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Quick Pulse

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FDA Softens Warnings about the Safety of Birth Control Patches

The FDA is warning women not to overreact to reports that using Johnson & Johnson's Ortho Evra (norelgestromin/ethinyl estradiol transdermal system) birth control patch may double the risk of developing a blood clot to taking an oral contraceptive. In mid-February 2006, Dr. Daniel Shames, director of the FDA's Division of Reproductive and Urologic Drug Products, Center for Drug Evaluation and Research (CDER), told reporters that the FDA has no plans for any specific regulatory action at this time.

Ortho Evra, the only approved transdermal delivery method for birth control, is a weekly prescription patch that releases an estrogen hormone and a progestin hormone. In November 2005, the FDA put a new bolded warning on Ortho Evra, telling women that it can expose them to ~60% more total estrogen in their blood than if they were taking a daily oral contraceptive. However, the maximal blood level of estrogen is ~25 percent lower with Ortho Evra than with typical oral contraceptives.

Now, new – but conflicting – data from one of two trials suggest that the patch may increase the risk of blood clots. However, the FDA has no plans to recall the product and is not putting a black box on Ortho Evra. Dr. Shames said, "At this time, we don't plan to take any specific regulatory action based on these preliminary results. In November we discovered in a pharmacokinetic (PK) trial that the estrogen exposure of women using Ortho Evra was 60% higher in women on the patch than for women taking an oral contraceptive. We felt this was important for patients and providers to know. At the time we stated – and still believe – that although we're not sure what it means clinically, it is information people need to know about…We are trying to stay ahead of the curve. This is the data as we have it now. Even though the data sometimes is not totally evaluated, it is going to bring up certain questions, but we all believe that everyone should be learning about this data as early as possible in order to make informed decisions."

Dr. Shames said that he doesn't want women to panic, but FDA wants to get safety information out as early as possible, even though some of it is preliminary data. He is advising worried women to discuss their risk with their doctor. He explained that announcing early study results is part of the FDA's new policy of "transparency," but he also is worried that this might confuse people before final results are analyzed and released. He said, "Our intention is not to raise an alarm about this data but to make sure we're communicating information from the appropriate sources in the FDA in the most appropriate manner…We believe this information will better inform patients and providers so they can make appropriate decisions regarding their healthcare…By chance, it's possible they (the two

studies) are telling us the same thing – that the chance of adverse events (with the patch) compared to an oral contraceptive may in fact be the same, or it may be twice as high, but we don't know the answer yet; it's preliminary."

The data are conflicting. Two ongoing epidemiologic trials, both sponsored by J&J's Ortho-McNeil Pharmaceutical, reached different conclusions about the risk of thrombotic adverse events in women using the patch. One study showed that women using the patch may be twice as likely to develop blood clots as those on the pill. However, another similar study found no such risk.

- **No increased blood clot risk.** The first study, conducted by the Boston Collaborative Drug Surveillance Program and published online in the journal ***Contraception***, did ***not*** find any increase in venous thromboembolic events (VTEs) in first-time Ortho Evra users vs. women on an oral contraceptive pill (norgestimate/estrogen). Researchers concluded, "The risk of non-fatal VTE for the contraceptive patch is similar to the risk for oral contraceptives."
- **Increased blood clot risk.** A recently reported interim evaluation of currently available data from an ongoing study showed women on Ortho Evra had almost double the risk of VTE as women on an oral contraceptive containing 35 μg of norgestimate and ethinyl estradiol. The analysis of MI and stroke data from this unpublished trial is ongoing, but the available data do not suggest an increased risk of MI or stroke with Ortho Evra.

Both studies looked at women age 18-44 from huge U.S. medical insurance claims databases. An FDA official said, "There are probably hundreds of thousands and certainly tens of thousands of women (in the studies)…They were looking at all the women in a large insurance database."

The FDA was consulted on the design of both studies, which were funded by Johnson & Johnson. An FDA official explained, "These studies were undertaken by them after they conferred with us some time ago – maybe a year ago. We wanted additional, or more precise, information because we were getting adverse events, as we do with most contraceptives, from our spontaneous reporting system. Although that spontaneous reporting system is helpful, we believed that more controlled epidemiologic studies would be useful…In (one) study the incidence of (thrombotic events, including blood clots) was approximately the same between Ortho Evra and comparative contraceptives. In the most recent study, the incidences of thrombotic events was approximately two times compared to comparative (oral) contraceptives."

