March 30, 2010

Risks Seen in Cholesterol Drug Use in Healthy People

By DUFF WILSON

With the government’s blessing, a drug giant is about to expand the market for its blockbuster cholesterol medication Crestor to a new category of customers: as a preventive measure for millions of people who do not have cholesterol problems.

Some medical experts question whether this is a healthy move.

They point to mounting concern that cholesterol medications — known as statins and already the most widely prescribed drugs in the United States — may not be as safe a preventive medicine as previously believed for people who are at low risk of heart attacks or strokes.

Statins have been credited with saving thousands of lives every year with relatively few side effects, and some medical experts endorse the drug’s broader use. But for healthy people who would take statins largely as prevention — which would be the case for the new category of Crestor patients — other experts suggest the benefits may not outweigh any side effects.

Among the risks raising new concerns, recently published evidence indicates that statins could raise a person’s risk of developing Type 2 diabetes by 9 percent.

“It’s a good thing to be skeptical about whether there may be long-term harm from healthy people taking a drug like this,” said Dr. Mark A. Hlatky, a professor of health research and cardiovascular medicine at the Stanford University medical school.

There is also debate over the blood test being used to identify the new statin candidates. Instead of looking for bad cholesterol, the test measures the degree of inflammation in the body, but there is no consensus in the medical community that inflammation is a direct cause of cardiovascular problems.

The Food and Drug Administration approved the new criteria last month for Crestor, which is
made by **AstraZeneca** and is the nation’s second best-selling statin, behind **Lipitor** by **Pfizer**. AstraZeneca plans soon to begin a new marketing and advertising campaign for Crestor, based on the new F.D.A.-approved criteria.

Under those criteria, an estimated 6.5 million people in this country who have no cholesterol problems and no sign of heart problems will be deemed candidates for statins. That is in addition to the 80 million who already meet the current cholesterol-based guidelines — about half of whom now take statins.

The **new Crestor label** says it may be prescribed for apparently healthy people if they are older — men 50 and over and women 60 and over — and have one risk factor like smoking or **high blood pressure**, in addition to elevated inflammation in the body.

Some patients have long complained of **muscle aches** from taking statins. And doctors periodically check patients on the drugs to make sure liver enzymes are not abnormally high. Doctors, though, have generally seen those risks as being more than offset by the drugs’ benefits for people with high levels of “bad” cholesterol and a significant risk of cardiovascular disease.

But then came the unexpected evidence linking statins to a **diabetes** risk, reported last month in the British medical journal **The Lancet**. That report was based on an analysis of most of the major clinical studies of statins — including unpublished data and the results of the Crestor study that the F.D.A. reviewed. “We’ve had this drug for a while, and we’re just now finding out that there’s this diabetes problem with it?” said Dr. Hlatky.

The F.D.A. acknowledged the diabetes risk, and told AstraZeneca to add it to Crestor’s label. But the agency nonetheless approved the new use on the basis of the clinical study, which showed a small but measurable reduction of strokes, heart attacks and other “cardiovascular events” among people taking the statin, compared with patients taking a placebo.

“It’s an important milestone for the company and for the patient,” said Jim Helm, AstraZeneca’s vice president for cardiovascular products. “We are already discussing this with physicians.”

Dr. Eric C. Colman, a deputy director of the F.D.A. center for drug evaluation, said the decision provided an option, not a mandate, for doctors and patients. “It’s good to hear that physicians are debating the potential benefits and risks of drugs,” Dr. Colman wrote via e-mail on Tuesday.

An F.D.A. advisory committee had voted 12-4 in favor of expanding the usage in December, with some dissenters questioning the value of the test measuring elevated levels of inflammation.
The new Crestor guidelines continue a steady expansion of the number of people considered candidates for statins over the last decade. The recommendations and guidelines have been expanded by various advisory panels — many of whose members have also done paid consulting work for the drug industry.

Another of those panels is now preparing statin guidelines due next year, which are expected to further expand the number of candidates for the drugs.

The clinical trial on which the F.D.A. approved the new Crestor use was a global study of nearly 18,000 people. It looked only at patients who had low cholesterol and an elevated level of inflammation in the body as measured by a test called high-sensitivity C-reactive protein, or CRP.

It was the inventor of the CRP test, Dr. Paul M. Ridker, a Harvard medical professor and cardiologist at Brigham and Women’s Hospital in Boston, who persuaded AstraZeneca to pay for the statin study, which he then led.

Dr. Ridker said his proposals for such a study had been turned down by the National Institutes of Health and at least two other companies. One was Pfizer, whose statin Lipitor will lose patent protection next year and will be sold in inexpensive generic forms. The other was Bayer, whose statin Baycol was removed from the market in 2001 after it was linked to 52 deaths from a rare muscle disorder.

Compared with those companies, AstraZeneca had more of a business interest in sponsoring Dr. Ridker’s study. Crestor, which had sales of $4.5 billion last year, will not be subject to generic competition until 2016 — and so the company has more years to benefit from expanded use of the product at name-brand prices. The drug, taken as a daily pill, sells for at least $3.50 a day, compared with only pennies a day for some generic statins.

Dr. Ridker, meanwhile, receives undisclosed amounts of royalties from the CRP test. For a decade, he has argued that his test is sometimes a better diagnostic tool than cholesterol scores. And he says the Crestor study proved his case.

“We found a 55 percent reduction in heart attacks, 48 percent reduction in stroke, 45 percent reduction in angioplasty bypass surgery,” Dr. Ridker said recently. “I felt I had one shot at a controversial hypothesis,” he said, “and it worked really well.”

So well, in fact, that the study was halted after following patients an average of 1.9 years instead of the planned five years. With such improvement, a data monitoring board concluded it would have been unethical to continue the trial.
“I don’t understand the antipathy out there,” said Dr. Steven E. Nissen, chairman of cardiology at the Cleveland Clinic, who has consulted for AstraZeneca among many other companies but says he donates the money to charity. “If somebody comes into my office and meets the criteria, am I going to deny them a drug that reduces their chance of a heart attack or stroke by 40 or 50 percent?”

But critics said the claim of cutting heart disease risk in half — repeated in news reports nationwide — may have misled some doctors and consumers because the patients were so healthy that they had little risk to begin with.

The rate of heart attacks, for example, was 0.37 percent, or 68 patients out of 8,901 who took a sugar pill. Among the Crestor patients it was 0.17 percent, or 31 patients. That 55 percent relative difference between the two groups translates to only 0.2 percentage points in absolute terms — or 2 people out of 1,000.

Stated another way, 500 people would need to be treated with Crestor for a year to avoid one usually survivable heart attack. Stroke numbers were similar.

“That’s statistically significant but not clinically significant,” said Dr. Steven W. Seiden, a cardiologist in Rockville Centre, N.Y., who is one of many practicing cardiologists closely following the issue. At $3.50 a pill, the cost of prescribing Crestor to 500 people for a year would be $638,000 to prevent one heart attack.

Is it worth it? AstraZeneca and the F.D.A. have concluded it is.

Others disagree.

“The benefit is vanishingly small,” Dr. Seiden said. “It just turns a lot of healthy people into patients and commits them to a lifetime of medication.”