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Public Citizen Health Research Group

FDA Hearing on lomitapide for treatment of Homozygous Familial Hypercholesterolemia (HoFH)

October 17, 2012

* We do not have any financial conflicts of interest.

Statements from reviews of the use of apheresis for treating familial hypercholesterolemia*

- "LDL apheresis is currently the best treatment option to bring these [HoFH] patients closer to target LDL levels, and has been shown to reduce the risk of CVD along with LDL-C levels."

- "Before the availability of apheresis, homozygotes rarely survived the third decade of life; however, based upon clinical observation, the present-day life expectancy of homozygotes treated with different combinations of available treatment modalities can reach at least to the fourth and fifth decades."

*Thompson, et al. Current Opinion in Lipidology 2010, 21:492–498

Continued statement from published reviews of apheresis*

The annual cost for weekly LDL apheresis is about 58,000 British pounds (approximately $93,000, or less than 1/3 of the Aegerion-announced lomitapide cost of $300,000 per year.

***Thompson, et al. Current Opinion in Lipidology 2010, 21:492–498**

Further statements from published reviews of the efficacy of apheresis*

"In patients reported by Palcoux and in the sub-group treated in New York by Hudgins et al, it is possible to calculate that interval mean values of LDL cholesterol were 6.6 and 6.5 mmol/l respectively, which is a 64-69% reduction from baseline levels off all treatment."

*Thompson, et al. Atherosclerosis 208 (2010); 317-321

Other Safety Concerns from Clinical Trials

"Regarding hepatic fat, all eligible subjects had hepatic fat measured by NMRS/MRI at weeks 0, 26, 56, and 78 in the pivotal trial. The mean absolute change in % hepatic fat from baseline to week 26 was +8.1% and to week 78 was +7.4%. Eighteen (78%) of 23 subjects with available data demonstrated a maximum absolute increase in hepatic fat>5%, and three (13%) had an absolute increase >20%."

Reasons why clinical trials on lomitapide are insufficient

Given that apheresis (along with approved drugs known to lower cardiovascular risk) are the best treatments for this serious disease, more precise trials testing different combinations of lomitapide with apheresis need to be done. For example, lower doses of lomitapide with apheresis might yield more effective and safer treatments for these patients.

An FDA reviewer's comments on this topic are on point:

It should not be assumed that reducing the frequency or discontinuing apheresis will benefit patients with HoFH; in fact, this may be detrimental given the increase in time-averaged LDL-C concentration that likely accompanies the reduction or removal of an LDL-lowering treatment. Although this is a time-consuming, costly procedure associated with its own set of complications and challenges, ***the net risk/benefit of apheresis compared with lomitapide on clinical outcomes is unknown****.(emphasis supplied, page 104, FDA briefing document)*

Concerns with Effectiveness of the Proposed Risk Management Strategy

Given the strong, positive Wall Street reaction to the posting of these briefing documents and the fact that only a small fraction of the estimated 300 U.S. patients with HoFH are likely to be able to afford the estimated $300,000 cost per year, it is likely, if not certain, that these glowing financial predictions "depend" on sales for off-label use to treat elevated cholesterol in the larger number of patients who do not have HoFH.

In view of the FDA reviewer's statement that even for HoFH, ***the net risk/benefit of apheresis compared with lomitapide on clinical outcomes is unknown***, a more failsafe method of preventing any use outside of patients with HoFH must be devised in order to prevent large numbers of patients, with risks outweighing benefits, from using the drug. Earlier trials for this broader set of patients were "abandoned as a result of concerns regarding gastrointestinal tolerability, hepatic steatosis (fat), and a preclinical observation thought to be pulmonary phospholipidosis."

Further statements of concern from FDA staff in briefing documents

"We would like to reiterate our position that while the study of BMS-201038 [*i.e., lomitapide*] in high-risk patients such as those with homozygous FH is acceptable despite significant potential risk associated with drug-induced fat accumulation in the liver and lung (and perhaps the intestine), the use of BMS-201038 in a lower-risk population (e.g., heterozygous FH, type IIa and IIb patients) may not be justified in light of the documented preclinical toxicities observed at low multiple of the proposed clinical doses." (FDA briefing, page 22)

In summary, we oppose the approval of lomitapide because of the inadequacy of the studies testing what further benefits it yielded compared to the combination of apheresis and optimal doses of other FDA-approved drugs alone. Combined with the multiple signals of toxicity, possibly tolerable if the evidence of its benefits was clearer, approval would be unwise.

If it is approved, however, a serious re-thinking of the risk management program to more definitively exclude the possibility of its proven-to-be-too-dangerous use on patients who do not have HoFH is urgently needed.

Thank you