MEMORANDUM

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

DATE: January 25, 2007

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SUBJECT: Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Fluvastatin sodium (Lescol [NDA 20-261], Lescol XL [21-192])
Pediatric Exclusivity Approval Date: December 15, 2005

RCM # 2007-43

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1. EXECUTIVE SUMMARY

This document summarizes fluvastatin (Lescol, Lescol XL) pediatric adverse event reports in Adverse Event Reporting System (AERS). The Office of Pediatric Therapeutics requested this information in preparation for their Pediatric Advisory Committee (PAC) meeting scheduled for April 2007.

Fluvastatin was approved in December 1993, and pediatric exclusivity was granted on December 15, 2005. In the pediatric population, fluvastatin is indicated as an 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, 10-16 years of age with heterozygous familial hypercholesterolemia. The recommended starting dose for pediatric patients is 20 mg daily, which can be adjusted to a maximum daily dose of 80 mg. Fluvastatin is Pregnancy Class X.

A search of the AERS database on January 15, 2007 identified 2,455 fluvastatin reports (crude counts), of which 7 (all foreign reports) were reported in children less than 17 years of age. None of the seven reports were received during the one-year period following the date pediatric exclusivity was granted. There were no reports of death associated with fluvastatin use in the pediatric population.

Of the seven reports, three involved accidental ingestion, and there is one report each of 1) leukopenia and neutropenia, 2) chorioretinitis, 3) in-utero exposure, and 4) intentional overdose.

The **leukopenia and neutropenia** report involves an 11-year-old boy with history of steroid-resistant nephrotic syndrome, who experienced leukopenia and neutropenia about two months after switching from Sandimmune to Neoral 125 mg daily. The boy was also taking fluvastatin (started one week after Neoral therapy initiated), prednisolone, dipyridamole, alfacalcidol, warfarin, glutamine, and ketotifen. Ten days after Neoral was discontinued the WBC increased (fluvastatin therapy was not changed or discontinued). Neoral was eventually restarted at a lower dose and a month later the WBC had returned to baseline. The **chorioretinitis** report involves a 14-year-old boy with a history of "three relapses of chorioretinitis" who experienced another episode of chorioretinitis an unknown time after starting fluvastatin. The **in utero exposure** report involves 43-year-old mother, who was treated during her entire pregnancy with metformin and hydrochlorothiazide/valsartan, and for an unknown duration with fluvastatin and diosmin (an agent categorized as a vascular protectant). The baby was born at 37 weeks gestation, and diagnosed with severe pulmonary hypertension, hypertrophic cardiopathy, and renal failure. Statins are contraindicated during pregnancy because of the statin's ability to lower cholesterol and cholesterol byproducts necessary during fetal development. The one report of **intentional overdose** involves a 16-year-old female who, "in an act of suicide ideation," ingested her mother's medications: fluvastatin 280 mg, tramadol 1000 mg, and an unknown amount of the neuroleptic, prothipendyl. The girl was hospitalized with "convulsions," but recovered. Three reports involved **accidental ingestion** of fluvastatin. All three children were younger than four years of age and were taken to the hospital. No outcome information was provided for any of the three reports.

The review of the seven pediatric fluvastatin 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, the most commonly reported adverse events associated with statin therapy are related to the muscles, and range from myalgia (muscle pain or soreness) to rare cases of serious muscle toxicity like rhabdomyolysis. Hepatotoxicity is another serious, but rare adverse event associated with statin therapy. As of January 15, 2007, there are no fluvastatin pediatric reports involving the muscles or liver in the AERS database. However, statin-associated muscle and liver events are well documented in the adult population and the lack of pediatric reports may be related to limited usage of fluvastatin in the pediatric population and underreporting of adverse events.

The National Cholesterol Education Program 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. 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. 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. 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 hypertriglyeridemia at risk for pancreatitis, 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.

