

EXECUTIVE SUMMARY FOR PEDIATRIC SUPPLEMENT

NDA #	20-261 and 21-192
Drug name	Lescol® (fluvastatin sodium)
Applicant	Novartis
Indication	Treatment of Pediatric Heterozygous Familial Hypercholesterolemia

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. No clinical pharmacology studies were required or conducted in support of this supplement.

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.

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