Petition to the FDA to Ban Third Generation Oral Contraceptives Containing Desogestrel due to Increased Risk of Venous Thrombosis (HRG Publication #1799)

February 6, 2007

Andrew Von Eschenbach, M.D., Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Von Eschenbach:

Public Citizen, representing more than 100,000 consumers nationwide, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately ban the third generation oral contraceptives containing desogestrel due to the approximately doubled risk of venous thrombosis (30 cases for every 100,000 users per year of third generation oral contraceptives compared to 15 cases for every 100,000 users of second generation oral contraceptives) and lack of evidence of clinical benefit as compared to the second generation oral contraceptives. The third generation oral contraceptives containing desogestrel are:

Desogestrel and Ethinyl Estradiol (Duramed/Barr and Watson Pharmaceuticals)

Desogen (Organon)	Mircette (Duramed/Barr)
Velivet (Duramed)	Apri-28 (Duramed/Barr)
Kariva (Duramed/Barr)	Ortho-Cept (Ortho-McNeil)
Reclipsen (Watson)	Cyclessa (Organon)

It is estimated that women in the U.S. filled more than 7.5 million prescriptions for third generation oral contraceptives this past year (November 2005 to October 2006) (IMS, National Prescription Audit). By banning third generation oral contraceptives, the FDA will potentially save hundreds of young women a year from developing venous thrombosis and its disabling and sometimes fatal consequences.

Venous thrombosis (blood clot) most typically manifests itself in the lower extremities but can occur in the abdomen, the veins of the brain, the upper extremities, and in superficial veins of the extremities. Symptoms of venous thrombosis are pain, swelling, and redness in the affected extremity. The blood clot can travel from the site where it formed and block blood flow at another location, a phenomenon known as venous thromboembolism. The potentially lethal complication of venous thrombosis is pulmonary embolism in which the blood clot becomes dislodged from a peripheral vein and travels to the lungs where it can cause partial or total obstruction of blood flow to the lungs resulting in shortness of breath because of a loss of lung function. One study found that 2% of patients with a first-recognized episode of venous thromboembolism who were younger than 40 years, died in the hospital, most of them probably from a pulmonary embolism.[1]

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In addition to a risk of a fatal pulmonary embolism, venous thrombosis contributes to significant functional disability, with an estimated one-third to over one-half of patients with venous thrombosis developing post-thrombotic syndrome, a chronic complication that consists of pain, swelling, and occasionally ulceration of the affected extremity.[2,3,4] Finally, the recurrence risk of venous thrombosis is high at several percent per year.[5]

BACKGROUND

Combination oral contraceptives contain both estrogen and progestins. Second and third generation oral contraceptives (OCs) differ in their progestin component. Third generation OCs contain desogestrel (available in the US), norgestimate or gestodene (neither are available in the US), while second generation OCs contain norgestrel, levonorgestrel, or norethindrone. Third generation oral contraceptives were developed in the 1980s with a goal of producing an oral contraceptive that had less androgenic adverse effects such as hirsutism and acne typically associated with the first and second generation oral contraceptives.

The use of any combined oral contraceptives has long been associated with an increased risk of venous thrombosis. But three independent studies published in December 1995 all concluded third generation oral contraceptives had about twice the risk of venous thrombosis when compared to second generation oral contraceptives.[6,7,8] Numerous similar studies have found generally the same increased risk with the most common estimate of this risk being 1.5 to 2.4 -fold higher compared to second generation oral contraceptives.[9,10,11,12,13,14,15,16,17,18,19]
The difference in venous thrombosis risk between second and third generation OCs is even higher among women who use oral contraceptives for the first time.[17]

Another alarming report came from a case-control study of fatal pulmonary embolism in New Zealand women. The increased risk of death from a pulmonary embolus for women who took levonorgestrel OCs was 5.1 to 1(compared to non pill-users), but the risk of death from a pulmonary embolus for women who took desogestrel or gestodene containing OC's was 14.9 to 1. Our calculation for the risk of fatal pulmonary embolism comparing 3rd generation OC users with 2nd generation OC users is 2.1 (95% CI 0.45-10.15). The authors state that "the high mortality in New Zealand may partly reflect the extensive use of third-generation oral contraceptives, which seem to carry a higher risk of VTE than older contraceptives."[20]

Accounting for possible flaws in study design and methods in previous studies, two meta-analyses in 2001 both concluded that oral contraceptives containing desogestrel increases the risk of venous thrombosis more than those OCs containing levonorgestrel (a 2nd generation OC) by a factor of 1.7.[21,22] These studies are summarized in Table 1. The overall risk estimates from the two meta-analyses are likely to be conservative; the studies with lower risk estimates in these meta-analyses were studies sponsored by the manufacturers.[21]

Table 1. Summary of studies comparing 3rd vs. 2nd Gen. OCs and the risk of venous thrombosis

