A4), which can result in an increased risk of myopathy or rhabdomyolysis. The second report involves a 14-year-old boy on simvastatin for two years who developed thigh stiffness and CK of 792 after his methylphenidate dose was increased. Simvastatin was discontinued (methylphenidate continued) and the symptoms resolved. The boy was then switched to atorvastatin, and ezetimibe added. About 9 months later, the boy complained of muscle symptoms and the CK was 24,265. Atorvastatin and ezetimibe were discontinued and a month later the CK was 218. It is not clear why the boy experienced thigh stiffness and elevated CK when his methylphenidate dose was increased. There is no documented metabolic drug interaction between methylphenidate and statins (including simvastatin)<sup>6</sup> and methylphenidate therapy was not interrupted to evaluate dechallenge. In regards to the boy's redevelopment of muscle symptoms and elevated CK while taking atorvastatin and ezetimibe, the atorvastatin labeling does not mention a drug interaction between statins and ezetimibe. However, there are published reports of muscle symptoms associated with ezetimibe monotherapy or ezetimibe used in combination therapy with statins.<sup>7,8</sup>

There was one report of thrombotic thrombocytopenic purpura (TTP) that occurred in an 8-year-old female with systemic lupus erythematosus, lupus nephritis, and Sjogren's syndrome. The child experienced TTP about three months after starting simvastatin 5 mg daily. The child was also taking alfacalcidol, dipyridamole, azathioprine, famotidine and prednisolone. Simvastatin was discontinued, but the TTP persisted. TTP has been reported in association with underlying systemic lupus erythematosus, as well as possibly associated with simvastatin use in adults.<sup>9,10,11</sup>

There were three reports of in utero exposures. The first reports a spontaneous miscarriage that occurred in a 32-year-old female who took simvastatin 20 mg daily for about two weeks during the first trimester. The second report describes a female infant born in 1996 with congenital abnormality of right lower limb (one bone of tarsus missing and shorter fibula and tibia on right side compared to left side). The mother was on simvastatin 20 mg daily for about four weeks during the first trimester, but was also taking aspirin, codeine, acetaminophen and propoxyphene. The third report involves a male newborn with a "simple skin outgrowth on the fifth finger of the left hand and a spherical outgrowth with an anlage of a fingernail. The 30-year-old-mother started simvastatin 10 mg daily for about two weeks during the first trimester. During the seventh month of pregnancy, the mother was hospitalized for three weeks with premature labor and treated with salbutamol. Statins are contraindicated during pregnancy (Pregnancy Category X) because of their ability to lower cholesterol and cholesterol byproducts necessary during fetal development.

Since marketing approval, FDA has received 2 reports of pediatric death associated with simvastatin use. Both were in utero exposures. The first report of death was of a spontaneous miscarriage that occurred in a 32-year-old female. The other involved a premature infant with "severe hypotrophy" who died three days after birth.

The review of the few simvastatin pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the few number and incompleteness of the reports.

In adults, liver dysfunction and muscle-related events are known, labeled risks associated with all statins. The National Lipid Association Safety Assessment Task Force<sup>13</sup> recently concluded: 1) Dose-related, asymptomatic elevations in ALT or AST more than three times the upper limit of normal are seen with all statins. These elevations are typically transient and resolve spontaneously. 2) Liver dysfunction or liver failure associated with statin use cannot be ruled out. FDA has received reports of liver dysfunction and liver failure associated with statins. It is possible liver failure is an idiosyncratic reaction that occurs very rarely with statin therapy, but it is also argued that the rate of liver failure in those individuals taking statins is about the same as the population not taking statins. 3) The most prevalent and significant adverse events associated with statin therapy are related to muscle symptoms or signs. Myalgia is the most common muscle symptom, and more likely to occur at higher statin doses or other situations resulting in elevated blood statin levels. Serious muscle toxicity associated with statin therapy is rare. 4) For individuals requiring statin therapy, the benefit outweighs the risk.

The current labeling for simvastatin outlines liver, muscle, and pregnancy risks, and provides recommendations for monitoring and managing these risks.

In conclusion, the benefit of statins in adults is well documented, and there is growing evidence that statins are efficacious and well tolerated in the pediatric population. However, liver and muscle adverse events remain important risks associated with statin therapy. In addition, it is likely that pediatric patients who require lipid-lowering drugs may use these drugs for many years, and the long-term safety profile of statins (including use during the growth period) is unknown. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. The Division of Drug Risk Evaluation will continue to monitor.

## 2. INTRODUCTION

This document updates a previous (2003) Office of Surveillance and Epidemiology (OSE) consult regarding the one-year post-pediatric exclusivity adverse event review for simvastatin.<sup>1</sup> During the one-year post-pediatric exclusivity period, the AERS database contained few (n=4) simvastatin pediatric reports so the participants at the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee (held June 12, 2003) requested additional follow up.<sup>2</sup>

## 3. PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

### 3.1. Simvastatin Products Available in the United States (Table 1)<sup>3</sup>

Product	NDA	US Approval Date	Tablet Strengths
Simvastatin (Zocor®)*	019766	12/23/1991	5, 10, 20, 40, 80 mg
Ezetimibe/Simvastatin (Vytorin®)	021687	7/23/2004	10/10, 10/20, 10/40, 10 mg/80 mg

\*generic available

<sup>1</sup> Chang J. Avigan M. ODS Postmarketing safety review: one-year post pediatric exclusivity postmarketing adverse events review for simvastatin (PID 030177). 2003 Jun 5:1-7

<sup>2</sup> FDA-CDER. Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee. Adverse event reports as per Section 17, BPCA. 2003 Jun 12. Available at: <http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3965T2.htm>.

