CLINICAL REVIEW

Application Type	20-261 and 21-192
Submission Number	S-036
Submission Code	SE-5
Letter Date	October 14, 2005
Stamp Date	October 17, 2005
PDUFA Goal Date	April 17, 2006
Reviewer Name	Mary H. Parks, MD
Review Completion Date	March 21, 2006
Established Name	fluvastatin sodium
Trade Name	Lescol XL and Lescol
Therapeutic Class	Lipid-altering
Applicant	Novartis
Priority Designation	standard-pediatric supplement (6 months)
Formulation	extended-release tablets and capsules
Dosing Regimen	once or twice daily
Indication	treatment of heterozygous familial hypercholesterolemia in pediatric patients
Intended Population	pediatric patients ages 10-(b)(4) yrs, inclusive

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None recommended.

1.2.2 Required Phase 4 Commitments

None requested.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Two clinical studies were conducted in support of an indication for the treatment of pediatric patients with heterozygous familial hypercholesterolemia (heFH). The studies were conducted in accordance with a Written Request letter issued by the agency on December 4, 2001 and amended on July 15, 2002.

Study CXUO320BZA01 (hereafter referred to as ZA01) was an open-label, uncontrolled, dose-titration trial that evaluated the efficacy and safety of fluvastatin sodium capsules at a dose of 20, 40, and 80 mg daily in pre-pubescent boys with heFH. Boys aged 9 to 12 years, inclusive, who had an LDL-C > 90th percentile for children and had a parent with primary hypercholesterolemia or a family history of premature heart disease/tendon xanthomas were enrolled in a 6-week screening/dietary period followed by a 6-week, placebo, run-in period. At the end of this run-in period, patients entered an 18-week, dose-titration period wherein all patients were initiated on therapy with fluvastatin 20 mg daily. At 6-week intervals, if LDL-C levels did not fall into the target range of 96.7 mg/dL to 123.7 mg/dL, the dose was increased to 20 mg bid (40 mg daily)

then 40 mg bid (80 mg daily). Upon completion of the titration period, patients entered a follow-up phase with an intended maximum period of 8 years.

Study CXUO320B2301 (hereafter referred to as B2301) was also an open-label, uncontrolled, dose-titration study. This study evaluated the efficacy and safety of fluvastatin sodium capsules and extended release (XL) tablets at a dose of 20, 40, and 80 mg daily in pediatric males and **females** with heFH. Patients 10 to 16 years of age, inclusive, with the following were eligible: LDL-C levels ≥ 190 mg/dL; or LDL-C ≥ 160 mg/dL and one or more risk factors for heart disease; or proven LDL-C receptor defect and LDL-C > 160 mg/dL. Patients first entered a 6-week dietary run-in period followed by an 18-week, dose-titration treatment period with all patients initiated on therapy with fluvastatin XL 20 mg for 6 weeks. Thereafter, the dose could be titrated at 6 week intervals up to a maximum of 80 mg daily to achieve an LDL-C < 130 mg/dL. Patients who achieved this treatment goal at the 20 or 40 mg dose were to continue on that dose for the remainder of the 18-week titration period. After this period, patients were maintained at the dose achieving an LDL-C < 130 mg/dL for 2 years.

In both studies, the primary efficacy measure was percent change from baseline in LDL-C. Number and percentage of patients achieving an LDL-C < 130 mg/dL were also evaluated.

1.3.2 Efficacy

Treatment with fluvastatin in both studies resulted in significant mean percent reductions in LDL-C from baseline. In study ZA01, the mean percent change from baseline in LDL-C at Year 2 was -27% (95% CI: -34.7%, -19.4%). In Study B2301, the mean percent change from baseline in LDL-C at Week 114 was -28.3% (95% CI: -33.3%, -23.4%) in the pubertal and post-pubertal patients and - 40.5% (95% CI: -46.3%, -34.8%) in the pre-pubertal patients.

The majority of patients were titrated to the maximum daily dose of fluvastatin 80 mg. Approximately 30% of patients in Study ZA01 achieved an LDL-C target of ≤ 130 mg/dL at Year 2, and 26 to 27% of patients in Study B2301 achieved an LDL-C target of ≤ 130 mg/dL at Week 114.

1.3.3 Safety

No deaths occurred in either study.

Five serious AEs were reported in Study ZA01; four were pre-planned elective surgeries and one was a case of bronchospasm resulting in hospitalization. The most common adverse events reported in Study ZA01 were in the *respiratory systems disorder* category and included influenza, rhinitis, and upper respiratory infections. In Study B2301, the most common adverse events reported were in the MedDRA category *infections and infestations*. Similar to Study ZA01, the specific events were influenza, nasopharyngitis, and rhinitis. Three serious AEs were reported in Study B2301: one appendicitis; one joint injury; and one anxiety/depression. Given the uncontrolled study designs, no conclusions can be made about these findings.

Serious muscle toxicity has been associated with statin use. No cases of rhabdomyolysis were reported in these two studies. One patient had CK elevation to 2216 U/L which was > 10x ULN (ULN 195 U/L) that was considered secondary to intensive sports activities by the investigator. The patient remained in the study and CK elevations resolved. Mean values of transaminases were increased over baseline at all post-baseline measurements but remained within the normal range. None of the elevations resulted in a clinical AE.

Overall, no serious and unexpected safety findings were observed in these two pediatric studies. Eleven patients received drug treatment out to 5 years in Study ZA01. Sixty-six patients received drug treatment out to 114 weeks in Study B2301.

Assessments of growth and development revealed that in both studies, patients progressed in Tanner staging and linear growth while receiving treatment with fluvastatin.

1.3.4 Dosing Regimen and Administration

Fluvastatin sodium is available as 20 and 40 mg immediate-release capsules or 80 mg extended-release tablets. Treatment should be initiated with Lescol 20 mg capsules once daily and titrated up to the maximum dose of 80 mg daily either as 40 mg capsules twice daily or 80 mg XL tablets daily.

