THE EVIDENCE GAP

For Widely Used Drug, Question of Usefulness Is Still Lingering

By ALEX BERENSON
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When the Food and Drug Administration approved a new type of cholesterol-lowering medicine in 2002, it did so on the basis of a handful of clinical trials covering a total of 3,900 patients. None of the patients took the medicine for more than 12 weeks, and the trials offered no evidence that it had reduced heart attacks or cardiovascular disease, the goal of any cholesterol drug.

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Daniel Rosenbaum for The New York Times

"I don't think the answer on Zetia is in," said Dr. Robert J. Temple of the Center for Drug Evaluation and Research.

The lack of evidence has not stopped doctors from heavily prescribing that drug, whether in a stand-alone form sold as Zetia or as a combination medicine called Vytorin. Aided by extensive consumer advertising, sales of the medicines reached $5.2 billion last year, making them among the best-selling drugs in the world. More than three million people worldwide take either drug every day.

But there is still no proof that the drugs help patients live longer or avoid heart attacks. This year Vytorin has failed two clinical trials meant to show its benefits. Worse, scientists are debating whether there is a link between the drugs and cancer.

Researchers reported last month that patients in three clinical trials had a 40 percent higher chance of dying from cancer if they took Vytorin instead of a sugar pill or another medicine, although the leader of that study says the finding might be due to chance.

Now some prominent cardiologists say that the evidence has swung so decisively against the drugs that they should not be sold. "The only place people should be taking it is in a clinical trial," Dr. Allen J. Taylor of the Walter Reed Army Medical Center said of Zetia. (Vytorin is a single pill that combines Zetia with a statin, an older form of cholesterol-lowering medicine whose effectiveness and safety are not in question.)

On Tuesday, in a sign of the high level of interest among doctors that Vytorin and Zetia have generated, the New

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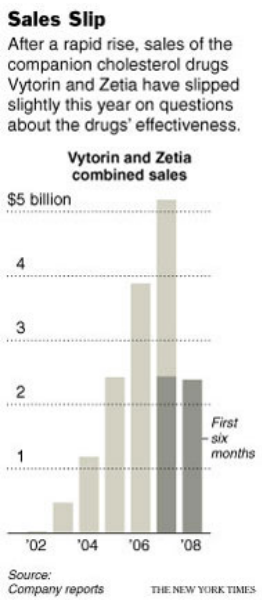

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Dr. Terje Pedersen, a cardiologist, said he doubted that the medicine caused the excess of cancers seen in a recent study.

England Journal of Medicine will publish online two articles and an editorial about the trials that raised the potential cancer concerns.

Merck and Schering-Plough, which jointly make Vytorin and Zetia, strongly defend their medicines. The companies say that ezetimibe, the generic name for Zetia, showed no cancer risk in animal trials and argue that the cancer finding is probably a result of chance. Some independent scientists agree with the companies, saying that they are dubious of a link to cancer and that ezetimibe is a valuable treatment no matter which brand it is sold under.

About the only point on which both sides agree is that no one can judge ezetimibe's safety and benefits for certain without more data, ideally from a clinical trial covering more than 10,000 patients and lasting several years, long enough to show that the drug actually helps patients live longer or avoid heart attacks.

But patients and doctors will have to wait years more for those results. Merck and Schering did not begin such a trial until October 2005, three years after ezetimibe was approved. And the completion date for the trial has been repeatedly postponed. Now the companies estimate that it will not be finished until at least 2012. By then tens of millions of people will have taken ezetimibe.

"I don't think the answer on Zetia is in," said Dr. Robert J. Temple, director for the office of medical policy at the Center for Drug Evaluation and Research, which is part of the F.D.A.

The lack of data about ezetimibe highlights an aspect of the drug approval system that even sophisticated patients may not understand. Many medicines are approved on the basis of what scientists call surrogate endpoints, like proof that they lower cholesterol, rather than because they have been shown to reduce the risk of death or disease.

For example, a cancer drug might be approved because it causes tumors to shrink, not because its manufacturer can prove that patients live longer after taking it.

Using these measures makes sense in certain circumstances, researchers say. If no treatments exist for a disease, the F.D.A. may approve a drug based on its promise in short-term trials and hope that the medicine succeeds later in larger trials where its potential to reduce death and disease will be examined directly.

But several drugs approved this way have recently proved ineffective or even dangerous. In 1999, for example, the F.D.A. approved the diabetes drug Avandia on the basis that it reduced blood sugar. Sales of Avandia and two related medicines reached $3 billion in 2006. But in 2007, an analysis of 44 clinical trials of Avandia showed that it could increase heart attacks. Since then, prescriptions for Avandia have plunged, although the drug remains on the market.

Ezetimibe is in a similar situation. The medicine has been proved to lower patients' LDL, or bad, cholesterol by 15 to 20 percent. Decades of research links lower cholesterol to a reduced risk of heart attacks. And cholesterol-lowering drugs called statins, including

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Lipitor and Crestor, have been proved to reduce heart attacks. But statins work very differently than ezetimibe, and no one has proved that ezetimibe offers the same benefits as statins.