<sup>3</sup> FDA/CDER (Drugs@FDA). Simvastatin (Zocor and Vytorin) Approved Labeling. Silver Spring (MD): Food and Drug Administration. c2006 – [cited 2006 Aug 23]. Available from: [www.accessdata.fda.gov/scripts/cder/drugsatfda](http://www.accessdata.fda.gov/scripts/cder/drugsatfda).

### 3.2 Simvastatin Approved Indications (Table 2)<sup>3</sup>

Table 2 describes FDA-approved indications for simvastatin (Zocor).

<b>Table 2. Simvastatin (Zocor) Approved Indications.</b> Source: 8/7/2006 Approved Labeling.
<b>Reductions in Risk of CHD Mortality and Cardiovascular Events:</b> In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease: <ul style="list-style-type: none"><li>▪ Reduce the risk of total mortality by reducing CHD deaths</li><li>▪ Reduce the risk of non-fatal myocardial infarction and stroke</li><li>▪ Reduce the need for coronary and non-coronary revascularization procedures</li></ul>
<b>Hypercholesterolemia:</b> <ul style="list-style-type: none"><li>▪ Reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson types IIa and IIb)</li><li>▪ Treat patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia)</li><li>▪ Treat patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia)</li><li>▪ Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable</li></ul>
<b>Adolescent Patients with Heterozygous Familial Hypercholesterolemia:</b> <ul style="list-style-type: none"><li>▪ Adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heterozygous familial hypercholesterolemia, if after an adequate trial of diet therapy the following findings are present:<ul style="list-style-type: none"><li>a. LDL-C remains <math>\geq</math> 190 mg/dL, or</li><li>b. LDL-C remains <math>\geq</math> 160 mg/dL and there is a positive family history of premature cardiovascular disease OR two or more other CVD risk factors are present in the pediatric patient</li></ul></li></ul> <p>The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C &lt;130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.</p>

### 3.3 Pediatric Labeling

#### 3.3.1 Pediatric Mentions in Simvastatin Labeling

##### Indications and Usage

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

The NCEP classification of cholesterol levels in pediatric patients with a familial history of either hypercholesterolemia or premature cardiovascular disease is summarized below.

**NCEP Classification of Cholesterol Levels in Pediatric Patients  
with a Familial History of Either HeFH or Premature CVD**

<b>Category</b>	<b>Total-C (mg/dL)</b>	<b>LDL-C (mg/dl)</b>
Acceptable	<170	<110
Borderline	170-199	110-129
High	≥200	≥130

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy. ZOCOR is indicated to reduce elevated LDL-C and TG levels in patients with Type IIb hyperlipidemia (where hypercholesterolemia is the major abnormality). However, it has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

**Clinical Pharmacology**

*Clinical Studies in Adolescents*

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (heFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy and received simvastatin 40 mg or placebo. ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B. Results from the extension at 48 weeks were comparable to those observed in the base study.

**Lipid-lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia (Mean Percent Change from Baseline)**

Dosage	Duration	N		Total-C	LDL-C	HDL-C	TG†	Apo B
Placebo	24 weeks	67	% Change from Baseline (95% CI)	1.6 (-2.2, 5.3)	1.1 (-3.4, 5.5)	3.6 (-0.7, 8.0)	-3.2 (-11.8, 5.4)	-0.5 (-4.7, 3.6)
			Mean baseline, mg/dL (SD)	278.6(51.8)	211.9(49.0)	46.9 (11.9)	90.0 (50.7)	186.3 (38.1)
			(95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15.8, 0.0)	-32.4 (-35.9, -29.0)
Zocor	24 weeks	106	Mean baseline, mg/dL (SD)	270.2 (44.0)	203.8 (41.5)	47.7 (9.0)	78.3 (46.0)	179.9 (33.8)
			(95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15.8, 0.0)	-32.4 (-35.9, -29.0)

† Median percent change

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with heterozygous familial hypercholesterolemia. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

**Precautions, Pregnancy**  
Pregnancy Category X

**Precautions, Pediatric Use**  
Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial

hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. See CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents*; ADVERSE REACTIONS, *Adolescent Patients*; and DOSAGE AND ADMINISTRATION, *Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*. Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

#### Adverse Reactions

##### *Adolescent Patients (ages 10-17 years)*

In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolemia (n=175), the safety and tolerability profile of the group treated with ZOCOR (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see CLINICAL PHARMACOLOGY, *Clinical Studies in Adolescents*, and PRECAUTIONS, *Pediatric Use*).

#### Dosage and Administration

##### *Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia*

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10-40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Pediatric Panel Guidelines and CLINICAL PHARMACOLOGY). Adjustments should be made at intervals of 4 weeks or more.

### 3.4 Pediatric Filing History

Table 3 below contains relevant regulatory activity for the pediatric use of simvastatin.

<b>Table 3. Relevant Regulatory Activity for Pediatric Use of Simvastatin</b>	
<b>Date</b>	<b>Regulatory Activity</b>
6/12/03	Pediatric Advisory Subcommittee meeting for atorvastatin and simvastatin <sup>2</sup>
2/22/02	Pediatric exclusivity granted
8/31/99	Written Request issued for sponsor to conduct a clinical study in pediatric boys and girls with heterozygous familial hypercholesterolemia to characterize the efficacy and safety of simvastatin. <sup>4,5</sup>

<sup>4</sup> Parks M. Review of request to amend pediatric written request. 2001 Sep 10. Available at: <http://enterprisearch.fda.gov/index.htm>

<sup>5</sup> Pariser AR. Medical Officer's Review of Supplemental NDA (Request for Pediatric Use Indication). 2002 Sep 23. Available at: <http://enterprisearch.fda.gov/index.htm>

