DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202057/S-005

COMPLETE RESPONSE

Amarin Pharma Inc.
US Agent for Amarin Pharmaceuticals Ireland Limited
Attention: Steven Ketchum, PhD
President of Research and Development, SVP
1430 Route 206
Bedminster, NJ 07921

Dear Dr. Ketchum:

Please refer to your supplemental New Drug Application (sNDA) dated and received February 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vascepa (icosapent ethyl) capsules, 1 gram.

We acknowledge receipt of your amendments dated April 1, 3 and 17, June 24, July 3 and 19, September 3, 4, and 17, November 25 and 27 (2), December 12 and 17, 2013, January 13 and 23, March 5, April 9 and 23, May 7, 21, and 28, November 25, 2014.

This "Prior Approval" efficacy sNDA provides for the following indication: "as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent."

To support this indication, you submitted the results from study AMR-01-01-017 (ANCHOR). The purpose of this study was to assess the effect of Vascepa on serum triglycerides (TG) and other lipids and lipoproteins in statin-treated patients with a baseline fasting TG level ≥185 mg/dL and <500 mg/dL (with one qualifying value ≥200 mg/dL) and a baseline LDL-C value of ≥40 and ≤115 mg/dL. Following a 6- to 8-week lead-in period for dietary instruction, washout of non-statin lipid-modulating drugs, and stabilization of statin therapy, individuals still meeting lipid eligibility requirements were randomly assigned to either placebo, Vascepa 2 g/day, or Vascepa 4 g/day. The primary endpoint was the percent change in TG levels from baseline to week 12. In the primary efficacy analysis, the median percent changes in fasting TG from baseline to Week 12 were +5.9% in the mineral oil (placebo) group and -17.5% in the Vascepa 4 grams/day group, yielding a treatment difference of -21.5% (95% CI, -26.7% to -16.2%; $p<0.0001$).

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

In your sNDA submission, you state that even after aggressive LDL-C control with statins, many patients remain at high risk for cardiovascular (CV) events, and that this residual risk is likely due to independent or direct activity of other biomarkers, including TG and other lipids/lipoproteins. We agree that the clinical rationale for reducing serum TG (or modifying other lipid/lipoprotein parameters) with Vascepa among statin-treated patients with TG 200-499 mg/dL would be to reduce CV risk further. We have concluded that, at present, there are insufficient data to support a drug-induced change in serum TG as a surrogate for reducing CV risk in this population. The ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE trials provide the most contemporary information regarding the potential CV benefits of modulating TG (or other lipoprotein parameters such as non-HDL-C and HDL-C), among statin-treated patients, with drugs that predominantly affect lipids other than LDL-C. Instead of confirming a hypothesis that further lowering of TGs or non-HDL-C (or raising HDL-C) in statin-treated patients reduces residual CV risk, these trials failed to demonstrate any additional benefit of lipid-altering drugs that target these lipid parameters in the overall trial populations. Although post hoc subgroup analyses have suggested that patients with both high TG and low HDL-C (defined in various ways) may benefit from the lipid-altering drugs that were studied, this remains to be confirmed in a prospective trial. Furthermore, there was no suggestion of benefit in any of these trials for the larger subgroup of patients selected based on high TG alone (i.e., regardless of HDL-C), which is the population relevant to your proposed indication since this is the population studied in the ANCHOR trial.

Given the current level of uncertainty regarding the benefits of drug-induced changes in lipid/lipoprotein parameters on CV risk among statin-treated patients with residually high TG (200-499 mg/dL), you will need to provide evidence that Vascepa reduces the risk of major adverse CV events in patients at high risk for cardiovascular disease, at LDL-C goal on statin therapy, with residually high TG. We anticipate that the final results from the REDUCE-IT trial could be submitted to satisfy this deficiency.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and

clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

James P. Smith, M.D., M.S.
Deputy Division Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
04/27/2015