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 summarizes fluvastatin (Lescol, Lescol XL) pediatric adverse event reports in the Adverse Event Reporting System (AERS). This information on pediatric

adverse event reports was requested by the Office of Pediatric Therapeutics in preparation for their Pediatric Advisory Committee (PAC) meeting scheduled for April 2007. Initial review of fluvastatin by the Pediatric and Maternal Health Team indicate there have been no serious pediatric adverse events or deaths associated with fluvastatin during the one-year period following the date pediatric exclusivity was granted on December 15, 2005. Therefore, the Office of Pediatric Therapeutics requests the Division of Drug Risk Evaluation (DDRE) review all fluvastatin pediatric adverse event reports since initial approval of fluvastatin in 1993.

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

3.1. Fluvastatin Products Available in the United States (Table 1)

Table 1. Description of Fluvastatin Products Available in the United States.
Source: 4/10/2006 Approved Labeling[1]

Product	NDA	US Approval Date	Available Strengths and Formulations
Fluvastatin (Lescol)	20-261	12/31/1993	20, 40 mg capsules
Fluvastatin, Extended Release (Lescol XL)	21-192	10/06/2000	80 mg tablet

3.2 Fluvastatin Approved Indications (Table 2)

Table 2. Fluvastatin (Lescol, Lescol XL) Approved Indications.
Source: 4/10/2006 Approved Labeling[1]

Hypercholesterolemia and Mixed Dyslipidemia ▪ As adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG levels and increase HDL-C in patients with primary heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) ▪ 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 to 16 years of age) with heterozygous familial hypercholesterolemia** if after trial of diet therapy the following are present: a. LDL-C remains $\geq$ 190 mg/dL, or b. LDL-C remains $\geq$ 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
Secondary Prevention of Coronary Events ▪ In patients with coronary heart disease (CHD), to reduce the risk of undergoing coronary revascularization procedures
Atherosclerosis ▪ In patients with CHD, to slow progression of coronary atherosclerosis

[1] FDA/CDER (Drugs@FDA). Fluvastatin (Lescol, Lescol XL) Approved Labeling. Silver Spring (MD): Food and Drug Administration. c2007 [cited 2007 Jan 14]. Available from: www.accessdata.fda.gov/scripts/cder/drugsatfda.

3.3 Pediatric Labeling

3.3.1 Pediatric Mentions in Fluvastatin Labeling[1]

This section describes fluvastatin labeling (Prescribing Information and Patient Information) specifically related to the pediatric population. See the most recently approved labeling (available at www.accessdata.fda.gov/scripts/cder/drugsatfda) for a complete and current description of pharmacology, indications, contraindications, warnings, precautions (including drug interactions), and adverse drug reactions.

CLINICAL PHARMACOLOGY
Special Populations
Pediatric:
Pharmacokinetic data in the pediatric population are not available.

CLINICAL STUDIES
Heterozygous Familial Hypercholesterolemia in Pediatric Patients
Fluvastatin sodium was studied in two open-label, uncontrolled, dose-titration studies which enrolled pediatric patients with heterozygous familial hypercholesterolemia. The first study enrolled 29 pre-pubertal boys, 9-12 years of age, who had an LDL-C level > 90th percentile for age and one parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthomas. The mean baseline LDL-C was 226 mg/dL (range: 137-354 mg/dL). All patients were started on Lescol capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (40 mg bid) to achieve an LDL-C goal of 96.7 to 123.7 mg/dL. Endpoint analyses were performed at Year 2. The second study enrolled 85 male and female patients, 10 to 16 years of age, who had an LDL-C > 190 mg/dL or LDL-C > 160 mg/dL and one or more risk factors for coronary heart disease, or LDL-C > 160 mg/dL and a proven LDL-receptor defect. The mean baseline LDL-C was 225 mg/dL (range: 148-343 mg/dL). All patients were started on Lescol capsules 20 mg daily with dose adjustments every 6 weeks to 40 mg daily then 80 mg daily (Lescol 80 mg XL tablet) to achieve an LDL-C goal of < 130 mg/dL. Endpoint analyses were performed at Week 114.