#### 4. AERS SEARCH RESULTS

##### 4.1 Count of Reports: AERS Search Including All Sources (U.S. & Foreign)

**Table 4. Crude counts\* of Simvastatin Reports in the AERS Database for All Sources from March 22, 2003 (previous OSE consult) through August 22, 2006**

Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	3,867 (2,293)	3,636 (2,079)	244 (81)
Peds (0-16 yrs)	6 (2)	6 (2)	1(1)
Age Unknown (Null)	661 (493)	616 (462)	59 (22)
Total	4,534 (2,788)	4,258 (2,534)	301 (104)

\*May include duplicates

†Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

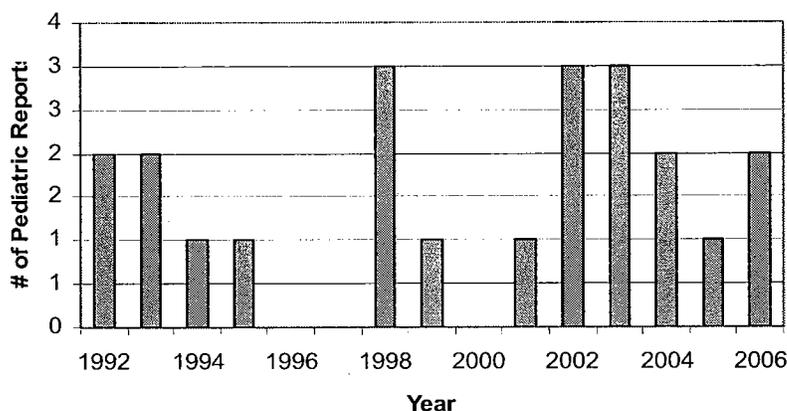
**Table 5. Crude counts\* of Simvastatin Reports in the AERS Database for All Sources Since Approval (December 17, 1996) through August 22, 2006**

Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	11,943 (8,387)	7,972 (4,508)	690 (236)
Peds (0-16 yrs)	22 (6)	21 (6)	2 (1)
Age Unknown (Null)	2,749 (2,358)	1,294 (939)	129 (54)
Total	14,714 (10,751)	9,287 (5,453)	821 (291)

\*May include duplicates

†Serious outcomes per regulatory definition, which includes death, hospitalization, life-threatening, disability, congenital anomaly, requiring intervention, and other.

**Figure 1: Reporting Trend For Simvastatin Pediatric Reports (approval date through 8/22/2006)**



## 5. POSTMARKETING REVIEW OF PEDIATRIC ADVERSE EVENT REPORTS

### 5.1 Case Characteristics:

<b>Table 6. Characteristics of Pediatric Simvastatin in the AERS Database (marketing approval through 8/22/06)</b>			
<b>Characteristic</b>	<b>Marketing To Previous OSE Consult (12/23/91-03/22/03)</b>	<b>Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)</b>	<b>Total Reports (12/23/91-08/22/06)</b>
<b>Number of Unique Reports</b>	<b>16</b>	<b>6</b>	<b>22</b>
<b>Origin of Reports</b>			
United States	4	2	6
Foreign	12	4	16
<b>Year (FDA Receive Date)</b>			
1992	2	-	2
1993	2	-	2
1994	1	-	1
1995	1	-	1
1996	0	-	0
1997	0	-	0
1998	3	-	3
1999	1	-	1
2000	0	-	0
2001	1	-	1
2002	3	-	3
2003	2	1	3
2004	-	2	2
2005	-	1	1
2006	-	2	2
<b>Gender</b>			
Male	6	3	9
Female	10	2	12
Unknown	0	1	1
<b>Age At Time of Event</b>			
0 - <1 month	4	3	7
1 month - 2 years	1	0	1
3 - 5 years	0	0	0
6 - 11 years	5	2	7
12 - 16 years	6	1	7
Unknown	0	0	0
<b>Indication For Use</b>			
Accidental Overdose or Overdose	3	0	3
Hypercholesterolemia	7	3	9
In Utero Exposure	4	3	7
Adrenoleukodystrophy (ALD)	1	0	1
Unknown Indication	1	0	2

**Table 6. Characteristics of Pediatric Simvastatin in the AERS Database (marketing approval through 8/22/06)**

<b>Characteristic</b>	<b>Marketing To Previous OSE Consult (12/23/91-03/22/03)</b>	<b>Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)</b>	<b>Total Reports (12/23/91-08/22/06)</b>
<b>Dose (Those Using For Dyslipidemia)</b>			
< 10 mg	2	2	4
10 to 20 mg	3	0	3
25 to 40 mg	2	1	3
Unknown	2	0	2
<b>Dose (Accidental Ingestions or Overdose)</b>			
2,600 mg	1	0	1
Unknown	2	0	2
<b>Dose (In Utero Exposures)</b>			
10 – 20 mg	3	3	6
Unknown	1	0	2
<b>Duration (Those Using For Dyslipidemia)</b>			
< 6 months	3	2	5
6 – 12 months	0	0	0
>12 months	1	1	2
Unknown	5	0	5
<b>Duration (Accidental Ingestion or Overdose)</b>			
Not applicable	3	0	3
<b>Duration (In Utero Exposures)</b>			
First trimester	2	3	5
Unknown	2	0	2
<b>Primary Reported Adverse Event (by System Organ Class [SOC])</b>			
<i>Blood and Lymphatic Disorder</i>			
Thrombotic thrombocytopenia purpura	0	1	1
<i>Gastrointestinal Disorder</i>			
Pancreatitis	1	0	1
<i>Hepatobiliary Disorder</i>			
Increased LFTs	1	0	1
<i>Investigations</i>			
Increased LDH	1	0	1
<i>Musculoskeletal and Connective Tissue Disorder</i>			
Increased CK	0	2	2
Lupus arthritis	1	0	1
Dermatomyositis	1	0	1
<i>Nervous System Disorder</i>			
Neuroleptic malignant syndrome	1	0	1
Seizures	1	0	1
Headache, paresthesia, motor weakness	1	0	1
<i>Renal and Urinary Disorders</i>			
Renal toxicity	1	0	1
<i>Other</i>			
Accidental Ingestion or Overdose	3	0	3
<i>In Utero Exposures</i>			
<i>Congenital abnormality, R limb</i>	0	1	1
<i>Congenital abnormality, acrochordons</i>	0	1	1
<i>Spontaneous miscarriage</i>	0	1	1
<i>Normal, healthy infant</i>	1	0	1
<i>Prematurity, epilepticus, surfactant</i>	1	0	1

