

NATIONAL PBM COMMUNICATION: FDA Issues an Early Communication about an Ongoing Safety Review of Ezetimibe/Simvastatin (Vytorin®), Simvastatin, and Ezetimibe (Zetia®)

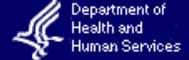
August 26, 2008

The FDA has announced that they are investigating data from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial for a possible association between the use of Vytorin (ezetimibe/simvastatin) and a potentially increased incidence of cancer. In the SEAS study, 1873 patients with aortic stenosis were randomized to receive ezetimibe/simvastatin or placebo for nearly five years. Although the primary endpoint (major cardiovascular events) was not met, an approximately 50% increase in the incidence of cancer was observed in the treatment group. An interim analysis of two large ongoing trials of ezetimibe/simvastatin (Study of Heart and Renal Protection [SHARP] and Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome [IMPROVE-IT]) did not find an increased cancer risk with ezetimibe combined with simvastatin. The FDA's intention is to evaluate the final study results from SEAS and to communicate their conclusions and recommendations to the public in the next nine months. Please refer to the FDA Early Communication below for detailed information or visit http://www.fda.gov:80/cder/drug/early_comm/ezetimibe_simvastatin_SEAS.htm

The VA Medical Advisory Panel and the Pharmacy Benefits Management Service have recently updated the non formulary criteria for using ezetimibe; please click the following link to access the criteria <http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Criteria%20For%20Use/Ezetimibe%20or%20Ezetimibe+Simvastatin%20Criteria%20for%20Nonformulary%20Use.doc>



U.S. Food and Drug Administration



CENTER FOR DRUG EVALUATION AND RESEARCH

Early Communication About an Ongoing Safety Review of Ezetimibe/Simvastatin (marketed as Vytorin), Simvastatin (marketed as Zocor) and Ezetimibe (marketed as Zetia)

FDA Investigates a Report from the SEAS Trial

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing this product. FDA is considering but has not reached a conclusion about whether this information warrants any regulatory action. FDA intends to update this document when additional information or analyses become available.

FDA is investigating a report from the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) of a possible association between the use of Vytorin (a combination of simvastatin plus ezetimibe) and a potentially increased incidence of cancer. Simvastatin (Zocor), a "statin" class drug approved in 1991, decreases production of cholesterol by the liver and is indicated to reduce LDL-cholesterol levels and reduce the risk of cardiovascular events such as heart attack and stroke. Ezetimibe (Zetia), approved in 2002, inhibits the absorption of cholesterol in the intestine and is indicated to reduce LDL-cholesterol levels. Vytorin, the combination product approved in 2004, is indicated to reduce LDL-cholesterol levels.

Recently, FDA obtained preliminary results from the SEAS trial. This clinical trial tested whether lowering LDL-cholesterol with Vytorin would reduce the risk of major cardiovascular events, including aortic valve replacement, congestive heart failure, and ischemic cardiovascular events in individuals with aortic stenosis (a tight heart valve). A lower overall cardiovascular risk was not found with Vytorin. However, there was an additional observation that a larger percentage of subjects treated with Vytorin were diagnosed with and died from all types of cancer combined (including skin cancer) when compared to placebo during the 5-year study.

Interim data from two large ongoing cardiovascular trials of Vytorin – the Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) – show no increased risk of cancer with the combination of simvastatin plus ezetimibe. The SHARP trial is expected to be completed in 2010. The IMPROVE-IT trial is scheduled for completion around 2012. Safety data from both of these trials are being evaluated on a regular basis by independent data safety monitoring boards. FDA has determined that, to date, these findings in the SEAS trial plus the interim data from ongoing trials should not prompt patients to stop taking Vytorin or any other cholesterol lowering drug.

FDA is aware of previous reports suggesting a link between low on-treatment cholesterol levels and an increased risk of cancer. A 2007 pooled analysis of 16 studies with 23 statin drug arms, published in the *Journal of the American College of Cardiology*, reported an association between the level of LDL-cholesterol achieved and incident cancer in patients receiving a statin.

However, most large prospective studies of statin drugs have reported no difference in cancer incidence between the active and placebo arms. For simvastatin, the Heart Protection Study randomized 20,000 patients to a daily dose of simvastatin 40 mg or placebo for up to 5 years. The incidence rate for cancer was 7.9% in the simvastatin group and 7.8% in the placebo group, and the deaths from cancer occurred at similar rates in both groups.

FDA anticipates receiving a final SEAS study report from the sponsors in about 3 months. Once FDA receives the final study report, it will likely take 6 months to fully evaluate the clinical trial data and other relevant information. As soon as this review is complete, FDA will communicate our conclusions and recommendations to the public.

An elevated LDL-cholesterol level is an established risk factor for heart disease and lowering cholesterol reduces the risk of death from heart disease and stroke. Patients should not stop taking Vytorin or other cholesterol lowering medications and should talk to their doctor if they have questions about whether to continue to take the medication. Until further information is available, healthcare professionals and caregivers should continue to monitor patients taking Vytorin as outlined in the prescribing information.

The FDA urges both healthcare professionals and patients to report side effects from the use of Vytorin to the FDA's MedWatch Adverse Event Reporting program

- on-line at www.fda.gov/medwatch/report.htm
- by returning the postage-paid FDA form 3500, available in PDF format at www.fda.gov/medwatch/getforms.htm to 5600 Fishers Lane, Rockville, MD 20852-9787
- faxing the form to 1-800-FDA-0178
- by phone at 1-800-332-1088

References

Alsheikh-Ali A et al. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. *J Am Coll Cardiol* 2007;50: 409-18.

Heart Protection Study Collaborative Group. MRC/BFH Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360: 7-22.