1.3.5 Drug-Drug Interactions

No specific drug-drug interaction studies were conducted in this patient population.

1.3.6 Special Populations

This pediatric supplement was submitted in response to a Written Response from the agency requesting efficacy and safety data for Lescol and Lescol XL in a specific pediatric patient population with heFH. The WR did not specify evaluation in any special population beyond the age and gender requirements. In both studies, the majority of patients were Caucasian. There were insufficient numbers of patients in other racial categories to allow for any meaningful analyses of safety and efficacy by racial subgroups.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Fluvastatin sodium 20 and 40 mg capsules were approved in 1993 and the 80 mg XL tablet was approved in 2000 for the following indications:

1) To reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and apolipoprotein B (Apo B) levels, and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb); and
2) To slow the progression of coronary atherosclerosis in patients with coronary heart disease (CHD)

An indication for the secondary prevention of cardiovascular events based on the Lescol Intervention Prevention Study (LIPS) was approved in 2003.

2.2 Currently Available Treatment for Indications

There are currently four statins approved in the U.S. for the treatment of heFH in the pediatric population.

Mevacor (lovastatin)
Mevacor is indicated as an adjunct to diet to reduce total-C, LDL-C and apolipoprotein B levels in adolescents boys and girls who are at least one year post-menarche, 10-17 yrs of age, with heFH if after an adequate trial of diet therapy the following findings are present:

- LDL-C remains > 189 mg/dL or
- LDL-C remains > 160 mg/dL and there is a positive FH of premature CVD or 2 or more CVD risk factors are present in the adolescent patient

This indication was based on results from two studies: a one-year, double-blind, placebo controlled study in boys and a 6-month, double-blind, placebo controlled study in girls.

Pravachol (pravastatin)
Pravachol is indicated as an adjunct to diet and life-style modification for treatment of heFH in children and adolescent patients ages 8 years and older if after an adequate trial of diet the following findings are present.

- LDL-C remains > 189 mg/dL or
- LDL-C remains > 160 mg/dL and there is a positive FH of premature CVD or 2 or more CVD risk factors are present in the patient

This indication was based on results from a single double-blind, placebo-controlled, two year study in 214 boys and girls.

Zocor (simvastatin)
Zocor is indicated as an adjunct to diet to reduce total-C, LDL-C, and ApoB levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with heFH, if after an adequate trial of diet therapy the following findings are present:

- LDL-C remains > 189 mg/dL or
- LDL-C remains > 160 mg/dL and there is a positive FH of premature CVD or 2 or more CVD risk factors are present in the adolescent patient

This indication was based on results from a single double-blind, placebo-controlled study in 175 boys and girls. The study duration was 24 weeks; however, 144 patients continued their assigned therapies in an additional 24-week extension period.

Lipitor (atorvastatin)
Lipitor is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heFH if after an adequate trial of diet therapy the following findings are present:

- LDL-C remains > 189 mg/dL or
- LDL-C remains > 160 mg/dL and there is a positive FH of premature CVD or 2 or more CVD risk factors are present in the pediatric patient

This indication was based on results from a single double-blind, placebo-controlled, 26-week study in 187 boys and girls. Patients were enrolled in an open-label, 26-week extension period wherein all received treatment with atorvastatin.

2.3 Availability of Proposed Active Ingredient in the United States

Fluvastatin is available as Lescol immediate-release capsules and Lescol XL (extended-release) tablets for the treatment of hypercholesterolemia (heterozygous familial and nonfamilial and mixed dyslipidemia) and for the secondary prevention of coronary events (reducing the risk of undergoing coronary revascularization procedures and to slow the progression of coronary atherosclerosis).

2.4 Important Issues With Pharmacologically Related Products

2.5 Presubmission Regulatory Activity

December 4, 2001 – original Written Request issued for Lescol capsules and Lescol XL tablets. Two studies were requested: one was an open-label study in prepubertal males with heFH and one was an open-label study in males and females, ages 10-18 yrs, with heFH.

July 15, 2002 – amendment to Written Request issued which only recommended slight modifications to the eligibility criteria for both studies.

December 15, 2005 – pediatric exclusivity board meeting. The Board determined that the terms of the Written Request were met and 6 months of pediatric exclusivity for Lescol capsules and Lescol XL tablets was granted.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

None required for this submission.

3.2 Animal Pharmacology/Toxicology

None required for this submission.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Two clinical studies were conducted in support of an indication for the treatment of pediatric patients with heterozygous familial hypercholesterolemia (heFH).

Study ZA01 was an open-label, dose-titration trial that evaluated the efficacy and safety of fluvastatin sodium capsules at a dose of 20, 40, and 80 mg daily in pre-pubescent boys with heFH. Boys aged 9 to 12 years, inclusive, who had an LDL-C > 90th percentile for children and had a parent with primary hypercholesterolemia or a family history of premature heart disease/tendon xanthomas were enrolled in a 6-week screening/dietary period followed by a 6-week, placebo, run-in period. At the end of this run-in period, patients entered an 18-week, dose-titration period wherein all patients were initiated on therapy with fluvastatin 20 mg daily. At 6-week intervals, if LDL-C levels did not fall into the target range of 96.7 mg/dL to 123.7 mg/dL, the dose was increased to 20 mg bid (40 mg daily) then 40 mg bid (80 mg daily). Upon completion of the titration period, patients entered a follow-up phase with an intended maximum period of 8 years.

