

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202057Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	July 25, 2012
From	Eric Colman, MD
Subject	Deputy Division Director Summary Review
NDA#	202057
Applicant Name	Amarin Pharmaceuticals
Date of Submission	September 23, 2011
PDUFA Goal Date	July 26, 2012
Proprietary Name /Established Name	Icosapenty ethyl/Vascepa
Dosage Forms / Strength	Capsule/1 gram
Proposed Indication	Severe hypertriglyceridemia
Recommended Action	Approve

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	Iffat Chowdhury, MD
Statistical Review	Japo Choudhury, PhD
Pharmacology/Toxicology Review	Stephanie Leuenroth-Quinn, PhD
CMC Review/OBP Review	Martin Haber, PhD/Houda Mahayni, PhD
Clinical Pharmacology Review	Jhiehong Li, PhD
Microbiology Review	John Metcalfe, PhD
OSI	Susan Leibenhaut, MD
OSE/DMEPA	Jamie Wilkins Parker, PharmD

OND=Office of New Drugs
 CMC=Chemistry, Manufacturing, and Controls
 OBP=Office of Biopharmaceutics
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction and Background

Lovaza, a mixture of seven omega-3 fatty acids, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is the only prescription “fish oil” FDA-approved for the treatment of severe hypertriglyceridemia (> 500 mg/dl).

Amarin Pharmaceuticals submitted a 505(b)(2) application for icosapent ethyl or ethyl-eicosapentaenoic acid (EPA) – tradename Vascepa - seeking an indication for the treatment of severe hypertriglyceridemia (\geq 500 mg/dl). The recommended daily dose is 4 grams.

This memorandum summarizes the major findings and recommendations of the individuals representing the major review disciplines.

2. CMC

The drug substance, icosapent ethyl, is a long-chain, polyunsaturated omega-3 fatty acid ester derived from fish oil. Dr. Martin Haber recommends approval of the application and notes that there are no outstanding CMC issues. I agree with his assessment.

3. Nonclinical Pharmacology/Toxicology

In a 2-year carcinogenicity study in Wistar rats, female animals in the high-dose group (safety margin 7x the 4 gram daily dose) had a significantly increased incidence of hemangiomas and hemangiosarcomas at the mesenteric lymph node. The incidence of hemangiomas and hemangiosarcomas at all anatomical sites combined was not statistically significant. There was no imbalance in the incidence of hemangiomas and hemangiosarcomas in male rats. These latter two findings, together with an absence of a significant imbalance in hemangiomas and hemangiosarcomas in male rats or in female or male mice in the 6-month transgenic mouse model, suggest that the finding in the high-dose female rats is of no to limited clinical significance.

Dr. Stephanie Leuenroth-Quinn recommends approval of the application and notes that there are no outstanding nonclinical pharmacology or toxicology issues. I agree with her assessment.

4. Clinical Pharmacology

Dr. Zhihong Li recommends approval of the application and notes that there are no outstanding nonclinical pharmacology or toxicology issues. I agree with his assessment.

5. Clinical Microbiology

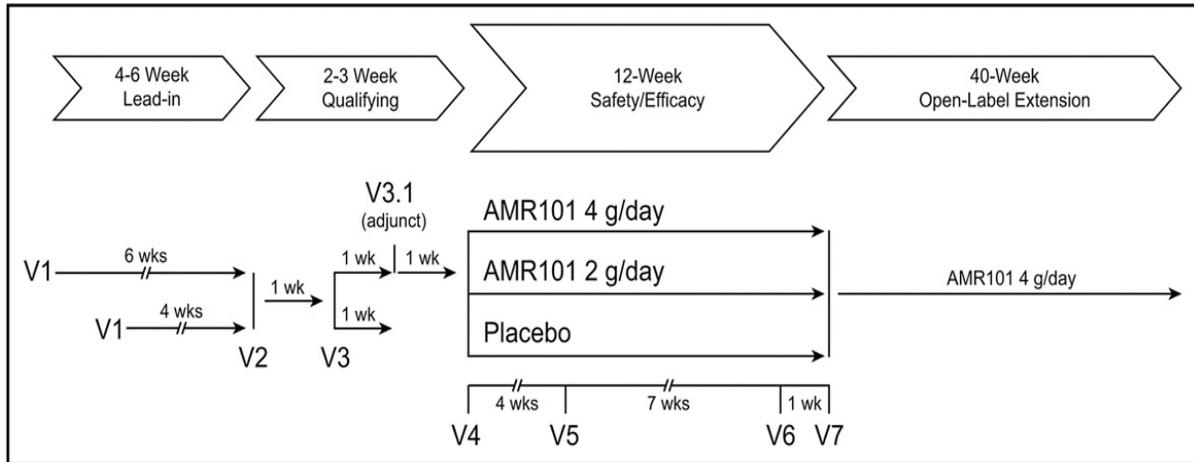
Dr. John Metcalfe recommends approval of the application and notes that there are no outstanding microbiology issues. I agree with his assessment.