In the first study, Lescol 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 21% and 27%, respectively. The mean achieved LDL-C was 161 mg/dL (range: 74-336 mg/dL). In the second study, Lescol 20 to 80 mg daily doses decreased plasma levels of total-C and LDL-C by 22% and 28%, respectively. The mean achieved LDL-C was 159 mg/dL (range: 90-295 mg/dL)

The majority of patients in both studies (83% in the first study and 89% in the second study) were titrated to the maximum daily dose of 80 mg. At study endpoint, 26 to 30% of patients in both studies achieved a targeted LDL-C goal of < 130 mg/dL.

The long-term efficacy of Lescol or Lescol XL therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

INDICATIONS AND USAGE
Heterozygous Familial Hypercholesterolemia in Pediatric Patients
Lescol® (fluvastatin sodium) and Lescol® XL (fluvastatin sodium) are indicated as an 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, 10-16 years of age, with heterozygous familial hypercholesterolemia whose response to dietary restriction has not been adequate and the following findings are present:

1. LDL-C remains ≥ 190 mg/dL or
2. LDL-C remains ≥ 160 mg/dL and:

- there is a positive family history of premature cardiovascular disease or
- two or more other cardiovascular disease risk factors are present

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

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

Children treated with fluvastatin in adolescence should be re-evaluated in adulthood and appropriate changes made to their cholesterol-lowering regimen to achieve adult treatment goals.

CONTRAINDICATIONS

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, **HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers.** Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

PRECAUTIONS

Information for Patients

Women should be informed that **if they become pregnant while receiving Lescol or Lescol XL the drug should be discontinued immediately** to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol or Lescol XL should not be taken during nursing.

Pregnancy

Pregnancy Category X

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m2 surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day.

A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, **rare reports of congenital anomalies have been received**

following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. Lescol or Lescol XL should be **administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol or Lescol XL, the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers
Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, **nursing women should not take Lescol or Lescol XL** *(see CONTRAINDICATIONS)*.

Pediatric Use
The safety and efficacy of Lescol and Lescol XL in children and adolescent patients 9-16 years of age with heterozygous familial hypercholesterolemia have been evaluated in open-label, uncontrolled clinical trials of 2 years' duration. The most common adverse events observed were influenza and infections. In these limited uncontrolled studies, there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. Adolescent females should be counseled on appropriate contraceptive methods while on fluvastatin therapy.

ADVERSE REACTIONS
Pediatric Patients
In two open-label, uncontrolled studies, 114 patients (66 boys and 48 girls) with heterozygous familial hypercholesterolemia, 9-16 years of age, were treated for 2 years with fluvastatin sodium administered as Lescol capsules 20 mg- 40 mg bid or Lescol XL 80 mg extended release tablets. The most common adverse events observed were influenza and infections.

OVERDOSAGE
There has been a **single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium**. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 x 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.

DOSAGE AND ADMINISTRATION
Heterozygous Familial Hypercholesterolemia in Pediatric Patients
The recommended starting dose is one 20 mg Lescol capsule. Dose adjustments, up to a maximum daily dose administered either as Lescol capsules 40 mg twice daily or one Lescol XL 80 mg tablet once daily, should be made at 6 week intervals. Doses should be individualized according to the goal of therapy (see NCEP Pediatric Panel Guidelines and INDICATIONS AND USAGE.)

PATIENT INFORMATION
Who should not take Lescol or Lescol XL?
LESCOL and LESCOL XL have **not been studied in children under 9 years of age**.

How should I store Lescol or Lescol XL?
Keep LESCOL and LESCOL XL out of the reach of children. Be sure that if you throw medicines away, it is **out of the reach of children**.

3.3.2 Safety-Related Updates to Product Labeling Since Pediatric Exclusivity Granted

During the one-year period following the date pediatric exclusivity was granted for fluvastatin, there was one labeling change that pertained to safety.[1] This labeling change, made in March 2006, involves a fluvastatin and fluconazole drug interaction. To the PRECAUTIONS, Drug Interactions subsection, a new "Fluconazole" paragraph was added to read:

Administration of fluvastatin 40 mg single dose to healthy volunteers pre-treated with fluconazole for 4 days results in an increase of fluvastatin C_{max} (44%) and AUC (84%). Based on this data, caution should be exercised when fluvastatin is co-administered with fluconazole.