Study B2301 was also an open-label, dose-titration study. This study evaluated the efficacy and safety of fluvastatin sodium capsules and extended release (XL) tablets at a dose of 20, 40, and 80 mg daily in pediatric males and **females** with heFH. Patients 10 to 16 years of age, inclusive, with the following were eligible: LDL-C levels ≥ 190 mg/dL; or LDL-C ≥ 160 mg/dL and one or more risk factors for heart disease; or proven LDL-C receptor defect and LDL-C > 160 mg/dL. Patients first entered a 6-week dietary run-in period followed by an 18-week, dose-titration treatment period with all patients initiated on therapy with fluvastatin XL 20 mg for 6 weeks. Thereafter, the dose could be titrated at 6 week intervals up to a maximum of 80 mg daily to achieve an LDL-C < 130 mg/dL. Patients who achieved this treatment goal at the 20 or 40 mg dose were to continue on that dose for the remainder of the 18-week titration period. After this period, patients were maintained at the dose achieving an LDL-C < 130 mg/dL for 2 years.

In both studies, the primary efficacy measure was percent change from baseline in LDL-C. Number and percentage of patients achieving an LDL-C < 130 mg/dL were also evaluated.

4.2 Tables of Clinical Studies

The results of only two studies were submitted in support of this efficacy supplement. See Section 4.1 for their descriptions.

4.3 Review Strategy

Submission was submitted electronically. Clinical study reports and datasets can be accessed at ||CDSESUB1\N20261\S_036\2005-10-14.

As the two studies involved different study designs and study populations, each study was reviewed individually and no pooling of data was performed.

4.6 Financial Disclosures

Financial disclosure information was obtained from 92% (11/12) of the clinical investigators in Study B2301 and 100% of those in Study ZA01. No investigators were full or part-time employees of Novartis Pharmaceuticals Corp. No disclosable financial information was reported by any of the responding investigators. The information reviewed was deemed acceptable.

5 CLINICAL PHARMACOLOGY

None submitted with this supplement.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication - Heterozygous Familial Hypercholesterolemia in Pediatric Patients

6.1.2 General Discussion of Endpoints

The primary endpoint in both studies was mean percent change from baseline in low-density lipoprotein cholesterol (LDL-C). Elevated LDL-C (and total-C) is an established risk factor for heart disease. Based on strong epidemiologic evidence, animal models, and genetic disorders of LDL-receptor defects, LDL-C has been considered a validated surrogate marker for heart disease and an acceptable efficacy parameter for drug development. Over the past two decades, multiple, placebo-controlled, landmark clinical outcome trials involving different statins and targeting different CHD risk populations, have also established that reducing LDL-C levels is associated with significant risk reductions for cardiovascular mortality and morbidity. As a result of the cumulative evidence, lowering LDL-C has become an established and validated biomarker for clinical benefit.

Heterozygous familial hypercholesterolemia has an estimated prevalence of 1:500. Patients have a defect of one of the LDL-receptor alleles which results in poor uptake of circulating cholesterol and consequent hypercholesterolemia. LDL-C levels are typically greater than 250 mg/dL and patients are at risk for heart disease in early adulthood (see Table 1).

Table 1. Estimated Risk of FH Heterozygotes Having Coronary Heart Disease Sxs or Dying from CHD by Age and Gender

Age	Male Heterozygotes		Female Heterozygotes	
	Coronary Sxs	Coronary Death	Coronary Sxs	Coronary Death
40 yrs	20%	--	3%	0%
50 yrs	45%	25%	20%	2%
60 yrs	75%	50%	45%	15%
70 yrs	--	80%	75%	30%

Table from Scriver et al. The Metabolic and Molecular Bases of Inherited Disease, 8th edition, Volume II, p2869

Clinically evident heart disease is atypical in childhood, particularly females; however, autopsy series of children and young adults have revealed early signs of atherosclerosis with fatty streaks noted in the aorta and in young adults, coronary lesions have also been observed.

Targeting elevated cholesterol levels in pediatric patients has been recommended by major medical and scientific organizations. In 1992, the National Cholesterol Education Program (NCEP) Expert Panel published its recommendations for managing hypercholesterolemia in the pediatric population. The strategy included a population approach and an individualized approach. The individualized approach included selective screening with lipoprotein analysis of individuals at highest risk and classification of the LDL-C as follows:

1. Acceptable LDL-C <110 mg/dL
2. Borderline LDL-C 110-129 mg/dL
3. High LDL-C ≥ 130 mg/dL

An intensive diet therapy (Steps 1 and 2) is recommended in individuals with borderline and high LDL-C levels and involves close monitoring by healthcare professionals and registered dietitians. Drug therapy is recommended only in children > 10 years of age if after a 6 to 12 month trial of dietary plan the following still remains:

1) LDL-C ≥ 190 mg/dL; *or*
2) LDL-C > 160 mg/dL *and*
   a) there is positive FH of premature CVD (before age 55 yrs), or
   b) 2 or more other CVD risk factors are present in the pediatric patient

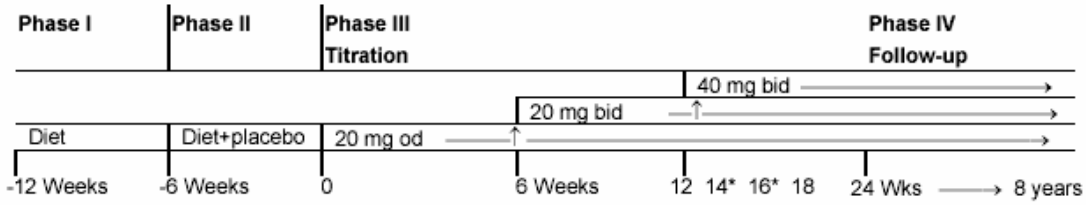
Consequently, lipid-altering drug trials in pediatric patients have targeted LDL-C as the primary efficacy variable. In addition, evaluating the percentage of patients achieving a goal of < 130 mg/dL is often specified as a secondary analysis. None of these trials is designed to evaluate the long-term effects of drug treatment initiated in childhood on the development of clinical heart disease in adulthood. All drug labeling should carry this disclaimer statement.