**Table 6. Characteristics of Pediatric Simvastatin in the AERS Database (marketing approval through 8/22/06)**

Characteristic	Marketing To Previous OSE Consult (12/23/91-03/22/03)	Previous OSE Consult to AERS Cutoff Date (03/22/03-08/22/06)	Total Reports (12/23/91-08/22/06)
<i>disease, and cardiac dysrhythmias</i>			
<i>Balanic hypospadias</i>	1	0	1
<i>Prematurity, severe hypotrophy</i>	1	0	1
<b>Reported Outcomes</b> (may not sum due to reporting of more than one outcome)			
Congenital Anomaly	0	2	2
Death	1	1	2
Disability	1	1	2
Hospitalization	7	0	7
Life-Threatening	1	0	1
Required Intervention	0	0	0
Other	6	2	8
Unknown/Not Reported	2	0	2

## 5.2 Summary of Cases Received

Since the previous OSE consult on March 22, 2003, FDA received 6 pediatric simvastatin reports. Two of the six reports were from the United States, the rest were foreign reports.

There were two reports of increased creatine phosphokinase (CK). The first (**CASE 5723093**) was a foreign report of a 6-year-old female with nephrotic syndrome who developed increased CK levels (518) in Jun04 after starting simvastatin 5 mg daily on 24May04. No muscle symptoms were reported, and the increased CK level was found on a "routine screen." The child was also taking cyclosporine and corticosteroids. The CK in Jul04 was 1,251 and simvastatin was DC. The child initially improved, but the CK again increased and cyclosporine was DC (switched to tacrolimus). The CK continued to increase (1,973 in 7Dec04), but then decreased (CK 731 on 21Dec04). Treatment measures not reported. The simvastatin labeling notes cyclosporine can increase the area under the curve (AUC) of statins such as simvastatin (presumably through inhibition of CYP3A4), which can result in an increased risk of myopathy or rhabdomyolysis (see WARNINGS). The labeling recommends, in patients taking cyclosporine, simvastatin therapy begin with 5 mg daily and not exceed 10 mg daily (see DOSAGE AND ADMINISTRATION). The second report (**CASE 5989383**) involves a 14-year-old boy with familial hypercholesterolemia who started simvastatin in Jan02 (dose increased from 10 mg to 40 mg on unknown dates). In Jun04, after his methylphenidate (Concerta) dose was increased from 36 mg to 54 mg, the boy developed thigh stiffness and CK of 792. Simvastatin was discontinued and the boy recovered. Atorvastatin 20 mg was started in Aug04, decreased to 10 mg in Jan05, and ezetimibe (Zetia) added in Jan05. In Sep05, CK was 831 without muscle complaints. In Jan06, the boy complained of muscle symptoms (including chest pain); CK was 24,265. Atorvastatin and ezetimibe were discontinued on 16Jan06. Three days later the CK was decreased to 3,674; on 6Feb06 CK normalized (218). Atorvastatin is labeled for muscle symptoms (including muscle tenderness, or weakness, myalgia, myopathy, myositis, leg cramps, and rhabdomyolysis)

and elevations in creatine phosphokinase (CK). It is not clear why the boy experienced thigh stiffness and elevated CK when his methylphenidate dose was increased. There is no documented metabolic drug interaction between methylphenidate and statins<sup>6</sup> and methylphenidate therapy was not interrupted to evaluate dechallenge. Methylphenidate has been very rarely associated with neuroleptic malignant syndrome (NMS) – that can lead to rhabdomyolysis. However, although this boy presented with muscle stiffness and increased CK, there was no mention of other common NMS-associated symptoms such as hyperthermia. In regards to the boy's redevelopment of muscle symptoms and elevated CK while taking atorvastatin and ezetimibe, the atorvastatin labeling does not mention a drug interaction between statins and ezetimibe. There is an FDA-approved statin-ezetimibe product, Vytorin (ezetimibe/simvastatin) on the market, for which myalgia was reported more frequently as an adverse reaction compared to monotherapy with ezetimibe or simvastatin (see ADVERSE REACTIONS). There are also published case reports of a possible association between ezetimibe and statins.<sup>7,8</sup>

There was one report of thrombotic thrombocytopenic purpura (TTP) that occurred in an 8-year-old female with systemic lupus erythematosus, lupus nephritis, and Sjogren's syndrome. The child started simvastatin 5 mg daily in Jan06, but was also taking alfacalcidol, dipyridamole, azathioprine, famotidine and prednisolone. On 1Mar06, the azathioprine dose was changed (not reported as increased or decreased). The child experienced TTP on 7Apr06. Simvastatin was DC on 12Apr06, but the TTP persisted. The simvastatin labeling describes hypersensitivity reactions that have been associated with the statin class (but not necessarily simvastatin), which may include features such as purpura and thrombocytopenia. The labeling does not specify TTP as a known reaction to simvastatin. However, there are published reports of simvastatin-associated TTP in adults.<sup>9,10</sup> There are also reports of TTP occurring in association with underlying systemic lupus erythematosus.<sup>11</sup>

The three remaining reports involved **in utero exposures**. The first (**CASE 4049926**) reports a spontaneous miscarriage that occurred in a 32-year-old female (gravida 1, para 1) who started simvastatin 20 mg daily on 23Jul03 for hypercholesterolemia and discontinued it on 22Oct03. On 11Nov03, the mother found out she was 5 weeks pregnant with an estimated delivery date of 14Jul04. The miscarriage occurred in — The second report (**CASE 4126332**) is a retrospective report (from 1996) relative to a

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<sup>6</sup> Lexi-Comp (Lexi-Interact On-Line). Methylphenidate: interacting categories. 2006. Available at [www.lexi-comp.com](http://www.lexi-comp.com).