6. Clinical/Statistical-Efficacy

The applicant conducted one pivotal phase 3 clinical trial – MARINE – to support the efficacy of Vascepa in reducing triglyceride levels in patients with severe hypertriglyceridemia. Supportive data were provided from a second phase 3 clinical trial – ANCHOR – of patients on statins with TG levels between 200 mg/dl and 500 mg/dl. This memorandum will limit discussion to the MARINE trial.

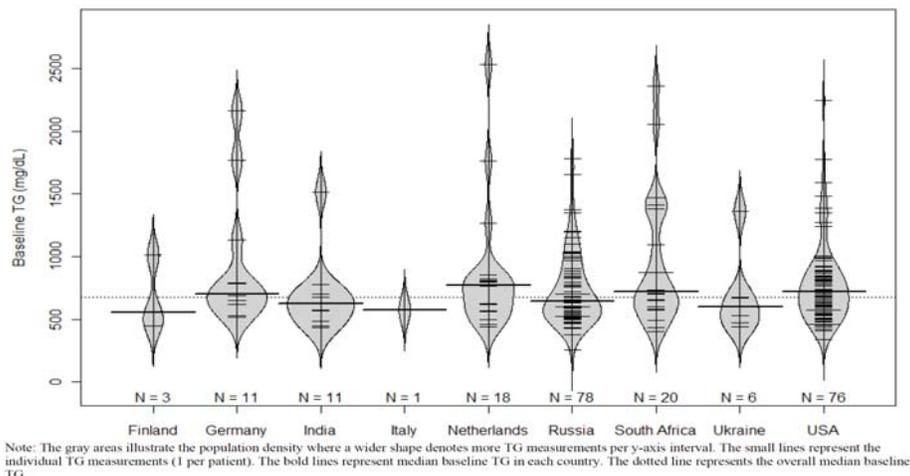
The pivotal trial was a multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label extension (MARINE) to evaluate the efficacy and safety of Vascepa in patients with fasting TG levels ≥ 500 mg/dl and ≤ 2000 mg/dl. The study was conducted at 54 centers in North America, Europe, India, and South Africa.

As shown in the figure below from Dr. Iffat Chowdhury’s review, patients who had a fasting TG level ≥ 500 and ≤ 2000 mg/dl (average of two measurements) following a 4-6 week diet and lifestyle stabilization period were randomized to one of three groups: placebo (n=76), Vascepa 2 grams daily (n=76), or Vascepa 4 grams daily (n=77). Randomization was stratified based on baseline TG level (above or below 750 mg/dl), gender, and use of statin (yes versus no). The double-blind treatment period was 12 weeks.



The primary efficacy endpoint was the percent change in TG from baseline to Week 12. The secondary efficacy endpoints were the percent changes in VLDL-C, Lp-PLA₂, and Apo B from baseline to Week 12.

With respect to baseline demographic characteristics, the mean age of the study subjects was 53 years, 76% were male, 88% Caucasian, and 75% were not on statin therapy. The mean baseline BMI was 31 kg/m² and the median TG level was 697 mg/dl. Approximately 40% of the subjects had a baseline TG level > 750 mg/dl. There were no significant differences in the major demographic characteristics among treatment groups. The below figures taken from Dr. Japo Choudhury’s statistical review illustrates the baseline TG levels by geographic region.



