FDA approval: Change to drug label provides evidence for using cholesterol-lowering treatment routinely in kidney disease patients

Following the US Food and Drug Administration’s (FDA) review of the Study of Heart And Renal Protection (SHARP), approval has been given for revised wording of the drug label for the combination simvastatin plus ezetimibe tablet (proprietary name “Vytorin”). The SHARP results now included in the label provide compelling evidence for using this cholesterol-lowering treatment in patients with chronic kidney disease.

Chronic kidney disease affects about 30 million people in the USA (and many more worldwide), and it is associated with a very high risk of cardiovascular disease. SHARP enrolled a wide range of people with kidney disease. Its results indicate that the use of Vytorin would typically reduce a patient’s risk of a heart attack, stroke, revascularization or coronary (“heart”) death by about one quarter.¹ No other treatment has been shown in a randomized trial to provide protection against cardiovascular disease in patients with kidney disease. The FDA’s approval of new labelling for Vytorin is an important step forward in the care of such patients.

The SHARP investigators specifically chose to test the combination of the moderate doses of simvastatin (20mg daily) plus ezetimibe (10 mg daily) in Vytorin because it can produce large reductions in LDL cholesterol while minimising the adverse muscle side-effects that may be associated with higher doses of statin treatment in kidney patients. The results of SHARP (which were reported in The Lancet in June 2011)¹ confirm the merits of this strategy by showing that Vytorin not only significantly reduces the risk of life-threatening cardiovascular events, but also is associated with few side-effects, in patients with kidney disease.
As part of its review process, the FDA convened a meeting of its Endocrinologic and Metabolic Drugs Advisory Committee in November 2011 to consider the SHARP trial. The FDA’s Advisory Committee praised the design and conduct of the trial, and voted unanimously in favour of approving Vytorin to reduce the risk of cardiovascular disease in patients with kidney disease who had not yet progressed to dialysis. The Committee felt that the data were less certain for dialysis patients. The FDA has now approved wording in the drug label which provides the evidence from SHARP that supports the use of this treatment in patients with chronic kidney disease.

Professor Colin Baigent, the Chief Investigator of the trial, said: “SHARP shows that lowering LDL cholesterol with the combination of simvastatin plus ezetimibe is both effective and safe in patients with kidney disease. It is important that the label for Vytorin has now been changed to include information that supports its use in patients with chronic kidney disease since they are at high risk of heart attacks and strokes.”

The FDA decided to approve revised wording in the Clinical Trials section of the Vytorin label, rather than to modify the Indications section, because SHARP does not assess the separate effects of ezetimibe and of simvastatin on vascular disease. Despite this decision, the Advisory Committee’s unanimous vote indicates that both the rationale for using the combination treatment in patients with kidney disease and the evidence for its safety and efficacy are compelling.

Professor Sir Rory Collins, Chair of the SHARP Steering Committee, said: “Now that the Vytorin drug label provides the evidence from SHARP to support the use of simvastatin plus ezetimibe, it is important that its use is now widely adopted in patients with kidney disease for whom no other treatment has been convincingly shown in a randomized trial to reduce their high risk of life-threatening cardiovascular events.”

SHARP was designed, conducted and analysed independently by the Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU) at the University of Oxford, which was the regulatory sponsor of the trial. Guidance was provided by an independent Steering Committee that included many of the world’s leading kidney specialists. Funding and drug supplies were donated by the manufacturer of Vytorin (Merck).

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NOTES:

1. The SHARP trial results were reported and interpreted by the SHARP investigators (independently of all funding sources), following scientific peer review, in The Lancet:


   http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2811%2960739-3/fulltext

   In that paper, the investigators explain how the actual use of 20 mg simvastatin plus 10 mg ezetimibe daily (as compared with the average of two-thirds compliance seen during the trial) typically would reduce LDL-cholesterol by about 1.3 mmol/l (which is approximately 50 mg/dl) and would reduce a kidney patient’s annual risk of suffering a “major atherosclerotic event” (defined as heart attack, non-haemorrhagic stroke, arterial revascularization procedure or coronary death) by about one quarter.

2. Further information about the SHARP trial is available at: www.sharpinfo.org