<sup>7</sup> Simard C, Poirier P. Ezetimibe-associated myopathy in monotherapy and in combination with a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. *Can J Cardiol* 2006 Feb;22(2):141-4.

<sup>8</sup> Bays H. Statin safety: an overview and assessment of the data-2005. *Am J Cardiol*. 2006;97 [suppl]:6C-26C.

<sup>9</sup> Sundram F, Roberts P, Kennedy B, and Pavord S. Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J*. 2004;80:551-552.

<sup>10</sup> McCarthy LJ, Porcu P, Fausel CA, Sweeney CJ, Danielson CF. Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998 Oct 17;352(9136):1284-5.

<sup>11</sup> Majithia V, Harisdangkul V. Thrombotic thrombocytopenic purpura in systemic lupus erythematosus: a frequent and severe consequence of active disease. *Rheumatology*. 2006 Sep;45(9):1170-1.

letter to the editor by Edison and Muenke.<sup>12</sup> The report describes a female infant born in 1996 with congenital abnormality of right lower limb (one bone of tarsus missing and shorter fibula and tibia on right side compared to left side). The mother was on simvastatin 20 mg daily for hypercholesterolemia, and was also taking aspirin, codeine, acetaminophen and propoxyphene. In Jan96, the mother became pregnant and all therapies were discontinued on 27Feb96. At 4-years-old, the child's length difference between both lower limbs was 1.5 centimeters; length difference between both feet was two sizes less for right foot. The third report (CASE 4137527) involves a male infant born on \_\_\_\_\_ weight: 2.97 kg, Apgar 10 at 1 and 5 minutes) with a "simple skin outgrowth on the fifth finger of the left hand and a spherical outgrowth with an anlage of a fingernail. A tourniquet was applied to the spherical outgrowth, which resolved within 48 hours. The 30-year-old-mother started simvastatin 10 mg daily for hypercholesterolemia on 14Jul89 (at two weeks gestation). Simvastatin DC on 28Jul90. During the seventh month of pregnancy, the mother was hospitalized for three weeks with premature labor and treated with salbutamol. There may be one additional report of an in utero exposure. CASE 4137527 references a letter to the editor by Edison and Muenke.<sup>12</sup> However, the letter describes two reports of congenital anomalies associated with simvastatin. The first is a report of right fibula and tibia shorter than left side (see CASE 4126332 above). The second is a report of left leg femur shorter than right side; foot: aplasia of metatarsals and phalanges 3, 4, and 5; additional VACTERL defects: left renal dysplasia, reversed lateral of aorta, disorganized lumbosacral vertebrae, single umbilical artery. It is not clear if the second report in the letter to the editor is the same as CASE 4137527 or it may be an additional report. Statins, including simvastatin, are contraindicated in nursing mothers and during pregnancy (Pregnancy Category X) because of their ability to lower cholesterol and cholesterol byproducts necessary during fetal development.

Since marketing approval, FDA has received 2 reports of pediatric death associated with simvastatin use. Both were in utero exposures. The first report of death was of a spontaneous miscarriage that occurred in a 32-year-old female (CASE 4049926). The other involved a premature infant with "severe hypotrophy" who died three days after birth (CASE 3784386).

Characteristics for all the pediatric simvastatin cases (n=22) found in the AERS database are described in Table 6 above and a summary of each case is provided in ATTACHMENT 1.

### 5.3 Limitation of AERS

It is possible there are additional pediatric simvastatin adverse event reports. The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the United States reflects underreporting and duplicate reporting. For any given report, there is limited certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential

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<sup>12</sup> Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *NEJM*. 2004 Apr 8;350(15):1579-1582.

drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

## 6. PEDIATRIC UTILIZATION DATA

The number of simvastatin pediatric prescriptions dispensed in retail pharmacies remains less than 0.1 percent of the total number of prescriptions dispensed in retail pharmacies (see Table 7). Use in the pediatric population appears to be decreasing over the past few years, but the numbers are small and based on projected values which may not represent actual trends. Furthermore, the decrease could be due to increased use of mail service (and mail service prescriptions aren't reflected in Table 7 below).

**\*\*The table below contains proprietary drug use data obtained by under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*\***

<b>Table 7. Total Number of Simvastatin Prescriptions Dispensed in Retail Pharmacies* Nationwide (By Year Since 2002).</b>				
Source: Verispan, Vector One®: National (VONA), Queried Sep 7, 2006				
<b>Age (in years)</b>	<b>Number of Prescriptions By Year</b>			
	<b>2002</b>	<b>2003</b>	<b>2004</b>	<b>2005</b>
<b>0-16</b>	13,498	12,397	11,427	10,466
0-1	2,105	1,214	895	648
2-5	4,222	3,863	2,913	2,089
6-16	7,171	7,320	7,619	7,729
<b>17+</b>	23,966,471	24,114,955	23,598,151	22,117,741
<b>Unspec. Age</b>	86,817	87,713	194,687	197,159
<b>Total</b>	24,066,786	24,215,065	23,804,265	22,325,366

\*Doesn't include mail service or long-term care. Numbers may be lower than previous consult that used data from IMS Health (which included mail service prescription data).

