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December 8, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Submission of Citizen Petition

Dear Sir/Madam,

Enclosed is a Citizen Petition requesting that the FDA's decision to rescind the Special Protocol Assessment for VASCEPA be reversed and that the PDUFA date for ANCHOR sNDA (sNDA 202057/S-005) be delayed.

The FDA reviewing division made critical errors of science, law and fact in its decision to rescind the ANCHOR SPA. As the Citizen Petition demonstrates, those errors would be revealed by careful and objective review. Doing so will unquestionably illuminate why the decision should, in the name of good science and public health, be reversed.

Sincerely,

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Encl
Cc (w/ encl):

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CITIZEN PETITION

The EPA Drug Initiative, an organization made up of individual citizens committed to improving cardiac health in the United States and representing more than 1,200 supporters nationwide, submits this petition under the relevant statutory sections of the Federal Food, Drug and Cosmetic Act or the Public Health Service Act or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs, under 21 CFR 5.10, to request the Commissioner of Food and Drugs to overturn the FDA's decision to rescind the Special Protocol Assessment for VASCEPA and to delay the PDUFA date for ANCHOR sNDA (sNDA 202057/S-005) .

A. Action Requested

1. The Commissioner is asked to overturn the FDA's decision to rescind the Special Protocol Assessment Agreement for the ANCHOR trial. This decision by the FDA's reviewing division was based on faulty assumptions and was not supported by the clinical trials cited by the reviewing division.

2. The Commissioner is asked to conduct an independent scientific review of the three outcome trials cited by the FDA reviewing division that were asserted to reveal "substantial scientific issue" and were given as justification for rescinding the ANCHOR SPA. As most of the patients in the three cited trials had normal or borderline elevated TG levels, these trials could not answer the question of whether TG lowering would be beneficial in patients with high TG levels. The FDA reviewing division erred in extrapolating that these 3 outcome trials showed that triglyceride (TG) lowering therapy would not be beneficial in patients with high TG level (≥ 200 and < 500 mg/dl), the population covered by the ANCHOR SPA.

3. The Commissioner is asked to rule that the outcome trials cited by the FDA reviewing division show that the patients with high TG level (≥ 200 mg/dl) and low HDL-cholesterol, the patient population covered by the ANCHOR SPA, had a reduction in cardiovascular disease (CVD) risks. Sub-group analyses from these trials indicate that patients with high TG and low HDL had a reduction in CVD risk of 28 and 37%.

4. The Commissioner is asked to delay the PDUFA date for the ANCHOR sNDA, currently scheduled on or before December 20, 2013, for 180 days to allow for a thorough investigation of the issues raised in this Citizen's Petition and to make a proper and just ruling. This delay is crucial to allow adequate time for the Commissioner to review the issues raised and to make a comprehensive ruling on this petition and prevent premature decision by the reviewing division. This delay will also allow further discussion between the reviewing division and Amarin Corp to come to an appropriate agreement and just decision. So far, the reviewing division has failed to engage in any discussion with the sponsoring company.

5. The Commissioner is asked to investigate the reviewing division for possible misconduct during the ANCHOR sNDA review process, including concern with the timely communication and conveying of key issues to the sponsor, improper processing of the briefing document, omission of key data and information related to the three trials cited by the FDA reviewer, improper and imbalanced review of the three referenced studies, improper rescinding of the ANCHOR SPA, improper handling of the FDA advisory panel meeting, and improper voting question not addressing ANCHOR SPA.

B. Statement of Grounds

In July 2012, ultra-pure eicosapentaenoic acid (EPA), trade name Vascepa, was approved for lowering TG in patients with very high TG levels (≥ 500 mg/dl). The FDA approval was based on the Marine trial (and Marine SPA), which evaluated the efficacy of Vascepa in lowering TG in patients with very high TG levels. Vascepa was found to be safe and efficacious by the FDA and no safety or toxicity issues were raised by the FDA.