Pediatric Filing History

Table 3. Relevant Regulatory Activity for Pediatric Use of Fluvastatin[2]

Date	Regulatory Activity
12/15/2005	Pediatric Exclusivity Granted
7/15/2002	Written Request amended for modifications to the eligibility criteria for both studies.
12/4/2001	Written Request letter issued for Lescol capsules and Lescol XL tablets. Two studies requested: one was an open-label study in prepubertal males with heFH (heterozygous familial hypercholesterolemia) and the other was an open-label study in both males and females, ages 10-18 years with heFH.

4. AERS SEARCH RESULTS

4.1 Count of Reports: AERS Search for Fluvastatin Reports Since Approval

Table 4. Crude Counts* of Fluvastatin Reports in the AERS Database for All Sources Since Approval (December 31, 1993) through AERS Cutoff Date (January 15, 2007).

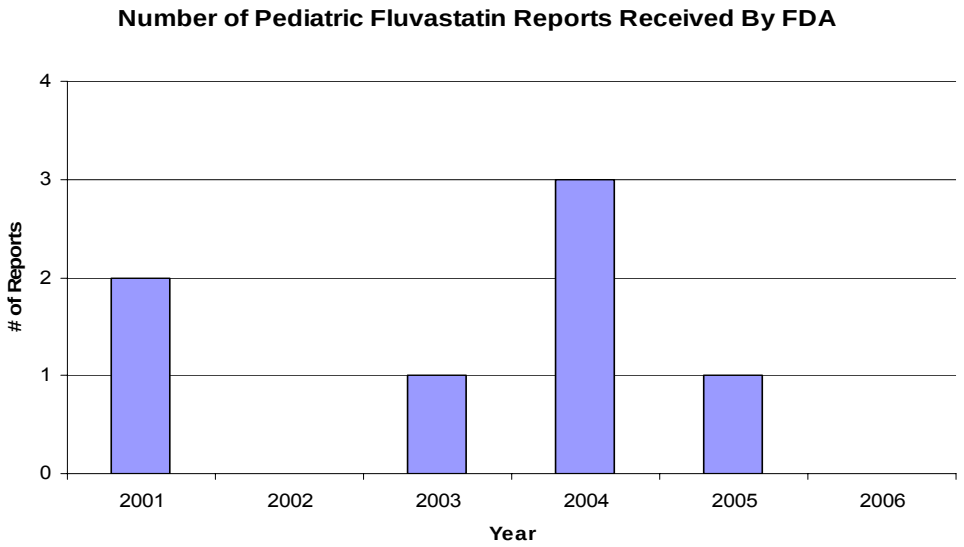
Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	1934 (850)	1510 (445)	125 (24)
Peds (0-16 yrs)	7 (0)	6 (0)	0 (0)
Age Unknown (Null)	414 (410)	213 (111)	16 (6)
Total	2455 (1260)	1729 (556)	141 (30)

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

[2] Parks MH. Lescol capsules/Lescol XL tablets: FDA clinical review for pediatric efficacy supplement. Oct 17 2005.

4.2 Reporting Trend For Fluvastatin Pediatric Reports Since Approval

(December 31, 1993 through January 15, 2007)



4.2 Count of Reports: AERS Search for Fluvastatin Reports During One-Year Period Following Date Pediatric Exclusivity Granted

Table 5. Crude counts* of Fluvastatin Reports in the AERS Database for All Sources From Date Pediatric Exclusivity Granted (December 15, 2005) through AERS Cutoff Date (January 15, 2007)

Age	All reports (US)	Serious† (US)	Death (US)
Adults (≥ 17 yrs)	164 (32)	158 (27)	9 (0)
Peds (0-16 yrs)	0 (0)	0 (0)	0 (0)
Age Unknown (Null)	16 (7)	16 (7)	2 (1)
Total	180 (39)	174 (34)	11 (1)

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

4.3 Limitation of AERS

It is possible there are additional pediatric fluvastatin 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 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.

