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Ad hoc Watchdog group focused on FDA irregularities

FDA puts patients at risk, now says lowering triglycerides will not protect from heart attack and stroke

November 16, 2013

On October 29th, 2013 the FDA quietly announced it had determined that “High” triglyceride (TG) (blood fats) levels in the 200-499 mg/dL range are no longer considered risk factors for cardiovascular disease (CVD) or cardiovascular events (CVE). Specifically, the FDA stated in a letter to the Amarin Corporation, PLC that it “no longer considers a change in serum triglyceride levels as sufficient to establish the effectiveness of a drug intended to reduce cardiovascular risk in subjects with serum TG levels below 500 mg/dL.” The FDA made this highly controversial announcement following a vote by independent panelists at the standard FDA Advisory Committee (ADCOM) meeting held to examine and discuss the expanded use of Amarin’s drug, Vascepa. Curiously, as important as this policy change on TGs is to healthcare professionals and patients alike, it first appeared in a SEC 8-K filing by Amarin, rather than being issued by the FDA recommending a change to the standard of care by physicians.

Vascepa is already FDA approved for lowering TGs in the “Very High” range, >500 mg/dL. Vascepa is distinguished from the other triglyceride lowering drugs (TLDs) due to its composition of 96% purified Eicosapentaenoic acid (EPA), and its remarkable safety profile similar to placebo.

A supplemental New Drug Application (sNDA)

Early this year, Amarin submitted a supplemental new drug application (sNDA) for Vascepa, as was stipulated in an existing agreement with the FDA called a Special Protocol Assessment (SPA). A SPA outlines the steps necessary to achieve approval by the FDA. It should be noted SPAs are binding agreement per FDA regulations and can only be broken by the FDA when the sponsoring company fails to follow the agreed to protocol or falsifies the data. The second provision which allows the FDA to break the agreement if a new scientific data is introduced that affects the safety or efficacy of the test drug. The second provision had never been used to break or rescind the SPA till now. The sNDA for Vascepa was for an expanded label that will permit Vascepa to be indicated (prescribed) for the treatment of “High” TG levels in the 200-499 mg/dL range in addition to the Very High TG levels already approved. Vascepa achieved the FDA approved primary and secondary endpoints. For the primary endpoint, Vascepa reduced TG by 21%. It also met secondary endpoints of reducing “bad” cholesterol, non-HDL-C by 13.6%; LDL-C by 6.2%; and VLDL-C (the worst cholesterol). It caused significant reduction of the cholesterol-associated proteins, Apo B and Lp-PLA2.
An additional prerequisite of the currently rescinded SPA was the obligation by Amarin’s to “substantially enroll” subjects into a large 5-year outcomes study of 8,000 subjects called REDUCE-IT. Amarin met the “substantially underway” enrollment requirement in late 2012, and this past summer announced it had enrolled 6,000 subjects, thus exceeding the SPA requirement. Now all that remains is the final decision on the application for Vascepa’s expanded indication. That decision is expected to occur on or before the PDUFA date of Dec. 20, 2013. Most agree, including Amarin, that “approval will be an uphill battle.”

Making the science fit

A closer look at the reasoning used by the FDA to argue that the lowering of High TGs levels does not affect CV risk, (and used to rescind the SPA) is proven to be weak and fundamentally flawed. Upon closer examination, the choice of the three academic studies presented to the ADCOM panel by the FDA was skewed. To begin with, the included study drugs were not of the same type as Vascepa. These non-EPA drugs were of the Niacin and the Fenofibrate/Fibrate classes. Each class has a different mechanism of action, and are processed differently by the body. Thus, the only conclusions that can be reasonably drawn from these reports are the efficacy of fibrates and Niacin drugs.

What the FDA did was to extrapolate the negative study results from these dissimilar compounds to Vascepa. The fact is, none of the three studies had been designed to examine or evaluate the effects of Niacin or fibrates in patients with “High” TG levels. Importantly, most of the subjects in the trials fit into the “Normal” or “Borderline” TG ranges. “High” TG levels were found in only minor subsets of patients. In fact, in these subsets of patient with High TG levels, there was a marked reduction (28 and 37% reduction) in CVD risk.

In supplying data only from non EPA-class drugs, the FDA was dismissive of the only directly comparable study--the JELIS report. That study is relevant to Vascepa, and did look at the same purified-EPA drug class. JELIS was a 5-year, randomized clinical trial, involving 18,000 subjects. The two trial arm groups were on either a statin alone, or a statin plus an EPA. JELIS compared the incidence of CVD events in these groups, and found that EPA reduced the incidence of events in the hyperlipidemia cohort by 53%. But despite being the only large outcomes study to use 96% purified EPA, this key information was deemed irrelevant by the FDA.

The impact

Many believe the contentious position by the FDA that dismisses any therapeutic value in lowering High TGs was never intended to be the subject of a public proclamation. Instead, it could have been used solely as a means to prevent Vascepa from being granted an expanded label. This new proclamation goes against the overwhelming scientific evidence that show high TG levels to be an important risk factor for CVD and the current standard of care to treat this high risk group. On the other hand, the FDA just saw fit to ban trans-fat from the American diet.