Subsequently, the "ANCHOR" sNDA was submitted to the FDA on February, 2013 to extend the use of Vascepa to mixed dyslipidemia patients with TG level between 200-500 mg/dl. The ANCHOR sNDA was based on the ANCHOR SPA, which was approved by the FDA in 2009, and examined the efficacy of Vascepa in lowering TG in patients with high TG levels (≥ 200 and < 500 mg/dl). **The ANCHOR trial fulfilled all aspects of the ANCHOR SPA and demonstrated the efficacy of Vascepa in lowering TG without raising LDL-cholesterol in patients with high TG levels.** [Compared to patients with normal (< 150 mg/dl) or borderline TG (≥ 150 and < 200 mg/dl) levels, patients with high TG levels (≥ 200 and < 500 mg/dl) have been consistently shown to be at higher risk for CVD complications. A recent meta-analysis of 726,030 patients, the largest such meta-analysis to date, showed that each 10 mg/dl increase in serum TG level predicted a 1.4 % increase in risk for CVD complications (Liu, Lipids Health Disease, 2013).]

The FDA's initial review did not raise any concerns and a "clean" "74 Day" letter was issued; and a PDUFA date of December 20, 2013 was assigned for an approval decision. No other issues or concerns were raised or conveyed to Amarin at any time prior to the releasing of the Briefing Document few days ahead of the FDA panel meeting.

The briefing document developed by the FDA's reviewing division for the ADCOM, released several days before the meeting, raised new issues never previously conveyed to Amarin and questioned for the first time whether TG lowering in the ANCHOR population (i.e. patients with high TG level ≥ 200 and < 500 mg/dl) leads to clinical benefit. The assessment of the clinical outcome was not part of the ANCHOR SPA but a topic matter of another separate SPA and clinical trial called REDUCE-IT, designed to assess the therapeutic efficacy of Vascepa in reducing CVD events in mixed dyslipidemia patients with elevated TG.

The FDA reviewing division specifically referenced three recently completed outcome trials (ACCORD -Lipid, AIM-HIGH and HPS2-THRIVE trials) as providing "substantial scientific evidence" that Vascepa lowering of TG in patients with high TG (≥ 200 and < 500 mg/dl) would not lead to clinical benefit. The briefing document and FDA presentation during the ADCOM omitted crucial information related to these three clinical trials that would support ANCHOR sNDA application and refute the FDA reviewer's assertion that TG lowering in high TG patients would not be clinically beneficial. These critical omissions misled the FDA advisory panel. The voting question

was convoluted and confusing, and did not cover ANCHOR SPA, in contravention of FDA policies and procedure, but asked whether a completion of an outcome trial (REDUCE-IT) was required for the ANCHOR approval. This action by the FDA's reviewing division violates the FDA's own "Guidance for Industry Special Protocol Assessment".

- **The voting question did not address the ANCHOR SPA (whether Vascepa was effective in lowering TG in patients with high TG levels with mixed dyslipidemia) but asked a confusing hypothetical question whether approval for the ANCHOR indication should wait until the outcome trial, REDUCE-IT, was completed.**

A review of the ADCOM proceedings shows that the panel members were confused during the proceedings and made specific requests to change or clarify the voting questions. Even when the panelists asked to change the voting question or revise the question to better "fit" the ANCHOR SPA, the FDA reviewing division was steadfast in insisting that the advisory panel link Vascepa approval for ANCHOR sNDA to clinical outcome and the completion of the outcome trial REDUCE-IT. **The voting question was inappropriate and did not address the efficacy question answered by the ANCHOR trial and covered by the ANCHOR SPA, i.e. whether Vascepa lowers TG in patients with high TG levels.** The FDA reviewing division appeared to be biased and intent on obtaining a negative vote, even if it meant asking a wrong question that was not addressed in the ANCHOR SPA.