6.1.3 Study Design

6.1.3.1 Study ZA01 - Efficacy and Safety in Prepubescent Boys with Heterozygous FH

This was an open-label, dose-titration study in prepubescent boys with heFH. Patients were to receive fluvastatin sodium capsule at doses of 20, 40, and 80 mg/day during an 18-wk titration period to achieve an LDL-C goal between 96.7 to 123.7 mg/dL. Patients were to continue on whichever dose that achieved targeted goals during the long-term follow-up period for a *planned* maximum duration of 8 years. The longest individual treatment duration was approximately 5.5 years. The applicant stated that due to administrative reasons, the study was discontinued prematurely.

Figure 3-1 Study design



6.1.3.1.1 Study Population

Boys ages 9 to 12 yrs, inclusive, were eligible if they had LDL-C > 90th percentile for age; a parent with primary hypercholesterolemia and either a family history of premature ischemic heart disease or tendon xanthoma. Patients were excluded if they had homozygous FH, obesity (BMI > 30 kg/m2), significant liver, kidney, or muscle disease (see study report for full list of exclusion criteria). The study was conducted at a single center in Cape Town, South Africa. It should be noted that lipid-lowering drugs other than fluvastatin sodium were not permitted during this study.

The following table summarizes the baseline characteristics of the study population.

Table 7-3 Patient baseline demographic characteristics (ITT population)

	N = 29 patients n (%)
Age (years)	
9	12 (41.4)
10	10 (34.5)
11	6 (20.7)
12	1 (3.4)
Mean (SD)	9.9 (0.9)
(min,max)	(9,12)
Ethnic group (CRF)	
Afrikaans	23 (79.3)
Jewish	1 (3.4)
Other European	2 (6.9)
Indian	0
Black	0
Other	3 (10.3)
Race (FDA)	
White	26 (89.7)
Native Hawaiian or Pacific Islander	0
Black or African Black	0
Asian	0
American Indian or Alaskan Native	0
Other	3 (10.3)
Ethnicity (FDA)	
Hispanic/Latino	0
Non Hispanic/Latino	29 (100)
Height (cm)	
Mean (SD)	141.7 (5.0)
Median (min,max)	142 (134,151)
Weight (kg)	
Mean ± SD	35.5 (7.6)
Median (min,max)	35 (24,54)
Body Mass Index (kg/m^2)	
Mean (SD)	17.6 (3.1)
Median (min,max)	17.3 (13,26)

Source: PTT 7.4-1 and 7.4-2

Other - Patients with a mixed racial composition with two or more components from the following three categories, African Black, White and Asian. Precise details on the composition for each patient are not available due to the local sensitivities involved in requesting racial information.

6.1.3.2 Study B2301 - Efficacy and Safety in Pediatric Males and Female with Heterozygous FH

This was also an open-label, dose-titration study in pediatric males and females with heFH. This study evaluated the efficacy and safety of fluvastatin sodium capsules 20 and 40 mg and the extended release (XL) 80 mg tablet administered daily. Patients 10 to 16 years of age, inclusive, with the following were eligible: LDL-C levels ≥ 190 mg/dL; or LDL-C ≥ 160 mg/dL and one or more risk factors for heart disease; or proven LDL-C receptor defect and LDL-C > 160 mg/dL. Patients first entered a 6-week, dietary run-in period followed by an 18-week, dose-titration treatment period with all patients initiated on therapy with fluvastatin 20 mg for 6 weeks. Thereafter, the dose could be titrated at 6 week intervals up to a maximum of 80 mg daily to achieve an LDL-C < 130 mg/dL. Patients who achieved this treatment goal at the 20 or 40 mg dose were to continue on that dose for the remainder of the 18-week titration period. After this period, patients were maintained at the dose achieving an LDL-C < 130 mg/dL for 2 years.

6.1.3.2.1 Study Population

The following table summarizes the baseline characteristics and demographics of patients in Study B2301.

Table 7-3 Patient baseline demographic characteristics (ITT population, pubertal and post-pubertal)

	Female N=38	Male N=31	Total N=69
Sex			
Female			38 (55.1%)
Male			31 (44.9%)
Age at Week -3 (years)			
Mean (SD)	12.8 (1.8)	13.5 (2.0)	13.1 (1.9)
(Min, Max)	(10,16)	(10,17)	(10,17)
Ethnic group (CRF)			
Caucasian	28 (73.7%)	22 (71.0%)	50 (72.5%)
Black	0 (0.0%)	0 (0.0%)	0 (0.0%)
Oriental	0 (0.0%)	1 (3.2%)	1 (1.4%)
Other	10 (26.3%)	8 (25.8%)	18 (26.1%)
Race (FDA)			
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	0 (0.0%)	1 (3.2%)	1 (1.4%)
Black or African American	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
White	28 (73.7%)	22 (71.0%)	50 (72.5%)
Other	10 (26.3%)	8 (25.8%)	18 (26.1%)
Ethnicity (FDA)			
Hispanic/Latino	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Hispanic/Latino	38 (100%)	31 (100%)	69 (100%)
Weight at Week -3 (kg)			
Mean (SD)	54.21 (13.43)	54.52 (11.95)	54.35 (12.69)
Median (Min,Max)	52.0 (30.9,83.0)	54.0 (31.0,74.0)	52.0 (30.9,83.0)
Height (cm)			
Mean (SD)	160.1 (8.56)	162.0 (11.33)	161.0 (9.86)
Median (Min,Max)	158.0 (144,176)	163.0 (138,184)	160.0 (138,184)
Body Mass Index (kg/m^2)			
Mean (SD)	21.0 (4.15)	20.6 (3.71)	20.8 (3.93)
Median (Min,Max)	19.9 (15,32)	19.5 (16,31)	19.5 (15,32)
Prior HMG CoA reductase inhibitor			
No	38 (100.0%)	29 (93.5%)	67 (97.1%)
Yes	0 (0.0%)	2 (6.5%)	2 (2.9%)

Source: PTT 7.4-1a

Comments:
Study ZA01 was completed before the Best Pharmaceuticals for Children Act (BPCA) was signed into law (January 2002). At the time this study was conducted, it was thought that the later onset of ischemic heart disease in women did not justify studying pediatric girls with heFH. At present, clinicians are not delaying therapy in these patients. Subsequently, during discussions regarding the Written Request, the agency felt that a second study was necessary to increase the patient exposure in both sexes but with that study enrolling more girls than boys.

