



Dear Healthcare Provider,

I am writing to inform you that Bayer has updated the US Prescribing Information (PI) for its drospirenone (drsp<sup>®</sup>)-containing combination oral contraceptives (COCs) to provide additional information for you and your patients, regarding potentially higher risk of venous thromboembolism (VTE) that may exist with these products. Specifically, epidemiologic studies<sup>1-8</sup>, included for review during the December 8, 2011 FDA Advisory Committee, have reported that the risk ranged from no increase to a three-fold increase when compared to COCs containing levonorgestrel or other progestins.

drsp-containing COCs marketed by Bayer include:

- Beyaz<sup>®</sup> (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- SAFYRAL<sup>®</sup> (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- YASMIN<sup>®</sup> (drospirenone/ethinyl estradiol) tablets
- YAZ<sup>®</sup> (drospirenone/ethinyl estradiol tablets)

April 10, 2012

Bayer HealthCare  
Pharmaceuticals Inc.  
Medical Affairs  
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Wayne, NJ 07470-6806

**Key Elements Related to the PI Update, in the Healthcare Provider and Patient Sections Include:**

- COCs containing drsp may be associated with a higher risk of VTE than COCs containing levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase
- The risk of VTE associated with pregnancy (5-20/10,000 women-years) is greater than the risk for any COC (3-9/10,000 women-years), which includes drsp-containing COCs
- Before initiating Beyaz, SAFYRAL, YASMIN, or YAZ in a new COC user or a woman who is switching from a contraceptive that does not contain drsp, consider the risks and benefits of a drsp-containing COC in light of her risk of a VTE [see PI Warnings and Precautions (5.1)]

**Additional Updates to the PI Relative to the Risk of VTE with all COCs:**

- The risk of VTE is highest during the first year of COC use. The greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC
- Known risk factors for VTE include smoking, obesity, family history of VTE, age (greater than 35)

Patient safety is Bayer's primary concern and we hope this information will help support you in your patient counseling. The evidence continues to support that drsp-containing COCs are safe and effective when taken as directed.

Additional information about these changes is provided in the subsequent pages of this letter. For complete information please refer to the enclosed full Prescribing Information, call 1-800-288-8371, or visit [Beyaz.com](http://Beyaz.com), [SAFYRAL.com](http://SAFYRAL.com), [YASMIN-us.com](http://YASMIN-us.com), or [YAZ-us.com](http://YAZ-us.com).

Sincerely,

A handwritten signature in blue ink, appearing to read "Leo Plouffe, Jr.".

Leo Plouffe, Jr, MD FACOG  
Vice President, Medical Affairs, Women's Healthcare  
Bayer HealthCare Pharmaceuticals

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**Overview of VTE Studies Evaluating Drospirenone**

A number of studies have compared the risk of VTE for users of YASMIN® [which contains 0.03 mg of ethinyl estradiol (EE) and 3 mg of drsp®] to the risk for users of other COCs, including COCs containing levonorgestrel. Those that were required or sponsored by regulatory agencies are summarized in Table 1.

**Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Current Users of YASMIN (drospirenone/ethinyl estradiol) Tablets Compared to Users of Oral Contraceptives that Contain Other Progestins**

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product (all are low-dose COCs; with ≤ 0.04 mg of EE)	Hazard Ratio (HR) (95% CI)
i3 Ingenix <sup>1</sup> (Seeger 2007) Initiators, including new users <sup>a</sup>	All COCs available in the US during the conduct of the study <sup>b</sup>	HR: 0.9 (0.5-1.6)
EURAS <sup>2</sup> (Dinger 2007) Initiators, including new users <sup>a</sup>	All COCs available in Europe during the conduct of the study <sup>c</sup> Levonorgestrel/EE	HR: 0.9 (0.6-1.4) HR: 1.0 (0.6-1.8)
“FDA-funded study” (2011) <sup>3</sup>  New users <sup>a</sup>  All users (i.e., initiation and continuing use of study combination hormonal contraception)	Other COCs available during the course of the study <sup>d</sup>  Levonorgestrel/0.03 mg EE  Other COCs available during the course of the study <sup>d</sup>  Levonorgestrel/0.03 mg EE	HR: 1.8 (1.3-2.4)  HR: 1.6 (1.1-2.2)  HR: 1.7 (1.4-2.1)  HR: 1.5 (1.2-1.8)

