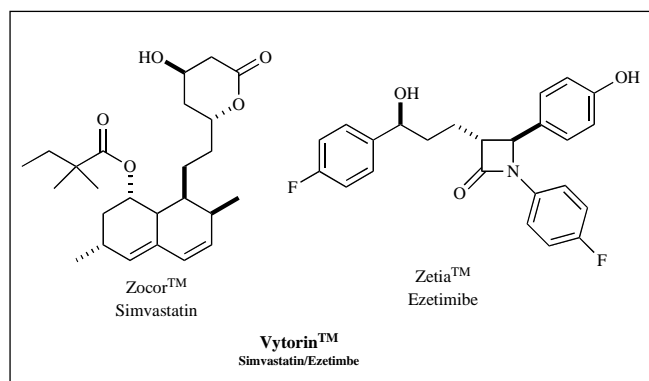


## Molecule of the Month

**Is Zetia™ a A ‘Do Nothing’ Drug?** After months of delays and on the eve of meetings with congressional investigators, results from the much anticipated ENHANCE clinical trial for Vytorin™ were finally disclosed (January 15, 2008) to the dismay of pharmaceutical giants Merck and Schering-Plough, with the announcement that Vytorin™ conferred no medical benefit over Zocor™ alone [1-4]. The ENHANCE trial was launched to demonstrate superior cardiovascular protection (fewer heart attacks and strokes) with Vytorin™ versus Zocor™ and enrolled 720 patients with heterozygous familiar hypercholesterolemia, a rare condition that predisposes them to abnormally high blood cholesterol. The two year study measured the amount of artery-clogging plaques in three areas and compared patients taking Vytorin™ versus high dose Zocor™ [1-4]. Vytorin™, approved by the FDA in 2004, is a combination drug consisting of Merck's Zocor™, an HMG-CoA reductase inhibitor (statin) that inhibits cholesterol production in the liver, and Zetia™, the first cholesterol absorption inhibitor (works in digestive track). These complimentary cholesterol lowering strategies in a single pill were touted to treat the two sources of



cholesterol - heredity and diet and provide superior protection from heart attack and stroke versus statin alone therapy. Zocor™ has proven to be a safe and effective statin which lowers cholesterol and decreases the risk of adverse cardiovascular events. Zetia™, was shown to lower LDL (bad cholesterol) 15-20% in a surrogate goal trial, with no clinical support that its effects on LDL confer cardio-protection - the chief concern of patients [1-4].

These data raised questions about aggressive marketing tactics, the delays to announce negative clinical data and the issue of Brand versus cheaper Generic medications with Vytorin™ [2-4]. Many physicians and clinicians voiced their displeasure and referred to Zetia™ and Vytorin™ as ‘Do Nothing’ drugs [2-4]. Moreover, both Vytorin™ and Zetia™ had achieved blockbuster status with billions in sales/year

and provided additional sales for Merck's Zocor™, which is now facing billion dollar generic competition, and a major component of Schering-Plough's annual revenue. Merck's Zocor™ is an excellent example of the impact of the loss of patent protection and generic competition. In 2005, the statins Lipitor™ and Zocor™ were ranked No.1 (\$7.6 billion) and No.2 (\$4.5 billion) in sales, and No. 1 and No. 11 in prescriptions dispensed, respectively. After generic variants of Zocor™ entered the market mid-year 2006, Pfizer's Lipitor™ remained No. 1 in terms of both sales (\$ 8.6 billion) and prescriptions dispensed (74,020) while Zocor™ slid to No.7 in sales (\$3.2 billion) and No. 25 in prescriptions dispensed [5-7]. With an increasing market share in each quarter of 2007, Vytorin™ was poised to recoupe much of Zocor's™ lost revenues for Merck, but the ENHANCE trial may derail this rally and drive more patients to request cheaper, generic simvastatin [1-7].

However, three larger clinical trials are underway, including the 10,000 patient IMPROVE IT trial, which Merck and Schering-Plough hope will conclusively demonstrate that Vytorin™ can reduce the number of details and major, adverse cardiac events versus Zocor™ alone [1-4]. Unfortunately, data from these trials will not be available for ~ three years and the moniker of ‘Do Nothing’ drug may linger until conclusive data proves otherwise.

### REFERENCES

- [1] For information on the ENHANCE trial see: [www.merck.com](http://www.merck.com), [www.schering-plough.com](http://www.schering-plough.com)
- [2] For information on the ENHANCE trial in the popular media see: [www.cnn.com](http://www.cnn.com), keyword Vytorin and [www. Healthrevolution.com](http://www.Healthrevolution.com), search Vytorin.
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