Both these studies lacked a concurrent control group. Several placebo-controlled pediatric studies with other statins have been conducted and reviewed by the agency. The data suggest similar LDL-lowering efficacy in the adult and pediatric population. As controlled studies of efficacy have already been conducted for fluvastatin in the adult population, the agency was willing to accept change from baseline in LDL-C in these uncontrolled studies as sufficient to characterize efficacy of fluvastatin in the pediatric population. The titrate-to-goal design precludes assessment of efficacy by dose but provides insight on how effective the dose range would be in achieving target cholesterol goals. The uncontrolled study design clearly limits

interpretability of safety findings. Consequently, the applicant was required to collect as much long-term exposure data, as other pediatric statin trials had only 12 to 24 months' duration of exposure.

6.1.4 Efficacy Findings

6.1.4.1 Study ZA01

The following table is from Dr. Janice Derr's statistical review of this supplement.

	N=29 for baseline, N=27 for Month 24*
LDL-(mg/dL)	
Baseline mean	226.0
(min, max)	(137.3, 353.8)
Mean at Month 24	160.6
(min, max)	(73.5, 336.4)
[95% CI]	[138.2, 182.9]
% Change at Month 24	-27.0%
(min, max)	(-57.9%, 10.6%)
[95% CI]	[-34.7%, -19.4%]
Total-C (mg/dL)	
Baseline mean	296.2
(min, max)	(203.0, 442.8)
Mean at Month 24	229.0
(min, max)	(158.5, 406.0)
% Change at endpoint	-21.1%
(min, max)	(-50.9%, 6.9%)
[95% CI]	[-26.8%, -15.4%]
HDL-C (mg/dL)	
Baseline mean	53.6
(min, max)	(29.0, 83.1)
Mean at Month 24	53.9
(min, max)	(30.9, 77.3)
% Change at endpoint	1.3%
(min, max)	(-40.7%, 61.5%)
[95% CI]	[-8.0%, 10.7%]
Triglycerides (mg/dL)	
Baseline mean	83.2
Baseline median	70.8
(min, max)	(35.4, 216.8)
Mean at Month 24	72.2
Median at Month 24	61.9
(min, max)	(35.4, 247.8)
% Change at Month 24	-7.0%
(min, max)	(-62.2%, 83.3%)
[95% CI]	[-22.1%, 8.0%]
Sources from ZA01 Clinical Study Report:	
Baseline	Table 7.4-29 p. 90/897

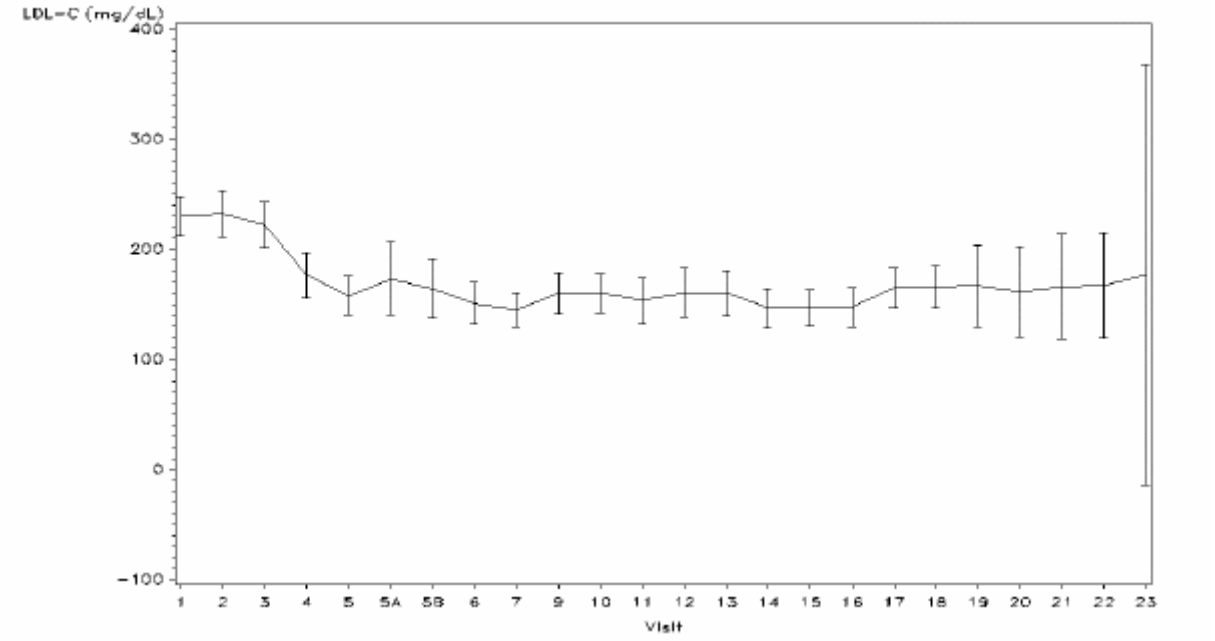
	N=29 for baseline, N=27 for Month 24*
Month 24	Table 9.1-1 pp. 103-106/897

* Patient 14 dropped out after week 6 and patient 28 dropped out after month 20. The descriptive statistics for month 24 are based on the remaining 27 patients.

