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Health Concerns Over Popular Contraceptives

By NATASHA SINGER

The oral contraceptives Yaz and Yasmin are the top-selling pharmaceutical line for Bayer HealthCare, largely as a result of marketing that presents them as much more than mere pregnancy prevention.

Yaz, in particular, the top-selling birth control pill in the United States, owes much of its popularity to multimillion-dollar ad campaigns that have promoted the drug as a quality-of-life treatment to combat acne and severe premenstrual depression.

Yaz, a newer sister drug to Yasmin, contains less estrogen. The franchise had worldwide sales of about \$1.8 billion last year, based on Bayer's successful positioning of Yasmin and Yaz as the go-to drug brands for women under 35.

But recently, the Yaz line's image has been clouded by concerns from some researchers, health advocates and plaintiffs' lawyers. They say that the drugs put women at higher risk for blood clots, strokes and other health problems than some other birth control pills do.

Those critics, though, are up against a large European health study, sponsored by Bayer, the German pharmaceutical giant, that reported the opposite conclusion. The Bayer-financed study said that cardiovascular risks in women taking Bayer products were comparable to those taking an older formula of birth control pills.

But regulators are finding other faults with the Yaz franchise. The Food and Drug Administration early this year asked Bayer to correct misleading television commercials. Last month, the agency cited the company for not following proper quality control procedures at a plant that makes hormone ingredients.

In e-mail responses to a reporter's queries, the American unit of the company said that its birth-control drugs had been and continued to be extensively studied and that the company stood behind their safety. The company also said it had responded to the F.D.A.'s questions about manufacturing practices, which it said it took very seriously.

But even if Bayer can adequately respond to the safety and other concerns, some industry analysts say that the avalanche of criticism could tarnish the Yaz line's image. Other

products by Bayer, like the erectile dysfunction drug Levitra and the intrauterine birth-control system Mirena, generate far less income than the Yaz product family.

“For Bayer, it is by far the highest margin and the fastest-growing brand,” Martin Brunninger, an analyst with the European investment bank Bryan, Garnier & Company, said in a phone interview from London on Wednesday. “Whether this turns out to be a serious issue or not, when a drug is stigmatized in public, people just withdraw from taking it.”

Bayer said that the company had been served with 74 lawsuits brought by women who charge that they developed health problems after taking Yaz or Yasmin. The company says it intends to defend itself vigorously against the suits.

The health questions and the lawsuits may rattle consumer confidence, but the warnings from federal health authorities about advertising and quality control raise larger questions about Bayer’s approach to complying with government rules, said Michael A. Santoro, an associate professor at the Rutgers Business School who has studied ethics in the pharmaceutical industry.

Birth control pills work by altering a woman’s hormone levels. Researchers have long known that taking a combination hormone birth control pill — which contains estrogen and a progestin hormone — can increase the risk of stroke and blood clots in the legs and lungs. That is because estrogen can play a role in blood coagulation. Indeed, since the introduction of oral contraceptives in the 1960s, drug companies have greatly reduced estrogen doses to decrease the risk of thrombosis, the medical term for blood clots.

With lower-dose estrogen pills now available, the safety debate, continuing for the last decade, has focused on whether the type of progestin in a formula may also play a role in the risk of cardiovascular problems.

In 2001, the F.D.A. approved Yasmin, which contains a novel progestin called drospirenone.

Yaz, which contains drospirenone and a lower dose of estrogen, received agency approval in 2006. For women seeking contraception, the drug is also approved to treat severe emotional and physical symptoms called premenstrual dysphoric disorder and for moderate acne. Because drospirenone can increase potassium levels in the body, it may put women who have liver or kidney problems at risk for serious heart problems, according to the drug label.

Studies on the safety of birth control pills have reported different results on the risks of progestins.

One large-scale study in Europe, sponsored by Bayer, reported that there was no difference in the risk of cardiovascular problems or death in women taking drospirenone birth control pills compared to women who took pills that contained levonorgestrel, a progestin that has been used since the 1970s.

But two other studies on Danish and Dutch women, published last month in The British Medical Journal, found a higher risk of venous blood clots for women taking newer progestins, including drospirenone.

The results of the new studies, conducted on European populations with specific genetic risk factors for blood clots, might not translate to a more ethnically diverse American patient population, said Dr. David A. Grimes, a clinical professor of obstetrics and gynecology at the University of North Carolina medical school. And even if the reported increased risk is realistic, he said, it is tiny.

“My dictum is that a multiple of a rare event is still a rare event,” said Dr. Grimes, who has been a paid consultant for Bayer and other makers of contraceptives.

And taking birth control pills involves much smaller blood clot risks than getting pregnant and having a baby, he said.

But Dr. Frits R. Rosendaal, a professor of clinical epidemiology at Leiden University Medical Center who was one of the authors of the Dutch study, said the reports of an increased risk were worth acting on — by switching to pills containing levonorgestrel.

“Even if the risk of thrombosis is low, why not choose the lowest risk, just in case?” he said.

A spokeswoman for the F.D.A. said the agency was reviewing the safety of birth control pills with a study designed to identify the incidence of blood clots, stroke and death among users of Yasmin and other oral contraceptives. Bayer, meanwhile, is conducting a postmarketing study comparing the safety of Yaz with other birth control pills.

Lawyers suing Bayer on behalf of plaintiffs who claim that they developed blood clots, heart attacks and other health problems because they took the drugs said they intended to argue that the company knew or should have known that the pills entailed a higher risk.

One such plaintiff is Anne Marie Eakins, a history teacher in Grafton, Ohio, who developed blood clots in both lungs in 2007 and, as a result, she said, lost partial use of her right lung. She had used a variety of different birth control pills over more than a decade before starting Yaz in 2007, she said.

“To be perfectly honest, I asked my doctor about Yaz because I had seen the commercial and it mentioned helping control your period symptoms and acne, which was very attractive to me,” said Ms. Eakins, 34. “I didn’t think it was going to be worse than any other pill.”

Because drug labels for Yasmin and Yaz contain warnings about the risk of side effects like blood clots and strokes, plaintiffs may have a difficult time winning cases with the argument that the company should have issued stronger alerts. But, armed with F.D.A. warning letters to Bayer, lawyers may find more success with the argument that misleading Yaz commercials enticed women to take the drug, thereby exposing them to health risks they might not otherwise have incurred.

Last October, the agency sent Bayer a warning letter, citing the company for running two false and misleading television ads about Yaz. According to the letter, the ads overstated the drug’s efficacy, promoted it for conditions like premenstrual syndrome for which the drug is not approved, and minimized serious risks associated with the drug. In February, Bayer agreed to spend \$20 million on a corrective advertising campaign to counteract misimpressions created by the original television spots.

Last month, the agency sent Bayer a warning letter about another problem — deviations from quality control standards at a manufacturing plant in Germany that makes drospirenone and other hormone ingredients used in Bayer’s birth control pills sold in the United States. The letter said that the way in which the facility calculated variability in ingredients did not meet American standards.

Bayer said it was taking the matter seriously. Maintaining good manufacturing practices and patient safety continue to be top priorities at Bayer, the company said in a statement.

But Mr. Santoro of the Rutgers Business School said that drug companies should set higher standards for themselves than those set by the F.D.A.

“It tells me,” Mr. Santoro said of Bayer, “that it is not understanding the business that it is in, that it is not understanding the health risks that it is posing to the public or the financial risk that it is creating for its shareholders.”