Zetia® and Vytorin® – FDA Advisory Meeting Recommendations

- On December 14, 2015, the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the results of the IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) and the proposed indication for Merck’s Zetia (ezetimibe), in combination with a statin, and Vytorin (ezetimibe/simvastatin), to reduce the risk of cardiovascular (CV) events in patients with coronary heart disease (CHD).

- Zetia and Vytorin are both approved for the treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia.
  - In addition, Zetia is approved for the treatment of homozygous familial sitosterolemia.
  - The current labels for Zetia and Vytorin state the effect of ezetimibe on CV morbidity and mortality, alone or incremental to statin therapy, has not been determined.

- IMPROVE-IT was a double blind trial involving 18,144 patients with high-risk acute coronary syndrome. Patients received a combination of ezetimibe/simvastatin or simvastatin alone. The primary endpoint was a composite of major CV events (CV death, nonfatal myocardial infarction, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke). The median follow-up was 6 years.
  - Patients randomized to ezetimibe/simvastatin had a 6.4% relative-risk reduction and a 2% absolute-risk reduction of major CV events compared with those who received simvastatin alone (p = 0.016).

- There was discussion at the meeting regarding the analysis and sub-analysis from the trial, patient population and subgroups, the definitions of statistical significance vs. clinical relevance, and low density lipoprotein cholesterol (LDL-C) management itself.

- The advisory panel voted 10-5 against expanding the use of ezetimibe plus statin therapy for the reduction of CV events in patients with CHD.
  - Many panel members were not convinced that the IMPROVE-IT trial results were clinically robust.
  - In addition, there were questions about how missing primary endpoint data for 11% of participants were handled.
  - The panel also expressed concerns over the small but troubling risk for hemorrhagic stroke in the ezetimibe group.
  - One suggestion was made to add data from IMPROVE-IT to the Clinical Studies section of the labels for Zetia and Vytorin.

- While the FDA considers the advisory panel’s recommendations when reviewing new indication applications, it is not bound by the advisory panel’s guidance.