## 7. SUMMARY AND RECOMMENDATIONS

The review of the few simvastatin pediatric reports in the AERS database did not identify adverse events unique to the pediatric population. However, the review was limited by the few number and incompleteness of reports. In adults, liver dysfunction and muscle-related events (such as myopathy, myalgia, and rhabdomyolysis) are known, labeled risks associated with all statins. In April 2006, following a comprehensive assessment of statin safety (primarily in adults), the National Lipid Association Safety Assessment Task Force concluded:<sup>13</sup> 1) Dose-related, asymptomatic elevations in ALT or AST more than three times the upper limit of normal are seen with all statins. These elevations are typically transient and resolve spontaneously. 2) Liver dysfunction or liver failure associated with statin use cannot be ruled out. There are published reports of statin-induced

<sup>13</sup> McKenney JM. Report of the National Lipid Association's Statin Safety Task Force. Am J Cardiol. 2006 Apr 17;97(8 Suppl 1):S1-S98.

hepatotoxicity and FDA has received statin reports of liver dysfunction and liver failure. It is possible liver failure is an idiosyncratic reaction that occurs very rarely with statin therapy, but it is also argued that the rate of liver failure in those individuals taking statins is about the same as the population not taking statins. 3) The most prevalent and significant adverse events associated with statin therapy are related to muscle symptoms or signs. In a practice setting, the incidence of muscle complaints associated with statin use ranges from 0.3 to 33 percent (1.5 to 3 percent in clinical trials). Myalgia (muscle pain or soreness) is the most common muscle symptom, and more likely to occur at higher statin doses or other situations resulting in elevated blood statin levels (such as that seen with drug interactions). Serious muscle toxicity associated with statin therapy is rare (rhabdomyolysis occurs in 1.6 patients per 100,000 person-years; myopathy in 5 patients per 100,000 person-years). 4) For individuals requiring statin therapy, the benefit outweighs the risk.

The current labeling for simvastatin outlines liver, muscle, and pregnancy risks, and provides recommendations for monitoring and managing these risks by reducing or withdrawing statin therapy or avoiding drug interactions.

The National Cholesterol Education Program (NCEP) recommends lipid-lowering drug therapy for children 10 years and older if, after an adequate trial of diet therapy, the LDL cholesterol remains  $\geq 190$  mg/dL or the LDL cholesterol remains  $>160$  mg/dL and there is a family history of premature CVD or the presence of two or more other CVD risk factors.<sup>14</sup> In the United States, available lipid-lowering drugs include: bile acid sequestrants, niacin or nicotinic acid, fibrates, intestinal cholesterol absorption inhibitors (ezetimibe), omega fatty acids (omega-3-acid ethyl esters), and statins. Of these agents, the bile acid sequestrants and statins are most commonly used in children.<sup>15</sup> However, bile acid sequestrants are associated with intolerability (poor palatability and gastrointestinal upset) and modest lipid-lowering effects. The statins are supported by a growing body of pediatric clinical trial data, significant lipid-altering effects, improved tolerability compared to other lipid-lowering agents, and widespread exposure in adults (in 2005 there were more than 140 million prescriptions dispensed in the United States<sup>16</sup>).<sup>15,17,18</sup> Niacin or nicotinic acid products are not routinely used in children due to significant adverse effects such as flushing and myopathy. The fibrates are generally reserved for children with hypertriglyceridemia at risk for pancreatitis,<sup>17</sup> and the use of omega fatty acids are limited by lack of published pediatric studies. Ezetimibe (approved by FDA in 2002) has been shown efficacious in children with homozygous familial hypercholesterolemia or sitosterolemia, but is not yet approved by FDA for use in children.<sup>15</sup>

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<sup>14</sup> American Academy of Pediatrics. National Cholesterol Education Program: Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 1992;89(3 Pt 2):525–584.

<sup>15</sup> Holmes KW, Kwiterovich PO. Treatment of dyslipidemia in children and adolescents. *Curr Cardiol Rep*. 2005 Nov;7(6):445-56.

<sup>16</sup> IMS Health. Top-line industry data. 2006 (cited Jul 27, 2006). Available at: [http://www.imshealth.com/ims/portal/front/indexC/0.2773.6599\\_5264\\_0.00.html](http://www.imshealth.com/ims/portal/front/indexC/0.2773.6599_5264_0.00.html)

<sup>17</sup> McCrindle BW. Hyperlipidemia in children. *Thrombosis Research*. 2006;118:49-58.

<sup>18</sup> Rodenburg J, Vissers MN, Daniels SR, Weigman A, Kastelein JJ. Lipid-lowering medications. *Pediatr Endocrinol Rev*. 2004 Nov;2 Suppl 1:171-80.

In summary, the benefit of statins in adults is well documented, and there is growing evidence that statins are efficacious and well tolerated in the pediatric population. However, liver and muscle adverse events remain important risks associated with statin therapy. In addition, it is likely that pediatric patients who require lipid-lowering drugs may use these drugs for many years, and the long-term safety profile of statins (including use during the growth period) has not been established. There are too few reported adverse events in any one area to make a conclusion regarding safety signals unique to the pediatric population. The Division of Drug Risk Evaluation will continue to monitor.