J&J will present the final results of the second study to the FDA in a few months. In the meantime, an FDA official cautioned, "These (results) are preliminary, and further evaluation is necessary to understand what these results mean …The other thing the investigators are doing for these trials, especially the second one, is to look to see if there was an imbalance between the two groups. For example, if there were more smokers or obese people in the Ortho Evra group, that would mean the adverse events weren't due to drug alone but to underlying events. So these are the ongoing analyses. We may get further information by May of this year."

FDA officials addressed several questions:

- ***Why were the two studies initiated?*** "They came about because – and I think this is a trend we're trying to go for – when we find that there are significant adverse events reported with a drug…We try to get better information. As we all know, there is some information from spontaneous reporting systems that is prone to certain biases, for example, publicity. This particular drug was getting a lot of publicity and it was hard to determine what the real incidence of some of these events was. So, we worked together with the company. They understood that there was concern in the public. We decided to do more precise studies, which are these epidemiologic studies. They presented their protocols to our experts here in the Office of Drug Safety, we looked over the protocols, and we told them to go and do the studies."

- ***Was there a problem with blood clots in any of the Ortho Evra clinical trials?*** "In this NDA (new drug application), which was ~2,000-3,000 women, we usually have one or two significant blood clot events. In this case we had two. One was a person who had undergone surgery and who was fairly heavy, and she should have stopped her patch. The other was a fairly expected blood clot. So, this one (NDA) had two instead of one, but statistically it had no meaning with 2,000 people, so it's hard to say. This drug is in the class of drugs that, as we all know, tends to cause blood clots. All of these estrogens, etc., cause blood clots, so looking backward, maybe. It's hard to say if there was a clear signal."

- ***What was the incidence of blood clots in the studies?*** "In the first study (which found no VTE risk), where the point incidence was one, it could be as high as somewhere around two. It's just an estimate that it's two. It's the best estimate we have, but it could be somewhat lower or higher. The more numbers you have, the tighter the intervals are and the more precise the information…I'd say the most was in the order of 5-10 per 10,000 woman years, so the absolute numbers are fairly low. It's a fairly unusual event."

- ***What are the overall health effects of VTEs, and how could the results of the two trials be so different when they were done using the same database?*** "We get lots of adverse event reports for contraceptives like breast tenderness, headaches, or whatever. VTEs are very small; one percent or less of adverse events are VTEs. As for the second question; they used different databases. We are in an ongoing discussion between the investigators in the two studies and outside consultants and our internal experts about why there's a difference between the two studies, but statistically the two

studies may be the same. There are, however, ongoing discussions on a lot of fronts about why there might be differences. We're letting people know and ultimately the second study will be published…The label does warn of all these events since the drug has been out and with the November labeling change people should have a heightened awareness for the possibility of these events."

➢ ***What advice is the FDA giving women using the patch?*** "We say discuss this with your healthcare provider. But we (also) put out this information. It is more sophisticated information than the average patient may understand, and we hope their providers will be able to assimilate the information and discuss the issues with the patient. In this case, for some people, the patch may be better (than the pill) because some people don't reliably take the pill, or they forget to take it. The patch does offer them some alternative for contraception. On the other hand, we need to interpret what these results mean. These results are preliminary, so we can't make really hard comments about it. If there is a downside to being more transparent, this may be it. Patients can look and make decisions with what they have."

➢ ***Please put the risk of blood clots into context.*** "The risk (for all birth control products) is about 3-5 (non-fatal blood clots) per 10,000 woman years…A woman year is a woman on a contraceptive for a year. The risk of a woman not on a contraceptive is about one per 10,000 woman years, so you increase your risk three to five times when you take an oral contraceptive."

➢ ***Why is there an increased level of hormone release associated with the patch?*** "It's because it is designed to be absorbed directly as opposed to the pill, which is taken by mouth. When you take an oral medication, it gives you a very high elevation and then drops down. The contraceptive you take by mouth gives you a higher peak blood level, but the patch gives more even blood level. But if you look at level of estrogen in this particular patch at this dose, it is higher, and it has to do with the way it is absorbed."

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