

You may have seen commercials recently regarding YAZ[®], YASMIN[®], and Ocella[™] (a generic form of YASMIN[®], manufactured by Bayer and sold by Barr Pharmaceuticals) and some potentially dangerous side effects. These advertisements, sponsored by medical malpractice law firms, reference recent studies which claim to prove these drugs to increase the occurrence of venous thrombosis. The commercials also cite FDA warnings to Bayer Healthcare Pharmaceuticals, Inc. regarding misleading advertisements for YAZ[®] and YASMIN[®].

First Things First:

It is important to note that these commercials, just like those put out by Bayer in support of YAZ[®] and YASMIN[®], are designed to gain clients and earn money. Advertisements are short, incomplete, and impersonal sources of information. All decisions about medications, including oral contraceptives, should be made between you and your doctor or health care professional.

Why are YAZ[®] and YASMIN[®] being singled out in these commercials?

The most common oral contraceptive pills are combination pills, including both an estrogen component and a progestogen component. The majority of birth control pills contain the same estrogen component (ethinyl estradiol), but there are a few more options in the types of progestogens. All combination birth control pills on the market today increase the risk of blood clots (venous thromboembolism), which can lead to deep vein thrombosis, stroke, pulmonary embolism, or heart attack. The venous thrombosis risk increases from 3.01 in 10,000 women per year in non-users of combination contraceptives, to 6.29 in 10,000 women per year in current users of combination oral contraceptivesⁱ. In other words, using combination birth control pills “doubles” the risk of these thrombosis side effects, and while 3 extra women in 10,000 would have one of these severe side effects associated with “pill” use, nearly 9,997 would not...a very low risk. Venous thromboembolism side effects are well known and well-publicized and should be discussed with your doctor if you are considering any oral contraceptive.

What has led to the recent surge in debate over YAZ[®] and YASMIN[®], and by implication Ocella[™], is that these drugs contain a progestogen called drospirenone, which differentiates them from many other oral contraceptives. Two initial studies sponsored by Bayer Healthcare Pharmaceuticals, Inc. showed that the risk of venous thrombosis associated with drospirenone is comparable to the increase caused by other birth control pills with different progestogen components^{ii - iii}.

More recently, two studies – one in Denmark and one in the Netherlands - have shown that there may be a statistically significant difference between the thromboembolism risk caused by pills with drospirenone and those with other progestogens. According to a Danish study, the risk for levonorgestrel (used in both studies for the basis of comparison) was 5.8 in 10,000 women per year, as compared to 7.8 in 10,000 women per year for drospirenone. These results were similar to those from a Dutch study^{iv}. This means that for every 10,000 women, every year, there were two more cases of venous thrombosis in the progestogen used for YAZ[®] and YASMIN[®] than the more common progestogen, levonorgestrel.

It should be noted that this increase in risk is similar to the increase in risk between low-dose estrogen pills and higher-dose estrogen pills. Furthermore, neither study demonstrating the differences between the progestogens was of the so called “gold standard experimental design”: a randomized placebo controlled trial. Both studies were observational – data was simply collected from national databases and analyzed statistically– and thus may have been subject to bias^v.

So what does this mean for YAZ[®], YASMIN[®] and Ocella[™] users?

While the risk for venous thrombosis is very low in reproductive age women, venous thrombosis is a serious complication of all combination oral contraceptives. The magnitude of this risk falls into the category of a rare risk as

defined by the World Health Organization (WHO). Rare risks are those that occur in $> 1/10,000$ and $<1/1000$ ($> 0.01\%$ and $<0.1\%$). The risk also decreases with time on the pill (i.e. risk is highest in the first year on oral contraception, and then decreases as the patient continues to take the same medication). All oral contraception regimens should be discussed first with your doctor or healthcare professional, taking into account any additional risk factors. Women with risk factors such as obesity or a family history of venous thrombosis should focus on the lowest effective dose of estrogen and the lowest risk progestogens^{vi}. Regardless of the combination hormonal contraceptive that is chosen, all of the available combination oral contraceptives have a much lower risk of thrombosis and thrombosis related events than a pregnancy.

In healthy women with no family history of venous thrombosis, lower doses of estrogen are still recommended, but there is room for give and take based on individual patient needs and preferences^{vii}. If you have been taking YAZ[®], YASMIN[®], or Ocella[™] with no problems, your doctor or healthcare professional may recommend staying on your current regimen.

The FDA Warnings:

The FDA has issued warnings regarding commercials for YAZ[®] and YASMIN[®], which did not explain all side effects for the drugs^{viii-ix}. In response to these warnings, Bayer recently released a follow-up commercial to explain in more detail the specific uses and side effects of YAZ[®] and YASMIN[®]. The FDA also warned that commercials for the two drugs were misleading in regards to the treatment of Premenstrual Dysphoric Disorder (PMDD). The follow-up commercial released by Bayer also addressed this subject by emphasizing that only YAZ[®], not YASMIN[®], has been proven to treat PMDD; and that neither drug has been proven to treat the less severe Premenstrual Syndrome (PMS).

Now, going back to the lawsuit commercials: it may seem, based on the wording of these ads, that the FDA has issued warnings regarding the drugs themselves. This is not the case. YAZ[®] and YASMIN[®] remain FDA approved oral contraceptives. There are no current FDA warnings suggesting the removal of either drug from the market or suggesting that the drugs are ineffective or unsafe.

ⁱ Dunn, N. Editorials: Oral contraceptives and venous thromboembolism. *BMJ* 2009;339:b3164.

ⁱⁱ Dinger JC, Heinemann LAJ, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on oral contraceptives based on 142,475 women-years of observation. *Contraception*. 2007;75:344-354.

ⁱⁱⁱ Seeger JD, Loughlin J, Eng M, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol*. 2007;110:587-593.

^{iv} Vlieg AvH, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:h2921.

^v Dunn, N. Editorials: Oral contraceptives and venous thromboembolism. *BMJ* 2009;339:b3164.

^{vi} IBID

^{vii} IBID

^{viii} Abrams, T. Warning Letter. Re: NDA # 21-676, 21-873, 22-045 YAZ[®] (drospirenone and ethinyl estradiol) Tablets MACMIS ID# 16473. Department of Health and Human Services. Federal Food and Drug Administration. Letter to: Franzen, R. Bayer Healthcare Pharmaceuticals, Inc. October 3, 2008.

^{ix} Doshi, S. Letter. RE: NDA No. 21-400 LEVITRA[®] (vardenafil HCl) Tablets. NDA No. 21-676, 21-873, 22-045. YAZ[®] (drospirenone and ethinyl estradiol) Tablets. NDA No. 21-225 Mirena[®] (levonorgestrel-releasing intrauterine system) MACMIS ID # 17307. . Department of Health and Human Services. Federal Food and Drug Administration. Letter to: Almanakly, F. Bayer Healthcare Pharmaceuticals, Inc. March 26, 2009.