Source	Study Design	3rd vs. 2nd Gen. OCs (Estimated Relative Risk or Odds Ratio with 95% CI)
Bloemenkamp et al,[8] 1995	Case-Control	2.2 (0.9-5.4)
Spitzer (Transnational),[9] 1996	Case-Control	1.5 (1.1-2.2)
Bloemankamp et al,[13] 1999	Case-Control	1.9 (0.8-4.5)
Jick et al (UK-GPRD),[14] 2000	Cohort/ Case-Control	1.9 (1.3-2.8)/ 2.3 (1.3-3.9)
Farley et al (WHO),[6] 1995	Case-Control	2.4 (1.3-4.6)
Jick et al (UK-GPRD),[7] 1995	Cohort/ Case-Control	1.9 (1.1-3.2)/ 2.2 (1.0-4.7)
Lidegaard et al,[12] 1998	Case-Control	1.44 (0.83-2.50) 2.19 (1.17-4.07)[a]
Andersen et al,[15] 1998	Case-Control	9.7 (0.4-259.6)[b]
Heinemann et al,[16] 2002	Case-Control	1.7 (0.9-3.6)
Farmer (UK-MediPlus),[10] 1997	Cohort/ Case-Control	1.76 (0.91-3.48)/ 0.84 (0.38-1.85)
Farmer et al,[11] 1998	Case-Control	0.77 (0.38-1.57)
Herings et al,[16] 1999	Cohort	4.2 (1.7-10.2)
Farmer et al,[18] 2000	Cohort/Case-Control	1.0 (0.6-1.6)
Lidegaard et al,[19] 2002	Case-Control	1.6 (1.0-2.4)
WHO,[23] 1995	Case-Control	1.66 (1.04-2.65)[c] (Europe) 3.42 (1.35-8.65)[c] (Developing countries)
Kemmeren et al,[21] 2001	Meta-analysis	1.7 (1.4-2.0)
Hennessy et al,[22] 2001	Meta-analysis	1.7 (1.3-2.1) 2.1 (1.6-2.8)[d]

[a] Our calculations of OR and 95% CI for 3rd gen. OCs containing desogestrel vs. 2nd gen. OCs.
[b] 3rd gen. OCs vs. 1st and 2nd gen. OCs.
[c] Our calculations of OR and 95% CI for 3rd gen. OCs vs. 2nd gen. OCs.
[d] 3rd gen. OCs containing desogestrel vs. 2nd gen. OCs.

Based on the epidemiologic evidence from these studies, including two meta-analyses, Public Citizen has concluded that third generation oral contraceptives essentially double the risk of venous thrombosis when compared to second generation oral contraceptives. The FDA acknowledged this in a statement in November 1995 stating "new studies indicate about a two-fold increase in the risk of venous blood clots associated with products containing desogestrel." The risk essentially translates to about 1.5 additional incidents of thromboembolic disease per 10,000 women-years.

Kemmeren et al, in their meta-analysis of case-control and cohort studies assessing risk of venous thromboembolism among women using oral contraceptives before October 1995 calculated that four deaths per 1,000,000 woman-years could be prevented by switching from third to second generation oral contraceptives.[21] These lives are tragically being sacrificed for a class of drugs with double the risk of venous thrombosis and no proven superior clinical benefit when compared to safer classes of oral contraceptives with exactly the same efficacy profile.

The epidemiologic evidence that third generation oral contraceptives containing desogestrel are more prone to causing blood clots than 2nd generation oral contraceptives led to research investigating the underlying biological mechanisms.

BIOLOGICAL PLAUSIBILITY

Blood coagulation is a complex process of pro-coagulant proteins (they stimulate the formation of a clot) and anti-coagulant proteins that inhibit these proteins, as well as proteins that break down a clot once it has formed. Normal blood clotting depends upon a specific, delicately-balanced interaction between these classes of proteins. If one class of proteins has more activity than the other class, an abnormal state exists and a person becomes either at risk of excessive clotting (thrombosis) or excessive bleeding. It has long been known that changes in the female hormonal status seen in pregnancy, hormone replacement therapy, or oral contraceptive usage increase pro-coagulant activity in the coagulation process. Oral contraceptives affect levels of almost all of the proteins involved in the coagulation process. The progestogen found in third generation oral contraceptives, desogestrel, appears to cause resistance to one of the anti-coagulant proteins, activated Protein C (APC).[24] As compared to second generation oral contraceptives, third generation oral contraceptives significantly decrease total and free Protein S and cause a more pronounced APC resistance.[25] When APC and Protein S are not allowed to perform their natural function of inhibiting coagulation, clots tend to form more easily, thereby increasing the risk of venous thrombosis. These studies provide a biological explanation to the increased risk of venous thrombosis with third generation oral contraceptives containing desogestrel, compared to second generation OCs.

THE CURRENT LABEL

All of the third generation oral contraceptives contain the following warning in their product labels regarding the risk of venous thrombosis. The warning is not bolded and is under the heading "Risks of taking Oral Contraceptives." The warning provides proof that Organon and Ortho-McNeil acknowledge this increased risk of venous thrombosis with third generation oral contraceptives.