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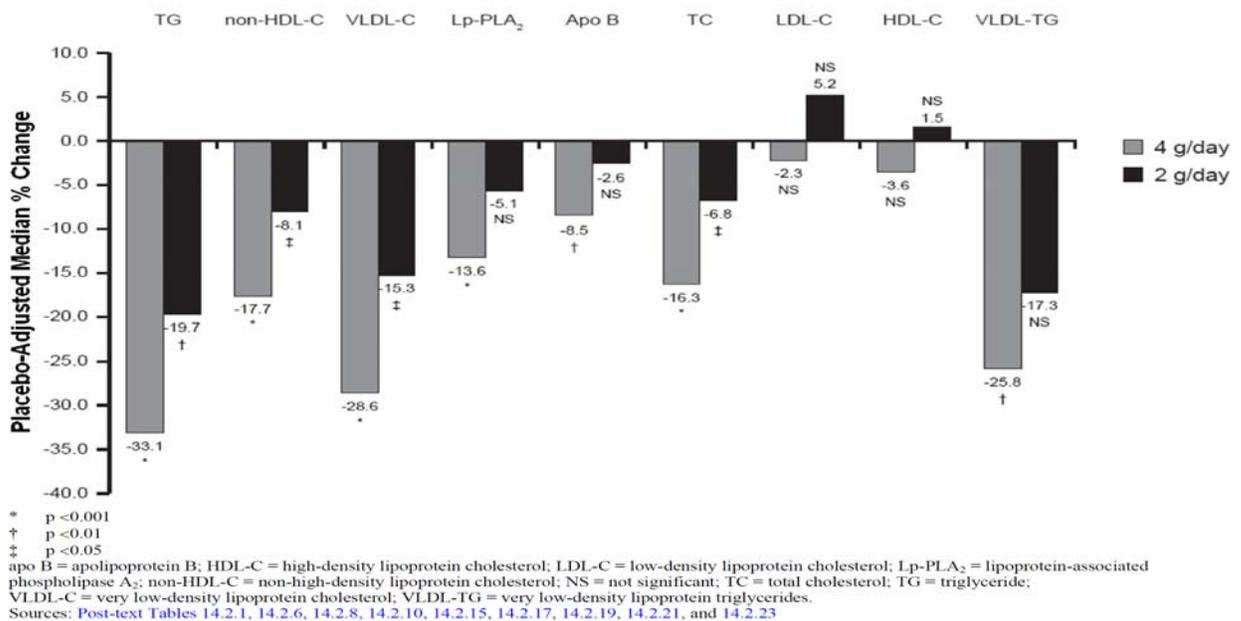
Approximately 94% of study subjects completed the 12-week double-blind treatment period; there were no significant differences in completion rates among treatment groups. “Withdrew consent” was the most common reason for not completing the 12-week treatment period.

In the primary efficacy analysis, the median percent changes in fasting TG levels were 9.7% in placebo, -7.0% in Vascepa 2 grams daily (p=0.005 versus placebo), and -26.6% in Vascepa 4 grams daily (p<0.0001 versus placebo). These results were consistent in several sensitivity analyses.

Given the increase in median TG levels in the placebo group from baseline to Week 12, Dr. Iffat Chowdhury requested that the applicant submit information about the composition of the placebo capsule used in the clinical study. The placebo was composed of light mineral oil or paraffin light liquid. Data submitted by the applicant support the assertion that light mineral oil does not increase serum TG levels. Dr. Chowdhury notes in her review that similar increases in TG levels were observed in the placebo groups from the Lovaza clinical trials of hypertriglyceridemic patients.

In the secondary efficacy analyses, the median percent changes in VLDL-C levels were 13.7% in placebo, 0.0% in Vascepa 2 grams daily (p=0.1 versus placebo), and -19.5% in Vascepa 4 grams daily (p=0.0005 versus placebo). The median percent changes in Lp-PLA₂ levels were -2.4% in placebo, -5.1% in Vascepa 2 grams daily (p=0.2 versus placebo), and -17.1% in Vascepa 4 grams daily (p=0.0006 versus placebo). The median percent changes in Apo B levels were 4.3% in placebo, 2.1% in Vascepa 2 grams daily (p=0.2 versus placebo), and -3.8% in Vascepa 4 grams daily (p=0.002 versus placebo). Similar results were observed when Dr. Japo Choudhury used parametric statistical tests to analyze the secondary efficacy variables.

The changes in primary, secondary, and some exploratory efficacy variables are shown in the following bar graph taken from Dr. Choudhury’s review.



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Clinical practice guidelines recommend a goal of TG < 500 mg/dl for patients with severe hypertriglyceridemia. In an exploratory analysis, the Vascepa 4 grams daily group 49% of subjects achieved this goal at Week 12 or Endpoint compared with 21% of placebo subjects (nominal p=0.002). Thirty-three percent of subjects in the Vascepa 2 grams daily group achieved a TG level < 500 mg/dl at Week 12 or Endpoint (nominal p=0.1 versus placebo).

There was not an increase in the levels of LDL-C with Vascepa 4 grams daily compared with placebo. There was a non-significant reduction in the levels of HDL-C in the Vascepa 4 grams daily group relative to the placebo group. Omega-3 fatty acid products containing docosahexaenoic acid (DHA) have been shown to increase levels of LDL-C and HDL-C relative to placebo.

Although the reduction in fasting TG levels was statistically significant in the Vascepa 2 grams daily group compared with the placebo group, the changes in secondary efficacy and some exploratory endpoints were not significantly reduced in the Vascepa 2 grams daily group relative to placebo. (b) (4)

Because it is general knowledge that omega-3 fatty acids lower serum TG levels and the results of the MARINE trial were statistically robust (i.e., p-value less than 0.0001 for 4 grams Vascepa versus placebo) and consistent in several sensitivity analyses, I believe that the applicant has provided sufficient evidence to conclude that 4 grams daily of Vascepa is effective in reducing fasting TG levels in patients with severe hypertriglyceridemia.