5. REVIEW OF POSTMARKETING PEDIATRIC ADVERSE EVENT REPORTS

5.1 Case Characteristics:

Table 6. Characteristics of Pediatric Fluvastatin Reports in the AERS Database (marketing approval on December 31, 1993 through AERS cutoff date of January 15, 2007)

Characteristic	Approval to Date Pediatric Exclusivity Granted (12/31/93-12/15/05)	Year Following Date Pediatric Exclusivity Granted (12/15/05-1/15/07)	Total Reports
Number of Unique Reports	**7**	**0**	**7**
Origin of Reports			
United States	0	-	0
Foreign	7	-	7
Year (FDA Receive Date)			
2001	2	-	2
2002	0	-	0
2003	1	-	1
2004	3	-	3
2005	1	-	1
2006	0	0	0
Gender			
Male	2	-	2
Female	3	-	3
Unknown	2	-	2
Age At Time of Event			
0 - <1 month	1	-	1
1 month - 2 years	2	-	2
3 – 5 years	1	-	1
6 – 11 years	1	-	1
12 – 16 years	2	-	2
Unknown	0	-	0
Reported Indication For Use			
Hypercholesterolemia	1		1
Steroid-resistant nephrotic syndrome	1	-	1
Other			
Accidental Ingestion	3		3
In Utero Exposure	1	-	1
Overdose, Intentional	1	-	1
Dose (Those Using For Hypercholesterolemia or Related Indication)			
10 mg/day (as 20 mg every other day)	1	-	1
20 mg/day	1	-	1
Dosage (Accidental Ingestions)			
10 mg capsule	1	-	1
80 mg tablets (unknown amount)	2	-	2
Dose (In Utero Exposure)			
Unknown	1	-	1
Dose (Overdose)			
280 mg	1	-	1

Table 6. Characteristics of Pediatric Fluvastatin Reports in the AERS Database (marketing approval on December 31, 1993 through AERS cutoff date of January 15, 2007)			
Characteristic	**Approval to Date Pediatric Exclusivity Granted (12/31/93-12/15/05)**	**Year Following Date Pediatric Exclusivity Granted (12/15/05-1/15/07)**	**Total Reports**
Exposure Time To Event (Those Using For Hypercholesterolemia or Related Indication)			
< 6 months	1	-	1
6 – 12 months	0	-	0
>12 months	0	-	0
Unknown	1	-	1
Exposure Time (Accidental Ingestions/Overdose)			
1-time exposure	4	-	4
Duration of Use (In Utero Exposures)			
Unknown	1	-	1
Primary Reported Adverse Event (by System Organ Class [SOC])			
Blood and Lymphatic Disorder			
Leukopenia and Neutropenia	1	-	1
Eye Disorders			
Chorioretinitis	1	-	1
Other			
Accidental Ingestion	3	-	3
Overdose, Intentional	1		1
In Utero Exposure (*cardio-respiratory distress, pulmonary hypertension, hypertrophic cardiopathy, renal failure, increased bone density, and abnormal phosphorus and calcium levels*)	1	-	1
Reported Outcomes (numbers may not sum due to reporting of more than one outcome)			
Congenital Anomaly	1	-	1
Death	0	-	0
Disability	0	-	0
Hospitalization	5	-	5
Life-Threatening	1	-	1
Required Intervention	1	-	1
Other	2	-	3
Unknown/Not Reported	1	-	1

5.2 Discussion of Cases Received

Since initial approval of fluvastatin in 1993, FDA received seven pediatric adverse event reports associated with fluvastatin. All seven were foreign reports. None of the seven reports were received by FDA during the one-year period following the date pediatric exclusivity was granted (December 15, 2005 through December 15, 2006). FDA did not receive any reports of death associated with fluvastatin use in the pediatric population.

