



Trends-in-Medicine

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Quick Pulse

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FDA APPROVES CONTINUOUS BIRTH CONTROL PILL – But Warns that Bleeding and Spotting Still Occur

The FDA approved Wyeth's Lybrel, concluding that it is safe and effective as a contraceptive, but Lybrel may not get the approval of many women. The problem with Lybrel is that two-thirds of women continue to have spotting or bleeding for an average 4-5 days a cycle. Wyeth will be required to conduct a Phase IV post-marketing study, but the details of that study have not been worked out.

The FDA held a teleconference with reporters to discuss the Agency's approval of Wyeth's Lybrel, the first continuous-use contraceptive. Lybrel comes in low-dose combination tablets that contain 90 µg of progestin (levonorgestrel) and 20 µg of estrogen (ethinyl estradiol). While traditional oral contraceptives are designed to be taken for 21 days, with a placebo taken the other seven days – during which time there is bleeding – Lybrel is designed to be taken without any off-time. It will be marketed in 28-day packs.

While some women like the idea of being period-free, Lybrel does not appear to fulfill that wish. FDA official said as many as half the women in the trials stopped taking Lybrel because of unscheduled bleeding or spotting. Of the remaining women who completed the trials, only 30%-35% had no bleeding or spotting. Bleeding and spotting occurred an average of 4-5 days per 28-day cycle, which is the same as for women on traditional birth control pills and even for women who don't take birth control pills at all.

Pressed for more detail on the number of women who dropped out of the studies, Dr. Scott Monroe, acting director of the FDA's Division of Reproductive and Urologic Products in the Center for Drug Evaluation and Research (CDER), said, "The number of people who have amenorrhea – no bleeding or spotting – at the end of 13 cycles is about 60%...(of) the women who reached the end (of the trials). Many – about half – dropped out, and of the women who finished, maybe 30%-35% had no bleeding or spotting. The rest had some bleeding or spotting. In the trials, we made the distinction that bleeding required sanitary protection, spotting did not."

Asked why so many women dropped out, he said, "I suspect that many dropped out because they weren't expecting the amount of spotting and bleeding that they had. These were the clinical trials, so the women didn't know exactly what to expect and were perhaps used to having a different experience, and many of them weren't happy about the bleeding and spotting. Now, we have that information, and women will be informed, healthcare providers will be informed, and women will decide."

Asked how long bleeding and spotting lasts when it occurs, Dr. Monroe said, "It's sporadic. The longer you are on the pill, the less chance you have of bleeding and spotting...The median number of bleeding days per 28 days ranged from 4-5 days. It could be 4-5 days of bleeding or spotting. Women are going to vary, and I think women are going to have to decide whether they want this experience and understand that it's going to take them a while before they get to where they want to be, which is having no bleeding or spotting. Clearly, this is a choice women are going to have to make...We are giving the information out in a straightforward manner so that patients – women and providers – can read the information and decide. This is not an option, clearly, for everyone."

Dr. Monroe said that the approval of Lybrel "concludes a comprehensive review process," but he indicated there are no pulmonary embolic (PE) event data on the drug, so the FDA has asked Wyeth for a post-marketing safety study. He said that the primary endpoint of the clinical trials was contraceptive efficacy, "They showed that this was a safe and effective contraceptive...We want to see if there are any long-term effects different from traditional oral contraceptives...such as clotting and pulmonary emboli...Progestin-alone products do eliminate periods for more than a year and for many, many years, and we haven't found any particularly significant adverse effects with those products. We don't suspect any surprises in terms of long-term use of this product."

The FDA and Wyeth have not yet worked out the details of the Phase IV post-marketing study. This is a little unusual since recently the FDA has been emphasizing that it wants companies to **begin** their Phase IV studies **prior** to approval.

According to Dr. Monroe, there was no difference in terms of the pregnancy rate between Lybrel and other contraceptives in the two trials: one in the U.S. and another in Europe. He said, "In the comparative (European) trial, they compared the efficacy of this product with an approved product (Wyeth's Alesse), which doesn't seem to have a problem with efficacy, and pregnancy rates were essentially the same."

In a statement, the FDA also said, "The safety and efficacy of Lybrel as a contraceptive method were supported by two one-year clinical studies, enrolling more than 2,400 women, ages 18-49. Healthcare professionals and patients are advised that when considering the use of Lybrel, the convenience of having no scheduled menstruation should be weighed against the inconvenience of unscheduled bleeding or spotting. The occurrence of unscheduled bleeding decreases over time in most women who continue to take Lybrel for a full year. In the primary clinical study, 59% of the women who took Lybrel for one year had no bleeding or spotting during the last month of the study."

The FDA said that with Lybrel, as with other low-dose hormonal contraceptives, women need to use other contraception if they miss taking a pill. He added, "We do make a point in the labeling that if you suspect pregnancy, go ahead and get

a pregnancy test. That's something that people need to keep in mind, no question."

Other points Dr. Monroe made included:

- The longer a woman stays on Lybrel, the less chance she will have of bleeding or spotting.
- If a woman goes off Lybrel, her periods – and ovulation – will come back fairly rapidly, probably within a few days, "Ovulation in many women will recur within days of stopping these pills."