Following the FDA advisory panel meeting, the FDA gave notice, without elaboration, that the ANCHOR SPA was being rescinded because a "scientific issue of substance," not known at the time that the ANCHOR SPA was completed as agreed, had now come to light. The issue being that the FDA reviewing division no longer considers high serum TG concentration as a CVD risk factor. (Curiously, this view is not reflected in other FDA publications or the latest scientific literature.) This extreme position of the reviewing division is not supported by the recently published meta-analysis or genetic studies in patients with hypertriglyceridemia.

The FDA briefing document for the ADCOM challenged whether Vascepa lowering of TG in the ANCHOR population leads to an improvement in clinical outcome. This was not part of the ANCHOR SPA; ANCHOR trial was not designed or intended to assess clinical outcome, but examined the efficacy of Vascepa in TG lowering in patients with high TG. This Citizen Petition will focus on the erroneous extrapolation made by the FDA reviewer Dr. Mary Roberts and the FDA reviewing division that the three recently completed outcome trials (ACCORD -Lipid, AIM-HIGH and HPS2-THRIVE trials) provide substantial evidence that TG lowering therapy in the ANCHOR SPA population (patients with high TG ≥ 200 and < 500 mg/dl and mixed dyslipidemia) does not lead to clinical benefit, the stated reason for rescinding the ANCHOR SPA.

- While ignoring a wide body of other research that would support Amarin's position, including the only pure EPA outcome trial (JELIS trial) of 18,645 patients showing a significant reduction in CV complications (Yokoyama, Lancet, 2007), the FDA's reviewing division incorrectly extrapolated the results of three recently completed clinical trials (ACCORD -Lipid, AIM-HIGH and HPS2-THRIVE trials) and concluded that these trial results indicated that TG lowering therapy in patients that have high TG levels (≥ 200 and < 500 mg/dl) does not reduce CVD risks. This conclusion is not supported by these clinical trials and, in fact, these trials showed a reduction in CVD risk in a high TG sub-population covered by the ANCHOR SPA.

Upon in-depth review, the facts are:

- The ANCHOR clinical trial design, including the primary outcome (the efficacy of Vascepa on TG lowering) and the absence of any clinical outcome parameters, was agreed to by the FDA in the ANCHOR SPA. The FDA had direct input into the final design of the clinical trial. **It was also stated by the FDA reviewing division (during the FDA panel meeting) when the ANCHOR SPA was agreed to that "a doubt existed as to whether Vascepa efficacy on TG lowering would lead to a clinical benefit." This possibility was known to the FDA and accepted by the FDA at the time of SPA agreement.** As stated by the FDA during the panel meeting, this potential issue was known prior to the SPA agreement and the issue still persists.

- Since the SPA is a binding agreement, any decision to rescind this binding agreement must have an indisputable or compelling evidence to show that TG lowering does not clinically benefit mixed dyslipidemia patients with high TG (≥ 200 and < 500 mg/dl). No such evidence existed before the ANCHOR SPA agreement and no such evidence exists now. In fact, recently completed genetic studies in high TG patients showed that lowering TG levels leads to an improvement in clinical outcome.

- The use of the three recently completed clinical trials by the FDA reviewing division to argue that they represent a "substantial new scientific discovery," and that these studies demonstrate that triglyceride-lowering therapy does not reduce the risk cardiovascular events in patients with high TG levels is completely unfounded, and is an improper extrapolation. **As most of the patients in these three trials had either normal or borderline TG levels (< 200 mg/dl), these studies were neither designed nor intended to inform whether lowering TG levels would lead to a reduction in CV risk in patients with high TG levels (≥ 200 and < 500 mg/dl), the ANCHOR population.**

- **The sub-group analysis from these clinical trials based on TG levels showed that a sub-population of patients covered by the ANCHOR SPA, those with high TG levels (≥ 200 mg/dl) and low HDL-cholesterol, had an impressive reduction in CV risk of 28 and 37 %, prompting the investigators in the Accord-Lipid and AIM-HIGH trials to conclude that this sub-group of patients "appeared to benefit from fenofibrate" and niacin therapy (Ginsberg HN, NEJM, 2010; Guyton JR, J Am Coll Cardiol,2013).**