Risk of developing blood clots:

Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the leg can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blockage of the vessel carrying blood to the lungs. The risks of these side effects may be greater with desogestrel-containing oral contraceptives, such as [brand name of drug] (desogestrel and ethinyl estradiol), than with certain other low-dose pills. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

3rd GEN. OCs SHOW NO CLINICAL BENEFIT COMPARED TO 2nd GEN. OCs

The FDA acknowledged the lack of any clinical benefit of third generation oral contraceptives compared to second generation oral contraceptives. The FDA sent a letter to Organon on July 28, 1999 in response to their "false and misleading" advertising for Desogen. The FDA stated that "no clinically significant differences between Desogen and other oral contraceptives have been demonstrated in adequate and well-controlled comparative studies" and "furthermore, there are no adequate and well-controlled studies that have demonstrated that the body can sense a difference between oral contraceptives."

The FDA also wrote in this letter "claims that imply that Desogen is superior to other oral contraceptive products because it has less side effects (i.e. hirsutism [unwanted hair] or weight gain) are false or misleading because they lack adequate substantiation from well-controlled clinical trials."

In an extensive literature review, we found no non-industry sponsored randomized controlled trials comparing supposed clinical benefits of third generation oral contraceptives to second generation contraceptives. Since there is no evidence of any superior clinical benefit, it is impossible to recommend that third generation oral contraceptives remain on the market when second generation oral contraceptives are equally effective and do not cause an increased risk of blood clots.

LESSONS LEARNED FROM THE BRITISH PILL SCARE OF 1995

The Committee on Safety of Medicines (CSM) in Britain issued a statement on October 18, 1995 based on, at the time, three unpublished studies warning that third generation oral contraceptives were associated with a higher risk of venous thromboembolism than oral contraceptives containing second generation progestogens. The CSM sent a "Dear Doctor" letter to 190,000 physicians and pharmacists along with a supplement to the press and broadcast media outlining this doubled risk. The end of the statement attempted to provide reassurance suggesting that "Women taking one of the relevant pills should, if possible, see their doctor before their current cycle ends. No one need stop taking the pill before obtaining medical advice." Subsequently, a "pill scare" developed in Europe, spurring various regulatory agencies to react with their recommendations concerning third generation OCs, and many investigations examining the public health impact of the pill scare.

Although there was initial concern that the pill scare may have increased conception and abortion rates, closer analysis of pharmaco-epidemiologic data showed no such effects. In the United Kingdom, there was no peak in pregnancies or pregnancy terminations.[26] Most women using third generation OCs switched to another oral contraceptive,[26,27,28] Women in the Netherlands also simply switched from third to second generation OCs.[29] Another study from the Netherlands showed a marked decrease in the number of women prescribed third generation OCs after 1995, without any change in overall use of oral contraceptives from 1995 to 2000.[30]

Still, FDA removal of third generation OCs from the market should be accompanied by a campaign directed at consumers and with advanced warnings to doctors and pharmacists so that they are prepared to talk to their patients.

Current users of third generation OCs should be advised to speak with their doctor about safer alternatives to birth control. Second generation OCs that do not show an increased risk of blood clots compared to third generation OCs are those containing low dose estrogen and levonorgestrel, norgestrel, or norethindrone. Examples of such second generation birth control pills are generic drugs such as Levonorgestrel and Ethinyl Estradiol, Levora and Trivora. Women should be warned that if the correct procedure for switching pills is not followed, there is a risk of pill-failure.

Of note, Public Citizens lists Yasmin (ethinyl estradiol and drospirenone) and Ortho Evra patch (ethinyl estradiol and norelgestromin) as "Do Not Use" drugs. Yasmin potentially increases the blood levels of potassium, while there is evidence that Ortho Evra increases the risk of blood clots.

CONCLUSIONS

Although third generation OCs have not shown any clinically significant benefit over second generation oral contraceptives, multiple studies and two meta-analyses show third generation oral contraceptives containing desogestrel are associated with a higher risk of

venous thrombosis than are the second generation oral contraceptives. Evidence exists of a biological mechanism underlying the association between desogestrel and blood clots. Venous thrombosis can lead to significant functional disability and possibly death.

Currently, the FDA gives the physician the authority to decide which type of oral contraceptive to prescribe to patients. Vandenbroucke et al, in a New England Journal of Medicine review article on oral contraceptives and the risk of venous thrombosis, state that "the ability to prescribe prudently by withholding oral contraceptives from women with known risk factors is limited by the absence, in the majority of cases, of clinically recognizable risk factors for venous thrombosis. An investigation in New Zealand of a series of deaths due to pulmonary emboli suggested that in most cases physicians could not have foreseen the risk."[31]

The FDA must ensure the well-being and safety of women in the U.S. and ban third generation oral contraceptives containing desogestrel. Women should discuss with their doctor alternative methods of birth control, such as the second generation oral contraceptives, and how to safely switch contraceptive methods.

ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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