Of these seven reports, three involved accidental ingestion, and there is one report each of 1) leukopenia and neutropenia, 2) chorioretinitis, 3) in-utero exposure, and 4) intentional overdose. A summary of the case characteristics are provided in Table 6 above. Summaries and discussion of each event are below.

5.2.1 Leukopenia and Neutropenia

The **leukopenia and neutropenia** report (ISR 3709176) involves an 11-year-old boy with history of steroid-resistant nephrotic syndrome, who experienced WBC of 4100 (the boy's baseline WBC is 7000) and neutrophils 1722 about four weeks after switching from Sandimmune (cyclosporine) to Neoral (cyclosporine microemulsion). The duration on Sandimmune is unknown. The boy was also taking fluvastatin 20 mg daily (started one week after Neoral therapy initiated), prednisolone, dipyridamole, alfacalcidol (vitamin D analog), warfarin, glutamine, and ketotifen (antihistamine/mast cell stabilizer[3]). A month later the WBC further decreased to 2940 (neutrophils 853, hemoglobin 12.3, and platelet count 356,000). The Neoral dose was decreased from 125 to 100 mg daily, and glutamate, alfacalcidol, and ketotifen were discontinued (fluvastatin therapy continued). About two weeks later, Neoral was discontinued because the WBC was 2880 (neutrophils 1641, Hb 14, and platelet count 361,000). Ten days *after* Neoral was discontinued, the WBC increased to 5830. About a month later, Neoral 50 mg daily was restarted. A month after restarting Neoral, the WBC had returned to baseline (7120).

The role fluvastatin may have played in the development of this boy's leukopenia and neutropenia is not clear. However, in follow up, cyclosporine was implicated as the primary suspect drug for several reasons: 1) The neutropenia improved after the cyclosporine daily dose was decreased from 125 mg to 100 mg (and glutamate, alfacalcidol and ketotifen were discontinued). 2) The leukopenia significantly improved following the discontinuation of cyclosporine and did not reappear when cyclosporine was restarted at a lower dose (50 mg daily), and 3) Fluvastatin therapy was not altered or interrupted.

Leukopenia has been reported with cyclosporine use. According to the approved labeling for Neoral (cyclosporine), up to three percent of rheumatoid arthritis patients, two percent of kidney transplant patients, and six percent of heart transplant patients experienced leukopenia while taking cyclosporine.[4] Leukopenia, but not specifically neutropenia, has been reported (typically as part of a hypersensitivity syndrome) with most of the statins (for example, rosuvastatin labeling states less than one percent reported leukopenia during clinical trials).[4] A fluvastatin-cyclosporine drug interaction resulting in leukopenia and neutropenia is possible because fluvastatin was started a week after Neoral. However, the leukopenia and neutropenia resolved without a change or interruption in fluvastatin therapy, and a drug interaction between fluvastatin and cyclosporine typically results in only minor increases (compared to other statins) of fluvastatin concentrations.[5]

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[3] Index Nominum and DrugDex- Drug Evaluations. Micromedex. 2007 [accessed Jan 26, 2007].
[4] FDA. Drugs@FDA. 2007. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm [accessed Jan 26, 2007].
[5] Neuvonen PJ, Niemi M, Backman JT. Perspectives in clinical pharmacology: drug interactions with lipid-lowering drugs-mechanisms and clinical relevance Clin Pharmacol Ther 2006;80:565-81.

5.2.2 Chorioretinitis

The **chorioretinitis** report (ISR 4298966) involves a 14-year-old boy with a history of "three relapses of chorioretinitis" experienced another episode of chorioretinitis an unknown time after starting fluvastatin 20 mg every other day. No other information provided.