A review of the design of the FDA referenced trials in comparison to the ANCHOR trial shows glaring differences in the drug tested, design of the trials, the patient population studied, and the outcome parameters studied in each of the trials, such that any extrapolation of the outcomes of these trials to ANCHOR population was illogical and incorrect. Drawing inferences from the findings of patients with normal or borderline triglyceride levels and applying them to patients with high TGs is problematic, scientifically unsound, and detrimental to patient care. **Certainly, one would not conclude that the failure of statins to show clinical benefit in patients with normal or borderline LDL-cholesterol levels also demonstrates that the statins would not also be clinically beneficial in patients with high LDL-cholesterol levels, the patient population that clearly benefits from statin therapy.** The ACCORD -Lipid, AIM-HIGH and HPS2-THRIVE clinical trials do not provide scientific evidence to support rescinding the ANCHOR SPA. **On the contrary, these studies suggest that a sub-population of patients in the ANCHOR population, those with**

high TG and low HDL-cholesterol, are the ones most likely to have a reduction in CVD complications from TG lowering therapy.

A summary of the clinical trials referenced by the FDA to rescind the ANCHOR SPA and how they relate to TG lowering in ANCHOR population are shown in the Table below:

Table 1. Summary of the Three Clinical Trials Cited by the FDA

Trial/Factor	Specific Purpose and Primary End Point	Did the trial assess TG lowering effects in patients with high TG (≥ 200 and < 500 mg/dl) ?	Did a sub-population of patients with high TG level have a reduction in CVD risk?
ACCORD-Lipid (Ginsberg HN, NEJM, 2010)	• Does the addition of fenofibrate to statin therapy compared with statin monotherapy alone reduce the risk of CVD in **patients with type 2 diabetes mellitus.** • Fenofibrates did not reduce CVD complication in patients with type 2 diabetes.	• Trial was not designed or intended to assess TG lowering effects in patients with high TG. • Median TG level in the study was 162 mg/dl. • Most of the patients in the trial either had normal or borderline TG levels (< 200 mg/dl).	• Patients with normal or borderline TG levels (<200 mg/dl) did not have reduction in CVD risk. • **Patients with high TG (>204 mg/dl) and low HDL-cholesterol levels (the sub-population covered by the ANCHOR SPA) had a 28% reduction in CVD risks.**
AIM HIGH (The AIM-HIGH Investigators, NEJM, 2011)	• Does treatment with an extended-release niacin-type lead to a reduction in CVEs in **patients with pre-existing CVD.** • Niacin therapy did not reduce risk of CVE in patients with pre-existing CVD.	• Trial was not designed or intended to assess TG lowering effects in patients with high TG. • Most of the patients in the trial had either normal or borderline TG levels (< 200 mg/dl). • **Only 12.8 % of patients had TG ≥ 200mg/dl.**	• Patients with normal or borderline TG levels (<200 mg/dl) did not have reduction in CVD risk. • **Patients with high TG (>200 mg/dl) and low HDL-cholesterol had a 37% reduction in CVD risk (p= .017).**
HPS2-THRIVE (HPS2-THRIVE , Eur Heart J, 2013)	• Whether niacin (2 g) reduces CVD risk in **patients with occlusive arterial disease.** • Niacin did not reduce CVD risk in this population.	• Trial was not designed or intended to assess TG lowering effects in patients with high TG. • The median TG level in the study was 125 mg/dl. • Most of the patients in the study had normal TG levels (< 150 mg/dl).	• As most of the patients in this trial had normal TG levels, sub-group analysis has not been performed to date.