By Month 24, the mean reduction in LDL-C from baseline was -27% (95% CI: -34.7%, -19.4%). This result is derived from 27 patients who had data at Month 24; no data were imputed from early drop-outs. Changes in Total-C mirrored the changes in LDL-C.

The majority of the enrolled patients (24 out of 29) required titration to the maximum daily dose of 80 mg to achieve LDL-C goals. The applicant reported that 62.1% of the enrolled population achieved LDL-C target at least once during the 2-year treatment period. This statement is misleading since the percentage of patients able to maintain LDL-C level at ≤ 130 mg/dL was much lower. At Month 24, only 29.6% (8/27) of patients achieved an LDL-C target of ≤ 130 mg/dL. The following figure from the applicant's submission reveals that over the course of the study treatment period, the mean LDL-C level achieved was consistently above 130 mg/dL.

Figure 9-1 Mean LDL-C over time with 95% CI intervals (ITT population)



Treatment with fluvastatin resulted in modest and clinically insignificant changes in HDL-C and TGs.

6.1.4.2 Study B2301

Efficacy in Study B2301 was analyzed by Baseline pubertal status (pre-pubertal or pubertal/post-pubertal). There were only 15 patients who were pre-pubertal at baseline and 69 patients were pubertal/post-pubertal. The following table from Dr. Derr's review summarizes the efficacy results in this study.

	ITT Pubertal and post-pubertal group (N=69*)	ITT Pre-pubertal group (N=15)
LDL-(mg/dL)		
Baseline mean	224.8	266.2
(min, max)	(148, 343)	(164, 390)
Mean at endpoint	158.5	157.3
(min, max)	(90, 295)	(98, 216)
[95% CI]	[147.5, 169.4]	
% Change at endpoint	-28.3%	-40.5%
(min, max)	(-57%, 52%)	(-63%, -25%)
[95% CI]	[-33.3%, -23.4%]	
Total-C (mg/dL)		
Baseline mean	288.9	334.6
(min, max)	(211, 411)	(241, 441)
Mean at endpoint	221.9	228.7
(min, max)	(139, 342)	(169, 299)
% Change at endpoint	-21.9%	-31.2%
(min, max)	(-49%, 41%)	(-49%, -18%)
[95% CI]	[-26.2%, -17.7%]	
HDL-C (mg/dL)		
Baseline mean	46.6	51.3
(min, max)	(29, 71)	(35, 66)
Mean at endpoint	47.8	55.5
(min, max)	(28, 69)	(42, 72)
% Change at endpoint	4.1%	9.1%
(min, max)	(-36%, 44%)	(-5%, 30%)
[95% CI]	[0.1%, 8.2%]	
Triglycerides (mg/dL)		
Baseline mean	87.1	85.4
(min, max)	(47, 262)	(57, 140)
Mean at endpoint	78.6	79.9
(min, max)	(31, 214)	(49, 105)
% Change at endpoint	-5.5%	-3.9%
(min, max)	(-71%, 187%)	(-46%, 35%)
[95% CI]	[-14.9%, 3.9%]	
Apo-B		
Baseline mean	171.1	198.5
(min, max)	(111, 252)	(125, 284)
Mean at endpoint	134.1	133.3
(min, max)	(81, 233)	(97, 162)
% Change at endpoint	-20.7%	-32.1%
(min, max)	(-52%, 45%)	(-54%, -16%)
[95% CI]	[-25.2%, -15.8%]	
Sources from BA2301 Clinical Study Report:	Pubertal and post-pubertal	Pre-pubertal
	Table 9.1-1a p. 210	
LDL	Table 9.2-1a, p. 228	Table 9.1-1b p. 214
HDL	Table 9.2-2a, p. 236	Table 9.2-1b p. 232
Tot-C	Table 9.2-4a, p. 249	Table 9.2-2b, p. 252

	ITT Pubertal and post-pubertal group (N=69*)	ITT Pre-pubertal group (N=15)
Triglycerides	Table 9.2-6a, p. 265	Table 9.2-4b, p. 256
Apo-B		Table 9.2-6b, p. 268

* For the ITT population of 69 pubertal and post-pubertal patients, the last observation carried forward method was used to impute values for five patients who discontinued the study prior to week 114: one patient after week 42, three patients after week 8, and one patient after week 102.

The mean change in LDL-C from baseline at Week 114 in the pubertal and post-pubertal group was similar to the results in the ZA01 study. Treatment with fluvastatin reduced LDL-C by 28.3%. The reduction in the pre-pubertal group was much greater with mean reduction of 40.5%, however, these results are only from 15 patients.

Similar to results in Study ZA01, approximately 65% of patients achieved an LDL-C ≤ 130 mg/dL at least once in the study; however, response is much lower if summarized by study visit or at the end of study. Only 27% and 26.1% of the pre-pubertal and pubertal/post-pubertal cohorts, respectively, achieved target LDL-C goal at the end of study. Approximately 96% of these patients were treated with the 80 mg XL tablet at the end of study.

6.1.6 Efficacy Conclusions

Treatment of pediatric patients with HeFH with fluvastatin 20 to 80 mg daily was associated with an average reduction from baseline in LDL-C of approximately 28%. The majority of patients required titration up to the maximum daily dose of 80 mg. Despite this, the majority of patients did not achieve an LDL-C goal of ≤ 130 mg/dL, a secondary efficacy assessment.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred in either study.

7.1.2 Other Serious Adverse Events

Five SAEs were reported in ZA01; none was considered drug-related. Four patients had pre-planned elective surgery and one patient had bronchospasm requiring hospitalization. Three SAEs were reported in Study B2301; none was considered drug-related. One female patient had joint injury and another had depression and anxiety. One male patient had appendicitis.