Jo Wyeth, Sept 12, 2006  
Jo Wyeth, Safety Evaluator

Lanh Green, Sept 12, 2006  
Lanh Green, Team Leader

Rosemary Johann-Liang, Sept 14, 2006  
Rosemary Johann-Liang, Deputy Director

8. **ATTACHMENT 1: Summary of Pediatric Simvastatin (Zocor) Cases in AERS Database, Categorized by Date Received (Marketing Approval Through AERS Cutoff Date of August 22, 2006)**

RECVDATE:	CSENUM:	DESCRIPTION
9/29/1992	4909479	Foreign report of a 2-year-old female who experienced accidental ingestion with simvastatin (amount unknown). The child was admitted to the hospital, during the night developed tachycardia (which resolved by morning).
11/30/1992	4928845	U.S. physician reports a 16-year-old female with history of lupus and nephrotic syndrome (on prednisone, azathioprine, hydroxychloroquine, and furosemide) started simvastatin 10 mg BID in Aug92 for hyperlipidemia. Two months later, the child developed renal toxicity (BUN: 56, SCr increased from 0.08 to 1.8). The child complained of headaches, but no muscle symptoms. Simvastatin DC and laboratory values improved.
11/3/1993	5047198	Foreign report of a 9-year-old female with hypotension who started simvastatin 5 mg daily 22Apr92 for familial hypercholesterolemia. Seven months later, the child experienced a 10-minute episode of severe headache, paresthesia of the right hand, motor weakness, and expressive aphasia. The child was hospitalized, simvastatin DC. MRI normal, EEG revealed unstable baseline activity with inconsistent theta waves. The patient recovered. Attending physician attributed events to simvastatin or "complicated migraine."
11/5/1993	5051838	Foreign report of a newborn (1.9 KG) born prematurely on — after 32 weeks amenorrhea developed surfactant disease, cardiac rhythm disorder, status epilepticus, and anemia. The 31-year-old mother had a history of hypertension (on perindopril) and started simvastatin 10 mg on 07Sep92 (stop date unknown). Laboratory analysis revealed increased CRP related to a gastric and ocular infection (from the mother). Treated with antibiotics, EEG normal, Transfontanels of skull ultrasonography abnormal. "Outcome was good," newborn placed on iron and vitamin D supplements.
7/26/1994	5151979	U.S. physician reports 11-year-old male on simvastatin 25 mg daily (duration unknown) and cholestyramine for hypercholesterolemia experienced increased ALT and AST (1.5 x UPLN), fatigue without muscle weakness. Report indicates therapy with "lovastatin" was discontinued because cholesterol-lowering effect "was minimal."
10/3/1995	5302410	Foreign report of a 15-year-old female who tried to commit suicide in — ingesting simvastatin, oxprenolol, gallopamil, diclofenac, ibuprofen, horse chestnut extract, aspirin, and renoprate (amounts unknown). The child developed unspecified "slight CNS symptoms" and gastrointestinal upset. She was hospitalized and recovered without treatment.
2/23/1998	3171332	U.S. pharmacist report of an 8-year-old hispanic male with history of myocardial infarction and PTCA (on amlodipine and aspirin) who was taking simvastatin (dose and duration unknown) for hypercholesterolemia. The reporter indicates the boy was also taking amylase (dose, duration, indication not known). In —, the boy was hospitalized with pancreatitis (lipase 5250, amylase 4800). No additional information provided.

RECVDATE:	CSENUM:	DESCRIPTION
7/13/1998	3134665	Foreign report of a 16-year-old female who attempted suicide / ingesting 130 tablets of simvastatin 20 mg. She was hospitalized for observation, but did not require overdose treatment.
9/3/1998	3142509	Foreign report of an 8-year-old female who started simvastatin 40 mg daily in 1997 for the treatment of familial hypercholesterolemia. More than four months later (on 10May98), the girl experienced a flu-like illness, paresthesias in the fingers and feet, "fingershaped" rash in her face and extremities, and "progressive myalgia and muscle weakness (starting proximal)." The girl was hospitalized and diagnosed with dermatomyositis (CK: 11,515, LDH 4,021, AST 877, ALT 256, anti-ANA positive). EMG showed "small complete polyphasic potentials with early degenerative events and complex repetitive discharges." Skin biopsy "didn't show anything specific." Child started corticosteroids and muscle symptoms improved. Simvastatin was DC on 6Jun98, but the child's dermatomyositis persisted.
1/28/1999	3201504	Foreign report of a male infant born "in good health" (weight: 3.5 kg, Apgar 10 at 1 and 5 minutes) with "balanic hypospadias without penis bend." The mother was taking simvastatin 10 mg daily (along with alpidem and fluoxetine). Simvastatin was DC 19Mar93 in the first trimester (see duplicate CASE 4127652/ ISR 4341734-7).
10/24/2001	3720761	Foreign report of a 13-year-old male who experienced seizures while taking simvastatin (dose, duration, indication unknown). No other information available.
2/28/2002	3787377	U.S. physician report of a 17-year-old female with diabetes started simvastatin 20 mg daily in Oct99 (dose increased to 30 mg the same month) for treatment of dyslipidemia. Reported concomitant therapy included: methotrexate, naproxen, and prednisone (start date and duration not provided). In Dec99, the child experienced "severe joint pains" and was diagnosed with lupus arthritis in Jan or Feb00. Simvastatin DC in Mar or Jul00, and according to physician, symptoms resolved. Patient continued arthritis medications until Aug00.
4/11/2002	3784386	Foreign report of a male infant born prematurely (32 weeks and 5 days of amenorrhea, weight: 1.1 kg) on with severe hypotrophy, and died at day 3 of "prematurity." The mother became pregnant on 5Jan97, and during the pregnancy, the mother took betamethasone (17Jul97-6Aug97), simvastatin (dose unknown) since Feb97, ferrous sulfate/folic acid/mucoproteose/ascorbic acid, oxerutins, and lysine aspirin (started 22Jun97).
4/23/2002	3781395	Foreign report of a published article (Rubio-Gozalbo ME et al, 2001) of an 8-year-old-boy with advanced cerebral adrenoleukodystrophy who (cALD) who experienced neuroleptic malignant syndrome (NMS) while taking simvastatin 1 mg/kg daily as part of a clinical trial. Concurrent medication included the antipsychotic, zuclopenthixol for "behavioral disturbance." One week after the zuclopenthixol dose was increased, the boy developed pyrexia, tachycardia, tachypnea, hypotension, and rigidity. He was diagnosed with NMS, and both zuclopenthixol and simvastatin (because "muscle damage is a known side effect") were DC. The child was treated with clonazepam and dantrolene and improved. The authors suggest an interaction between neuroleptics and statins.