It is possible, but unlikely fluvastatin contributed to the recurrence of this boy's chorioretinitis. First, the child experienced three episodes of chorioretinitis prior to starting fluvastatin. Second, chorioretinitis is an inflammation of the choroid and retina of the eye, usually caused by infection (although chorioretinitis can rarely result from a noninfectious disease like juvenile rheumatoid arthritis or chronic granulomatous disease).[6] Lastly, the Adverse Event Reporting System (AERS) does not contain any additional reports of chorioretinitis or uveitis (a general term used to describe inflammation of the eye) associated with fluvastatin or any other statin currently approved for use in the United States (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin). Similarly, chorioretinitis and uveitis are not labeled events for any of the statins approved for use in the United States.

5.2.3 In Utero Exposure

The **in utero exposure** report (ISR 465186) involves 43-year-old mother, who was treated during her entire pregnancy with metformin and hydrochlorothiazide/valsartan, and for an unknown duration with fluvastatin (dose unknown) and diosmin (an agent categorized as a vascular protectant used for microcirculatory problems, improvement of venous tone, venous leg ulcers, hemorrhoids, and microangiopathy associated with ankle edema[3]). The mother was not followed during pregnancy and "pregnancy was discovered at the time of delivery via caesarean section" at about 37 weeks gestation. At delivery, the female baby was cyanotic, hypotonic, and hyporeactive (weight: 2.94 kg, Silverman's index 3/10, and one-minute Apgar 8). The baby was diagnosed with severe pulmonary hypertension, hypertrophic cardiopathy (clarified as septal hypertrophy), and renal failure (echogram revealed bilateral hyperechogenicity of cortex and resistance index increased).

It is not clear which, if any, of the medications consumed by the mother contributed to the newborn's maladies. Statins are contraindicated during pregnancy (Pregnancy Category X) because of the statin's ability to lower cholesterol and cholesterol byproducts necessary during fetal development.[4] However, other medications that the mother reportedly was taking could also be implicated.[4] For example, hydrochlorothizide/valsartan carries a Black Box regarding use during pregnancy (along with Pregnancy Category C [first trimester] and Category D [second and third trimesters]). Metformin is assigned Pregnancy Category B (animal studies have not demonstrated teratrogenicity, but there are no adequate and well-controlled studies in pregnant women).

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[6] Riordan-Eva, P, Whitcher J, Vaughan, D, Asbury T. Vaughan and Asbury's general ophthalmology. 16th ed. New York: McGraw Hill; 2004.

5.2.4 Intentional Overdose

The one report of **intentional overdose** (ISR 38231890) involves a 16-year-old female who, "in an act of suicide ideation," ingested her mother's medications: fluvastatin 280 mg, tramadol 1000 mg, and an unknown amount of the neuroleptic, Dominal forte (prothipendyl). The girl was hospitalized with "convulsions" and required "artificial respiration." The girl recovered and was transferred to the psychiatric ward. The girl may have had a history of "epilepsy."

The convulsions that developed after the intentional overdose may be related to ingestion of tramadol (Ultram) and prothipendyl (a neuroleptic not available in the United States). The seizure risk with tramadol is well documented, and the risk of seizure is increased at doses above the recommended maximum daily adult dose of 400 mg or when used concomitantly with drugs such as neuroleptics that are known to lower the seizure threshold.[4] Convulsion or seizure is not a labeled adverse drug reaction for fluvastatin or any of the statins approved for use in the United States (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin).[4] The fluvastatin Prescribing Information indicates the maximum dose administered (to healthy individuals) with an extended-release formulation was 640 mg for two weeks. The 640 mg dose produced a variety of gastrointestinal complaints and increase in transaminase values. The Patient Information sheet advises storing fluvastatin out of the reach of children.

5.2.5 Accidental Ingestion

Three reports involved **accidental ingestion** of fluvastatin. The first report (ISR 4520026) involves a 2-year-old (gender unknown) who ingested an unknown amount of fluvastastin 80 mg extended-release tablets. The child was hospitalized, but outcome information wasn't provided. The second report (ISR 4210506) involves a 2-year old (gender unknown) who ingested one fluvastatin 10 mg capsule. The child was brought to the hospital, but additional information (including outcome) wasn't provided. The third report (ISR 4520027) involves a 3.5 year-old female who ingested an unknown amount of fluvastastin 80 mg extended-release tablets. The child was hospitalized, but outcome information wasn't provided.