7.1.3 Dropouts and Other Significant Adverse Events

There were no premature discontinuations due to AEs.

7.1.3.1 Patient Disposition

The following table summarizes the patient disposition in study ZA01.

Table 7-1 Patient disposition (Safety population)

	N = 29 n (%)
Total no. of patients	29 (100%)
Enrolled and treated	29 (100%)
Completed 12 months (1 year)	28 (96.6%)
Completed 24 months (2 years)	27 (93.1%)
Completed 36 months (3 years)	25 (86.2%)
Completed 48 months (4 years)	19 (65.5%)
Completed 60 months (5 years)	11 (37.9%)
Completed 68 months (5.5 years)	3 (10.3%)

Source: PTT 7.1-1

The most common reason for discontinuation was "study terminated by Novartis" or some variation of this (n=24) followed by "relocation" (n=3). One patient refused to return and another discontinued because mother was unable to bring child. No safety or lack of efficacy reasons were listed as cause for discontinuation.

The following table summarizes the patient disposition for study B2301.

Table 7-1 Patient disposition (Pubertal and post-pubertal)

	Female N=39	Male N=31	Total N=70
	n (%)	n (%)	n (%)
Patients who entered the active treatment phase	39 (100.0)	31 (100.0)	70 (100.0)
Completed	37 (94.9)	28 (90.3)	65 (92.9)
Discontinued			
Abnormal laboratory value(s)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event(s)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (2.6)	2 (6.5)	3 (4.3)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	1 (2.6)	1 (3.2)	2 (2.9)
Subject's condition no longer requires study drug	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	0 (0.0)	0 (0.0)	0 (0.0)

Source: PTT 7.1-1a

All 15 of the pre-pubertal patients completed the study.

7.1.5.3 Incidence of common adverse events

In Study ZA01, 96.6% of the patients reported at least one AE with the most common AEs occurring in the *respiratory systems disorder* category. The most frequent AEs by preferred term were (in order of frequency) influenza, rhinitis, and upper respiratory tract infection.

In Study B2301, 91.4% of patients reported at least one AE with the most common AEs occurring in the *infections and infestations* category. The most frequent AEs by preferred term were (in order of frequency) influenza, nasopharyngitis, and rhinitis.

7.1.7 Laboratory Findings

7.1.7.1 Study ZA01

Mean ALT and AST values increased over baseline in all post-baseline measures but remained within normal range. There was only one patient with a CK elevation > 10x ULN (2216 U/L; ULN 195 U/L). The investigator attributed this to intense sports activity. The patient remained in the study, on drug, with resolution of CK abnormalities.

7.1.7.2 Study B2301

Aside from LFTs and CK laboratory values, there was only one notable increase in laboratory measure. This was in a female patient who was reported to have a single increased creatinine level.

No patients had ALT or AST increases > 3x ULN and none had CK elevations > 10x ULN.

Endocrine laboratory assessments included TSH, FSH, LH, estradiol (females), cortisol, DHEAS, testosterone (males), and ACTH values. No clinically abnormal changes were noted in these assessments. Estradiol and testosterone levels increased from baseline in parallel with Tanner progression. Post-puberty these hormones decreased slightly towards adult steady state levels. Changes in LH and FSH also paralleled the changes in the sex hormones.

7.1.8 Vital Signs

No clinically significant changes were noted in either studies.

7.1.11 Human Carcinogenicity

No new studies conducted. See currently approved labeling.

7.1.14 Human Reproduction and Pregnancy Data

All statins are labeled Pregnancy Category X drugs. No additional pre-clinical studies were conducted for this pediatric efficacy supplement. Labeling must contain language regarding use of adequate contraceptive methods in adolescent females.

7.1.15 Assessment of Effect on Growth

7.1.15.1 Study ZA01

This study was limited to pre-pubescent males. Growth and development data from Tanner staging were evaluated by an (b) (4) There was no evidence of abnormal sexual development as assessed by Tanner staging.

Growth velocity (cm/yr) in pre-pubertal subjects was lower in the initial 12-24 months but as puberty progressed in all study subjects, growth velocity increased and was consistent with normal development.

Hand x-rays to assess bone age were also evaluated at baseline and end of study. Two patients did not have an assessment at end of study. Otherwise, all other films were read as *within normal limits*.

7.1.15.2 Study B2301

There were 15 pre-pubertal patients in Study B2301 (9 female, 6 males). At end of study, all 15 had entered puberty. Pubertal patients who were Tanner stage 2 and above at the beginning of the study continued to have normal pubertal progression; some achieved full sexual development during the study.

Growth velocity (cm/yr) was assessed at pre-specified intervals throughout the study. In the pubertal/post-pubertal group there was an overall trend towards increased growth velocity although a few patients had reduced velocity from Wk 90 to End of Study that may have signified reaching final height. None of the pre-pubertal patients showed evidence of decreased growth velocity during the study.

This study enrolled prepubertal and postpubertal menstruating females. All menstruating patients were queried at each visit regarding the start date of their monthly cycle. The applicant reported no marked changes in menstrual cycles.

7.1.16 Overdose Experience

No data on overdose were collected in this development program.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Safety data were collected in all patients who received drug in the two uncontrolled studies.

7.2.1.1 Study ZA01

Twenty-nine boys were enrolled in Study ZA01. Data from all patients contributed to the overall safety evaluation. The end of study timepoint was Year 2; however, patients were allowed to remain in study for an intended 8-year long-term follow-up. The study follow-up was out to 5.5 years; 3 patients had exposure out to 5.5 years.

The majority of patients required titration up to 80 mg (24 out of 29). The mean exposure at the 80 mg dose was approximately 3.5 years. The following table summarizes mean exposures by dose in days.