On November 12th, the ACC and AHA in collaboration with the NHLBI released a new guideline called “Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults”. This new guideline is intended to help identify patients at risk and reiterates the benefit of statins for primary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) based on risk factors such as smoking, Type 2 diabetes, HDL-C, blood pressure, etc. This guideline is focused on the broader use of statins; it does not provide specific direction to address other
lipid biomarkers which have been associated with increased risk. This guideline was never intended to be a comprehensive approach to lipid management for purposes other than ASCVD risk reduction.

If the agency is serious, the implications of the FDA’s October 29th communication to Amarin, rescinding the SPA, cannot be overstated, and defy accepted standards of care, exemplified by the NIH National Cholesterol Education Program (NCEP) - ATP III Risk Classification for CVD. Major professional associations, such as the ADA and AHA, are all on board. By following the new FDA logic, does it mean that the NIH would change these guidelines? Unlikely. Can Americans now add a few extra cheeseburgers and French fries to their diets and not worry, so long as their TGs do not reach 499?

The cost of diabetes-associated CVD to Medicare and Medicaid was 70% of the $245 billion of all diabetes-related costs in 2012. If the FDA’s assertion regarding the triglyceride relationship to CVD is incorrect, the effects might be profound. With such a large population at risk, the question of the standard of care cannot be left in an ambiguous state. If the FDA is permitted to operate as an omnipotent agency, immune from oversight, and without accountability, then the American public would be well served to be made aware of an agency intoxicated with power.

**Something smells fishy**

On Oct. 22, just 6 days after the FDA issued a letter to Amarin stating that the SPA was rescinded, the FDA granted a label expansion to the fibrate drug, Antara for treating High TGs. It is data from this very same drug class that was determined by the ADCOM to have no efficacy in reducing CVD risk and used as the pretext for rescinding the SPA. All of this begs the question... why did FDA feel compelled to go to such great lengths and take a position in direct opposition to well-established standards of care during the review of Vascpepa? We are then left to question; who or what could be threatened so severely by Amarin’s drug to warrant overthrowing the established standard of care for TGs? That is the most intriguing question that remains to be fully answered... but there are clues.

A rather indelicate topic is whether there might have been undue influence brought to bear on the FDA and/or ADCOM panelists by large pharmaceutical companies prior to the October 16th meeting. It is reasonable to assume that a small bio-pharmaceutical firm seen as potentially disrupting an industry that enjoys a $45 billion a year revenue stream from heart disease alone, might draw some unwelcome attention by a few “big guns” in the pharmaceutical industry, including some with a “no holds barred “ approach to eliminating competition.

In 2008, the Chief Counsel to the FDA, a Mr. Daniel Troy, was directly hired by GlaxoSmithKline, for its own Chief Counsel position, and to some fanfare. Although there are no statutes against this, per se, the fact that such hires take place is troubling. There are conflict of interest regulations at the FDA, yet the possibility exists that decisions may not always be made impartially.

**Paint by numbers**

The current competitor to Vascpepa, GlaxoSmithKline’s (GSK) Lovaza, brought in $1.0 billion in revenue in 2012, but faces coming patent expirations. Investment analysts covering Amarin, value an expanded label use for Vascpepa in the $2 billion a year range. But hidden in those estimates is a far larger number. The potential disruption of an established health care industry for CVD with overall revenues of $326 billion in 2012.
When the stakes are so high, no government agency is immune to undue influence and power brokering, and yet the FDA operates minimal oversight, and few there lose sleep over the fate of small biotech firms getting trampled by virtue of improper application of fairly applied process or information. In regard to the FDA’s new proclamation on TGs, it has set a precedent that will not only have numerous negative ramifications to all pharmaceutical companies, but ultimately, the health of the American people. Intentionally or not, it discredits the established NCEP standard for lipid disorders. All of this, without consultation with any recognized professional medical associations. This is unacceptable, and demands attention.

Vascepa is an efficacious triglyceride-lowering drug, such as recommended by the NCEP guidelines, and has no side effects. In an ideal world free from ulterior motive, the sNDA would be approved without hesitation. There are 40 million Americans with high triglycerides who could potentially benefit from preventive care. There are many potential losers should the application for the label expansion fail: the patients, new options for physicians-- and American taxpayers, who are projected to be footing an astounding $850 billion a year bill in 2030, when the cost of treating CVD is projected to triple. Then the winners might end up as a few large pharmaceutical firms, treating an increasingly larger population with CVD. The potential impact to society, both in terms of death related to CVD and financial health, could be staggering.

The FDA places considerable emphasis on the 16 October ADCOM vote. We encourage those with interest in learning more, to view the ADCOM video, and see first-hand the dynamics of the Vascepa ADCOM story. There is much more to explore, many more questions to ask. Should you desire to seek additional information on this topic we invite you to start here…

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