7. Safety

The safety of Vascepa was assessed in an overall Vascepa integrated database that contained information from two placebo-controlled clinical studies of patients with hypertriglyceridemia (MARINE and ANCHOR, the latter in patients on statins with TG levels ≥ 200 mg/dl < 500 mg/dl) and from eight placebo-controlled clinical studies of patients with CNS disorders (e.g., Huntington's disease). There were approximately 622 patients treated with Vascepa and 309 treated with placebo from the hypertriglyceridemia trials. There were approximately 700 patients treated with Vascepa and 519 treated with placebo from the CNS clinical trials.

Dr. Iffat Chowdhury has reviewed the safety data from the overall Vascepa integrated database. This memorandum will discuss the safety data from the two placebo-controlled trials of hypertriglyceridemic patients since these data are most relevant to the proposed indication. A total of 309 patients were exposed to placebo, 312 to Vascepa 2 grams daily, and 310 to Vascepa 4 grams daily. The median number of days of drug exposure was 84.

There was one reported death in the hypertriglyceridemia database; a 64-year-old male died from a myocardial infarction while participating in the ANCHOR trial. He was randomized to placebo.

As pointed out by Dr. Chowdhury in her review, the incidence of nonfatal serious adverse events was 2.9% in the Vascepa pooled group and 1.6% in the placebo group. Furthermore, there was no clear association with the dose of Vascepa and the development of any serious adverse event.

Two reported adverse events occurred at least 1% more in the Vascepa pooled group than the placebo group: arthralgia and oropharyngeal pain.

While there were more reports of “bleeding- or bruising-related” adverse events in the Vascepa versus the placebo group, the non-specific nature of many of these reported events makes it difficult to determine the clinical significance of the overall numeric imbalance. For example, there were five reports of anemia in the Vascepa group versus none in the placebo group. Iron-deficiency anemia might be due to blood loss, whereas pernicious anemia would not.

There were no reports of pancreatitis in the two hypertriglyceridemia clinical trials.

There were numerically more patients on Vascepa with mild elevations of ALT (up to 2xULN) than placebo, 12.8% vs. 10.3%, respectively. One subject in the Vascepa 4 grams daily group developed an ALT > 3xULN; absolute value 163 with AST within the normal range. This value was measured after the subject had completed the 12-week treatment period. There was no clinically meaningful difference between the Vascepa and placebo groups in the incidence of increases in fasting glucose levels.

8. Advisory Committee Meeting

The Division determined that an advisory committee meeting was not necessary for this application.

9. Pediatrics

The Division recommended that the Vascepa application receive a full waiver for pediatric patients because the necessary studies are impossible or highly impracticable due to the relatively small number of pediatric patients with TG levels > 500 mg/dl. The Pediatric Review Committee agreed with the Division’s plan to grant a full waiver for this indication.

10. Other Relevant Regulatory Issues

505(b)(2)

Because the applicant relied in part on published literature to support the nonclinical pharmacology and toxicology of Vascepa, and the Division considers this information necessary for approval, the application was submitted and reviewed under the 505(b)(2) pathway. The Agency’s 505(b)(2) committee discussed the application on 5 June 2012 and did not find any issues that would preclude approval.

Financial Disclosure

Dr. Chowdhury notes in her review the absence of financial interests and arrangements between the applicant and clinical investigators.

Inspections

Routine inspections by the Office of Scientific Investigations did not uncover any significant deficiencies or irregularities in reporting of clinical data.

Tradename Evaluation

The Division of Medication Error and Prevention Analysis and the Office of Prescription Drug Promotion concluded that the proposed tradename, Vascepa, is acceptable from safety and promotional standpoints, respectively. I agree with these assessments.

11. Labeling

(b) (4)

(b) (4) a disclaimer is included in the labeling that points out the lack of evidence that treatment with Vascepa reduces the risk for pancreatitis in patients with severe hypertriglyceridemia. Given the relative rarity of hypertriglyceridemia-induced pancreatitis, the Division has never required an applicant to demonstrate a statistically significant reduction in the incidence of pancreatitis before granting approval of a TG-lowering drug for the treatment of severe hypertriglyceridemia.

12. Risk-Benefit Assessment/Regulatory Action

The applicant has provided sufficient evidence that the benefit-risk profile of Vascepa 4 grams daily is favorable for the treatment of severe hypertriglyceridemia.

Therefore, I agree with Dr. Chowdhury that the application should be approved.

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

/s/

ERIC C COLMAN
07/26/2012