Table 8-1 Exposure to study drug (Safety population)

	Overall N=29	20 mg N=29	40 mg N=25	80 mg N=24
Exposure (days)				
Mean	1387.7	208.2	121.7	1298.5
(SD)	(476.7)	(460.0)	(143.8)	(398.5)
Median	1401	43	49	1311
(min,max)	(53,1949)	(35,1849)	(35,574)	(419,1857)

Source: PTT 8.1-3

7.2.1.2 Study B2301

Eighty-five patients were enrolled in Study B2301 and 80 patients completed the study. Approximately 80% of pubertal/post-pubertal cohort received drug out to Week 114. The majority of patients were on the 80 mg daily dose (96.4%). Approximately 67% of the pre-pubertal males and 78% of pre-pubertal females received drug out to Week 114. Eleven of these 15 patients (73.3%) were titrated up to 80 mg.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The recommended starting dose is one 20 mg capsule daily with dose adjustments up to a maximum daily dose of 80 mg (40 mg capsules bid or 80 mg XL tablet) based on LDL-C response.

8.2 Drug-Drug Interactions

No drug-drug interactions were conducted for this supplement. See approved labeling.

8.3 Special Populations

This pediatric supplement was submitted in response to a Written Response from the agency requesting efficacy and safety data for Lescol and Lescol XL in a specific pediatric patient population with heFH. The WR did not specify evaluation in any special population beyond the age and gender requirements. In both studies, the majority of patients were Caucasian. There were insufficient numbers of patients in other racial categories to allow for any meaningful analyses of safety and efficacy by racial subgroups.

8.4 Pediatrics

This supplement addresses this section.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

Medline search using terms *fluvastatin* and *pediatrics* produced one study in pediatric cancer patients. This was an exploratory study evaluating safety and tolerability of different fluvastatin doses in 12 patients with different types of malignancies. The study provided no relevant information to this supplement.

8.7 Postmarketing Risk Management Plan

None proposed.

9 OVERALL ASSESSMENT

9.1 Conclusions

Two open-label, uncontrolled studies evaluated fluvastatin sodium 20 to 80 mg daily in pediatric patients with heterozygous familial hypercholesterolemia. Both studies employed a titration-to-goal treatment approach. The LDL-lowering efficacy associated with fluvastatin 20-80 mg daily was similar at the end of both studies with a change from baseline of approximately -27%. The majority of patients required titration to the maximum dose of fluvastatin 80 mg; however, only a minority achieved desired target goal of LDL-C $\leq$ 130 mg/dL. As other statins have been approved for pediatric heFH with greater efficacy, the label for fluvastatin should include a discussion of the small percentage of patients achieving desirable LDL-C goal. If this statin is selected for pediatric use, it is likely that over time more potent therapies will be required to effectively treat the hypercholesterolemia.

There were no unexpected and serious safety findings associated with fluvastatin therapy. The uncontrolled nature of the two studies limited interpretability of the safety findings. One study had follow-up data in patients beyond 2 years' duration of therapy. Overall, fluvastatin was well-tolerated and there were no obvious negative effects on growth and development as assessed by Tanner staging, linear growth, and bone age films.

9.2 Recommendation on Regulatory Action

Approval.

9.3 Recommendation on Postmarketing Actions

None.

9.3.1 Risk Management Activity

none

9.3.2 Required Phase 4 Commitments

none

9.3.3 Other Phase 4 Requests

none

10 APPENDICES

10.1 Review of Individual Study Reports

See sections 6 and 7 for review of efficacy and safety of Studies ZA01 and B2301.

10.2 Line-by-Line Labeling Review

This section will summarize the proposed changes to the label with the reviewer comments after each section highlighted in yellow.

CLINICAL PHARMACOLOGY; Special Populations, Pediatrics – the following sentence has replaced previous language – *Pharmacokinetic data in the pediatric population are not available.*

Medical Reviewer Comments: this is acceptable.

CLINICAL STUDIES – a new pediatric subsection has been added with the following description of the two pediatric studies

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

(b) (4)

Medical Reviewer's comments: This section should discuss what LDL-C target was in both studies and the percentage of patients achieving this goal at the end of each study. Additional changes made to section will be conveyed to applicant prior to labeling negotiations.

INDICATIONS AND USAGE – a new pediatric indication has been added as follows:

Heterozygous Familial Hypercholesterolemia in Pediatric Patients

(b) (4)

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 or premature cardiovascular disease or*
   - *two or more other cardiovascular disease risk factors are present*

Medical Reviewer's comments: All statin labels with approved indications for pediatric use contain NCEP treatment recommendations in this patient population.

PRECAUTIONS – A Pediatric Use subsection has been added as follows:

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 (b) (4) *The most common adverse events observed were influenza and infections.* (b) (4) (b) (4) *there was no detectable effect on growth or sexual maturation in the adolescent boys or on menstrual cycle length in girls. See CLINICAL STUDIES: Heterozygous Familial Hypercholesterolemia in Pediatric Patients; ADVERSE REACTIONS: Pediatric Patients (9-17 years of age); and DOSAGE AND ADMINISTRATION: Heterozygous Familial Hypercholesterolemia in Pediatric Patients. Adolescent females should be counseled on appropriate contraceptive methods while on fluvastatin therapy (see CONTRAINDICATIONS: Pregnancy and Lactation).*

ADVERSE REACTIONS – A Pediatric subsection has been added as follows:

Pediatric Patients

In two open-label 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. See CLINICAL STUDIES: Heterozygous Familial Hyercholesterolemia in Pediatric Patients and PRECAUTIONS: Pediatric Use).

DOSAGE AND ADMINISTRATION – A pediatric dosing section has been added as follows:

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.

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/s/

Mary Parks
3/24/2006 01:48:37 PM
MEDICAL OFFICER