RECVDATE:	CSENUM:	DESCRIPTION
2/21/2003	3904056	Foreign report of a "normal, healthy female" newborn (weight: 2.95 kg), whose 26-year-old mother started simvastatin 10 mg on 12Jun01 for familial hypercholesterolemia, and discontinued it on 20Mar02 (LMP Jan02). On — mother underwent an emergency lower segment caesarean section (LSCS) due to foetal distress. The baby had no congenital anomalies or complications.
3/3/2003	3847821	Foreign report of a 14-year-old boy who started simvastatin 20 mg and 10 mg (alternating days) on 15Dec98 for familial hypercholesterolemia. Concomitant medication included ibuprofen as needed for joint pains. On an unknown date, the boy experienced "vague chest pain and mild body aches." ECG was WNL. In Aug02, routine laboratory evaluation revealed increased LDH level (629). Simvastatin switched to pravastatin. On 17Feb02, LDH was WNL (382), and the patient was reported to be recovering from the elevated LDH.
12/29/2003	4049926	U.S. physician report of a spontaneous miscarriage that occurred in a 32-year-old female (gravida 1, para 1) who started simvastatin 20 mg daily on 23Jul03 for hypercholesterolemia and discontinued it on 22Oct03. On 11Nov03, the mother found out she was 5 weeks pregnant with estimated delivery date of 14Jul04. The miscarriage occurred —.
4/16/2004	4126332	U.S. published article (Edison RJ, Muenke M, 2004) of a female infant born in 1996 with congenital abnormality of right lower limb (one bone of tarsus missing, shorter fibula and tibia on right side compared to left side). The mother was on simvastatin 20 mg daily for hypercholesterolemia, and was also taking aspirin, codeine, acetaminophen and propoxyphene. In Jan96, the mother became pregnant and all therapies were discontinued on 27Feb96. At 4-years-old, the child's length difference between both lower limbs was 1.5 centimeters, between both feet was two sizes less for right foot.
4/28/2004	4137527	Foreign report of a male infant born on —, weight: 2.97 kg, Apgar 10 at 1 and 5 minutes) with a "simple skin outgrowth on the fifth finger of the left hand and a spherical outgrowth with an anlage of a fingernail. A tourniquet was applied to the spherical outgrowth, which resolved within 48 hours. The 30-year-old-mother started simvastatin 10 mg daily for hypercholesterolemia on 14Jul89 (at two weeks gestation). Simvastatin DC on 28Jul90. During the seventh month of pregnancy, the mother was hospitalized for three weeks with premature labor and treated with salbutamol. This report references a letter to the editor (Edison RJ, Muenke M, 2004). However, this letter describes two reports of congenital anomalies associated with simvastatin. The first is a report of right fibula and tibia shorter than left side (see CASE 4126332). The second is a report of left leg femur shorter than right side; foot: aplasia of metatarsals and phalanges 3,4, and 5; additional VACTERL defects: left renal dysplasia, reversed lateral of aorta, disorganized lumbosacral vertebrae, single umbilical artery.

RECVDATE:	CSENUM:	DESCRIPTION
1/26/2005	5723093	Foreign report of a 6-year-old female with nephrotic syndrome who developed increased CK levels in Jun04 (518) while taking cyclosporine (started 28Mar04), simvastatin 5 mg daily (started 24May04), and corticosteroids. CK on 12Jul04 was 1,251. Simvastatin DC, and child initially improved, but CK again increased. Cyclosporine DC on 1Nov04 and tacrolimus started. CK continued to increase (1,973 in 7Dec04), but then began to decrease (CK 731 on 21Dec04). Treatment measures unknown.
3/10/2006	5989383	Foreign physician report of a 14-year-old, 100-kg male who experienced elevated creatine phosphokinase (CK) levels while taking lipid-lowering drugs for familial hypercholesterolemia and methylphenidate (Concerta). The child started simvastatin in Jan02 (dose increased from 10 mg to 40 mg). Methylphenidate increased to 54 mg in Jun04 and the child experienced thigh stiffness (CK: 792). Simvastatin DC and event resolved. In Aug04, atorvastatin 20 mg started; dose decreased to 10 mg in Jan05 and ezetimibe added (dose unknown). In Sep05, CK was 831, but no muscle symptoms were apparent. In Jan06, child complained of muscle symptoms (including chest pain). CK was 24,265. Atorvastatin DC. 19Jan05, CK was 3,674 and 218 on 6Feb06.
4/28/2006	6034667	Foreign report of an 8-year-old female with systemic lupus erythematosus, lupus nephritis, and Sjogren's syndrome who started simvastatin 5 mg daily for hyperlipidemia on 4Jan06. The child was also taking alfacalcidol, dipyridamole, azathioprine, famotidine, and prednisolone. On 1Mar06, azathioprine was changed (unknown if increased or decreased) to 40 mg. On 7Apr06 the child experienced thrombotic thrombocytopenic purpura (TTP). Simvastatin DC on 12Apr06, but TTP persisted. Final outcome not reported.