Conclusions:

- **Each of these trials used drugs that are quite different from Vascepa; the trials were neither designed nor intended to examine the therapeutic benefit of TG lowering in patient with high TG levels.**

- **The patient population in each of the three trials consisted mostly of patients with normal or borderline TG levels, and therefore, no conclusion can be inferred regarding therapeutic benefit in the ANCHOR population, patients with high TG levels.**

- **Sub-group analyses of these trials (based on TG levels) showed that individuals with similar characteristics as those for whom the ANCHOR trial was designed (patients with high TG and low HDL-cholesterol) had an impressive reduction in cardiac risk (28 and 37 % reduction) with triglyceride lowering medications, supporting clinical benefit in these patients.**

These three clinical trials cited by the FDA simply do not provide "substantial scientific evidence" that TG lowering in patients with high TGs would not lead to an improvement in clinical outcome; on the contrary, these trials suggest that a sub-population of patients covered by the ANCHOR SPA are the patients that are most likely to benefit from TG lowering therapy. **We request that the commissioner overturn the FDA reviewing division's decision to rescind the ANCHOR SPA as the clinical trials cited by the FDA do not provide "substantial new evidence" that TG lowering therapy is not beneficial in patients covered by the ANCHOR SPA.**

There is also an important concern regarding the improper conduct of the FDA's reviewing division related to ANCHOR sNDA review process. The FDA reviewing division failed to communicate or convey critical issues related to the sNDA submission to the sponsoring company in a timely manner. It appears that the FDA never notified Amarin of the concerns related to the "new scientific evidence" or possible decision to rescind the ANCHOR SPA. It would have been important for the FDA to have an open dialogue on this critical issue and solicit input from the sponsoring company, possibly avoiding the mistaken conclusions outlined above. Unfortunately, the sponsoring company was never given an opportunity to respond to FDA's concern. In this regard, the FDA reviewing division appeared to have hidden these key issues from the sponsoring company and did not allow Amarin Corp. to have an input or an opportunity to rebuttal the concerns raised.

The FDA reviewing division also omitted key information in the briefing document and in their presentation to the FDA advisory panel that were crucial for the advisory committee to fairly assess whether the outcomes of three clinical trials (ACCORD -Lipid, AIM-HIGH and HPS2-THRIVE trials) addressed the question of whether TG lowering in high TG patients would lead to clinical benefit. The primary intent and the study design of these trials should have been clearly presented in the briefing document and during the presentation to the advisory panel. The composition of the patients enrolled in the study was also omitted in the presentation to the panel so that the panel members were not aware that most of the patients in the trials had normal or borderline TG levels. This information would have been crucial to the FDA panel in assessing whether the outcomes of these clinical trials can be applied to the ANCHOR population. Furthermore, although directly relevant to the ANCHOR sNDA and ANCHOR SPA, the FDA reviewing division failed to present the sub-group analyses which showed that patients with high TG levels (≥ 200 mg/dl) and low HDL-cholesterol actually had a reduction in CVD risks. Whether inadvertently or by design, this key information, arguably the most crucial factor in the advisory panel members' decision making, was omitted from the FDA presentation. There have been number of important and compelling genetic, clinical, and epidemiologic studies that were recently published showing clinical benefit of treating hypertriglyceridemia; however these data were completely overlooked and ignored by the reviewing

division, raising the concern that the reviewing division may have been biased towards obtaining a "no vote" during the panel meeting.

Additionally, as noted above, the ADCOM voting question was confusing, misleading, and did not address ANCHOR sNDA. The voting question should have been "did the ANCHOR trial demonstrate efficacy of Vascepa in lowering TG in patients with high TG and mixed dyslipidemia" as outlined in the ANCHOR SPA, instead the voting question linked the ANCHOR sNDA approval to the completion of the REDUCE-IT outcome trial. Despite repeated requests from the panel members, the FDA reviewing division failed to clarify or change the voting question to fit the ANCHOR SPA or ANCHOR sNDA but insisted that they link the voting to the completion of REDUCE-IT outcome trial, in contravention to the FDA Industry Guidelines.