“The F.D.A. set the bar too low on the initial approval,” said Dr. Steven Nissen, chairman of cardiology at the Cleveland Clinic. “It would have been a lot better if the agency had said, ‘Show us that you do more than lower LDL a little bit, show us evidence of effectiveness.’ ”

Further, when the F.D.A. approved Zetia, several statins were already on the market, giving patients other options to lower their cholesterol. So the agency’s decision to approve Zetia without requiring larger trials is especially puzzling, Dr. Nissen said.

Dr. Temple said the link between LDL cholesterol and heart disease was so strong that the agency was comfortable approving drugs on the basis that they lowered cholesterol alone. “We accept LDL cholesterol as a valid surrogate,” he said.

But the failure nearly two years ago of torcetrapib, an experimental drug from Pfizer, spotlighted the risks of using drugs without long-term data. Torcetrapib raised HDL cholesterol — the so-called “good” cholesterol, which is known to reduce the risk of heart problems.

But the F.D.A. chose not to approve torcetrapib on the basis of its effects on HDL. Instead, the agency required that Pfizer first conduct a large trial. In December 2006, the trial revealed that torcetrapib raised patients’ risk of death by 60 percent, forcing Pfizer to discontinue development of the drug.

Dr. Curt D. Furberg, an epidemiologist and drug safety expert at Wake Forest University, said that before approving drugs the F.D.A. should require that drug companies conduct large trials on whether they reduce death and disease, except in rare cases where no alternatives exist. If the agency approves drugs without such data, that fact should be noted prominently on a drug’s label, Dr. Furberg said.

Pharmaceutical companies argue against changing the current approval system. Determining whether a drug reduces death or disease can require a trial that enrolls 10,000 or more patients and lasts four years or more. Requiring longer and costlier trials might discourage the development of new medicines, said Ken Johnson, senior vice president of the Pharmaceutical Research and Manufacturers of America.

He said the current system enabled patients “to access life-saving and life-enhancing remedies more quickly.”

The F.D.A. does seem to be taking a harder line on new diabetes and heart medicines. In April, the agency turned down an HDL-cholesterol-raising drug from Merck that did not have long-term trial data. And in July, an F.D.A. advisory panel recommended 14-2 that companies conduct long-term trials on new diabetes medicines.

But for drugs already on the market, no such requirement exists. So ezetimibe remains heavily prescribed despite questions about both its effectiveness and whether it is linked to cancer.

In January, Merck and Schering announced that Vytorin — the combination of ezetimibe and a generic statin called simvastatin — had failed a clinical trial meant to show that it could slow the growth of arterial plaque that could cause heart attacks.

Then, in July, Norwegian researchers reported that another trial showed that patients taking Vytorin died from cancer more often than those taking a placebo, or sugar pill. In two other clinical trials still going on, patients taking Vytorin have also been more likely

to die from cancer than those not taking it. In all, 136 of about 11,000 people taking Vytorin in the three trials have died of various kinds of cancer, compared with 95 out of 11,000 who took placebo or simvastatin alone.

With little long-term data about ezetimibe's risks, scientists are scrambling to find an explanation for the seeming cancer link. Some oncologists agree with Merck and Schering that the cancer findings are probably due to chance.

But other scientists say they have a plausible explanation for why ezetimibe may cause cancer. Ezetimibe works by blocking the intestine from absorbing cholesterol. But it also blocks the absorption of closely related compounds called plant sterols, which are found in nuts and vegetables. Some studies have shown that people who eat large amounts of plant sterols have lower cancer rates than those who do not.

Dr. Peter G. Bradford, a pharmacologist at the University of Buffalo who has extensively studied plant sterols, said that in laboratory tests, sterols promote cell death in a way that could make them valuable anti-cancer agents as weapons against tumors. By blocking sterol absorption, ezetimibe could be promoting cancer , he said.

"One might envision that link," he said. "This is a very large question."

Merck and Schering noted that the drug showed no carcinogenic effects in mice. In addition, the link between sterols and cancer remains hypothetical and has never been proved in a clinical trial. Further, cancer typically takes many years to develop in humans, so the theory that ezetimibe could cause cancer in a year or two is not plausible, they say.

Some leading cancer researchers agree. Dr. Tyler Jacks, director of the Koch Institute at the Massachusetts Institute of Technology, said Merck had asked him to examine the results of the Norwegian trial and he concluded it was probably a false signal. If ezetimibe causes cancer, its effects should have become more pronounced as the trial went on, Dr. Jacks said. Instead, the gap between patients who took Vytorin and those who took a placebo did not widen over the length of the trial, he said.

Dr. Terje Pedersen, the Norwegian cardiologist who conducted the trial, said he also doubted that Vytorin caused the excess of cancers seen in the study. Even very dangerous carcinogens — like cigarettes and radiation — typically require several years, even decades, to cause cancer. Given that fact, ezetimibe would have to be extraordinarily and implausibly carcinogenic to have noticeable effects in a three-year trial, he said.

"The duration of the trial is not long enough to believe that the treatment would cause cancer," Dr. Pedersen said.

Still, the concerns about ezetimibe's potential risks and lack of effectiveness have discouraged some patients from using the medicine. In the United States, prescriptions for Vytorin and Zetia have fallen 40 percent this year.

Dr. Jacks said Merck and Schering could not easily resolve the questions about ezetimibe's potential risks. "The answer is to get more data," he said.

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