The fluvastatin Prescribing Information describes two children (ages 2 and 3 years old) who may have ingested a maximum amount of 80 mg of fluvastatin. Vomiting was induced and no capsules were noted in the emesis. Neither child experienced adverse symptoms. The Prescribing Information advises, should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The fluvastatin Patient Information sheet advises storing fluvastatin out of the reach of children.

5.3 Published Pediatric Case Reports

A MEDLINE search using the terms, 'fluvastatin' or 'Lescol' and limited to English, Child (0 to 18 years), and Case Reports identified three articles, none of which described any adverse event reactions associated with fluvastastin. The authors of the first case report speculate

fluvastatin might be safer than other statins, based on their one patient who took fluvastatin 18 months before conception through 9 weeks gestation. The mother delivered a 2.9 kg female infant who, at 19 months, was within the 50th -70th percentile for weight and placed at 20.5 months development.[7] The second report is a case series of seven patients with familial heterozygous hypercholesterolemia, and includes two pediatric patients (ages 13 and 15 years). The two pediatric patients experienced muscle aches while taking various different statins (pravastatin, lovastatin, and simvastatin). However, the muscle aches disappeared when they switched to fluvastatin.[8] The last report describes a girl with type 1 membranoproliferative glomerulonephritis that was diagnosed at age 15 years through a series of three renal biopsies over four years. The girl started fluvastatin when she developed hypercholesterolemia at age 13 years, and fluvastatin therapy continued even when her cholesterol levels normalized (because fluvastatin may decrease proteinuria in patients with normal cholesterol levels and IgA nephropathy).[9]

6. SUMMARY AND RECOMMENDATIONS

The review of the few (n=7) fluvastatin 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, the most commonly reported adverse events associated with statin therapy are related to the muscles, and range from myalgia (muscle pain or soreness) to rare cases of serious muscle toxicity like rhabdomyolysis (estimated to occur in 1.6 patients per 100,000 person-years).[10] Hepatotoxicity is another serious, but rare adverse event associated with statin therapy. As of January 15, 2007, there are no fluvastatin pediatric reports involving the muscles or liver in the AERS database. However, statin-associated muscle and liver events are well documented in the adult population and the lack of pediatric reports may be related to limited usage of fluvastatin in the pediatric population and underreporting of adverse events.

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.[11] In the United States, available lipid-lowering drugs include: bile acid sequestrants, niacin or nicotinic acid, fibrates, intestinal cholesterol absorption inhibitors

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[7] Seguin J, Samuels P. Fluvastatin exposure during pregnancy. Obstet Gynecol. 1999 May;93(5 Pt2):847.
[8] Sinzinger H, Schmid P, O'Grady J. Two different types of exercise-induced muscle pain without myopathy and CK-elevation drug in HMG-Co-enzyme A-reductase inhibitor treatment. Atherosclerosis. 1999;143:459-460.
[9] Nishikura KK, Kojima M, Yamada y, Arisaka O, Tomita S, et al. A patient with membanoproliferative glomerulonephritis diagnosed by the third biopsy via endocapillary proliferative glomerulonephritis and focal membranoproliferative glomerulonephritis. Clin Exp Nephrol. 2003 Jun;7(2):157-162.
[10] 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.
[11] 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.

(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.[12] 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.[12,13,14] 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 hypertriglyeridemia at risk for pancreatitis,[13] 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.[12]

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.

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[12] Holmes KW, Kwiterovich PO. Treatment of dyslipidemia in children and adolescents. Curr Cardiol Rep. 2005 Nov;7(6):445-56.
[13] McCrindle BW. Hyperlipidemia in children. Thrombosis Research. 2006;118:49-58.
[14] Rodenburg J, Vissers MN, Daniels SR, Weigman A, Kastelein JJ. Lipid-lowering medications. Pediatr Endocrinol Rev. 2004 Nov;2 Suppl 1:171-80.

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