There were number of irregularities and apparent or inadvertent misconduct related to the ANCHOR sNDA by the FDA reviewing division that raises alarm and concern regarding the fairness and appropriateness of the sNDA review process. We respectfully request a full investigation into the reviewing division's actions and performance as related to the handling of the ANCHOR sNDA submission to identify any misconduct or areas for future improvement.

C. Environmental Impact

There are no issues which would impact the environment.

D. Economic Impact

- The scientific evidence from the outcome trials cited by the FDA shows that TG lowering therapy in the ANCHOR sub-population of patients with high TG and low HDL-cholesterol leads to a reduction in CVD complications. Thus, TG lowering in this high risk population could potentially save lives and reduce CVD complications. Vascepa, based on its excellent safety profile and therapeutic advantages in lowering TG and LDL-cholesterol, represents the best-in-class drug for lowering TGs and will be an important therapeutic option for patients with high TG levels and mixed dyslipidemia. Depriving Americans with high TG levels this safe and efficacious drug could lead to thousands of lives being lost that could have been saved, and the economic and emotional impact of lives lost could be enormous to individual households and to the United States.

- Delaying the expanded label of Vascepa would be a vast disservice to the multitude of patients and doctors in the United States who deserve to be educated regarding the safest and most effective drugs available to treat their respective conditions.

- The reality is that there are FDA approved products (fenofibrates, niacin) currently on the market for the same patient population identified in the sNDA ANCHOR for VASCEPA and these FDA approved products have more dangerous side effects than Vascepa. This exposes patients to undue risk. Vascepa has excellent safety profiles. Considering the changes occurring with recent health care reform, Vascepa plays a crucial role, allowing physicians and patients to choose a TG lowering product for the mixed dyslipidemia population without ANY side effects.

- To expand on the LDL-C parameter, Vascepa has proven to lower LDL-C in the ANCHOR trial patient population. In contrast, Fenofibrates and Lovaza substantially increase LDL-C which negates the statin efficacy. This information contradicts the most recent updated AHA and AAC cholesterol guidelines, whereas, Vascepa's lowering of LDL-C positively supports these new guidelines.

- The cost of the REDUCE-IT trial is estimated to be in excess of $150 million and has been completely funded by Amarin. It is a major undertaking and the results will be of great benefit to the cardiac patients. Amarin's plans were to continue to fund the REDUCE-IT clinical trial from revenue gained from the expanded label of ANCHOR. The FDA's decisions have also ensured that without a change, the REDUCE-IT trial will be all but impossible for Amarin to continue.

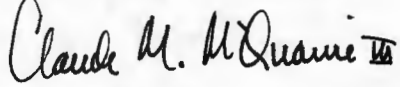
- The markets discussed are extremely large and lucrative and competition is fierce. As a small and vulnerable bio-pharmaceutical company, Amarin has strong competitive advantages. Vascepa has superior safety and efficacy over those of competitors such as GlaxoSmithKline (GSK) and its product, Lovaza. No other company has a clinical program as advanced as Amarin. Finally, the intellectual property of Vascepa is protected by patents through to 2030, in some cases. In contrast, companies like GSK and AstraZeneca are faced with "patent cliffs" in the next year and the loss of revenue from generic manufacturers.

- The decision sends a chilling message to the pharmaceutical industry that may stifle innovation. The expense of exploring new medical discoveries may not be worth the risk as agreements "may not be worth the paper on which they were printed." For Amarin, it is an arbitrary and crippling blow.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data, and information, known to the petitioner which are unfavorable to the petit.

Respectfully submitted,



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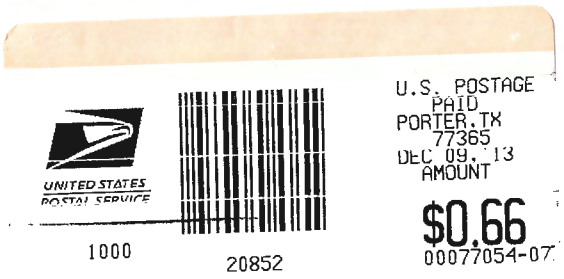

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