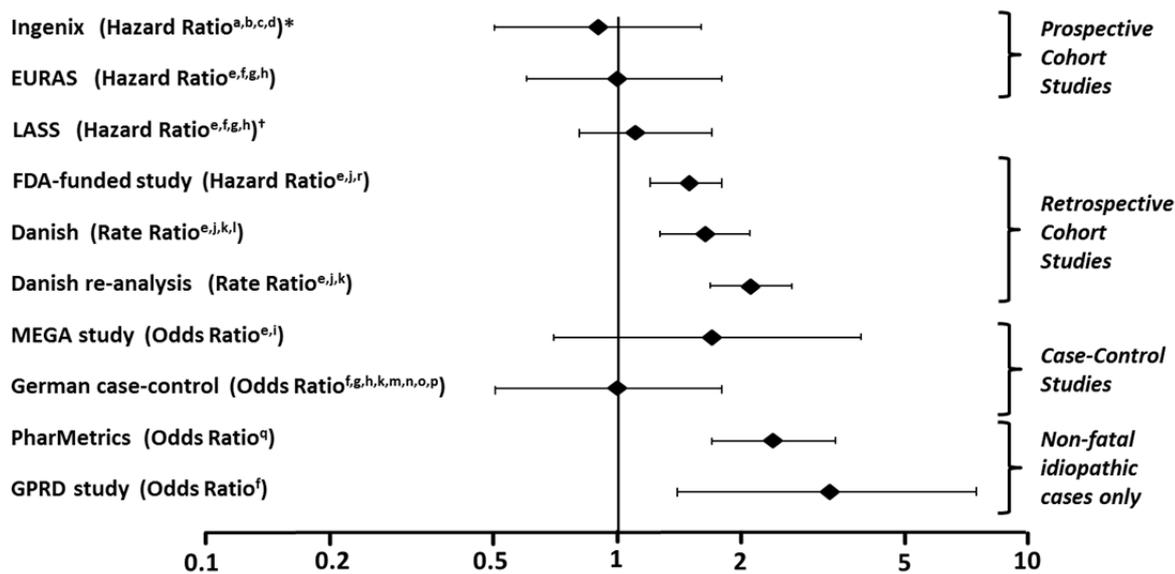
- a) “New users” - no use of combination hormonal contraception for at least the prior 6 months
- b) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, levonorgestrel, desogestrel, norgestrel, medroxyprogesterone, or ethynodiol diacetate
- c) Includes low-dose COCs containing the following progestins: levonorgestrel, desogestrel, dienogest, chlormadinone acetate, gestodene, cyproterone acetate, norgestimate, or norethindrone
- d) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel



**Overview of VTE Studies Evaluating Drospirenone (Cont'd)**

In addition to these “regulatory studies,” other studies of various designs have been conducted. Overall, there are two prospective cohort studies (see Table 1): the US post-approval safety study Ingenix [Seeger 2007]<sup>1</sup> and the European post-approval safety study EURAS (European Active Surveillance Study) [Dinger 2007]<sup>2</sup>. An extension of the EURAS study, the Long-Term Active Surveillance Study (LASS), did not enroll additional subjects, but continued to assess VTE risk. There are three retrospective cohort studies: one study in the US funded by the FDA [Sidney, 2011]<sup>3</sup> (see Table 1), and two from Denmark [Lidegaard 2009<sup>4</sup>, Lidegaard 2011<sup>5</sup>]. There are two case-control studies: the Dutch MEGA study analysis [van Hylckama Vlieg 2009]<sup>6</sup> and the German case-control study [Dinger 2010]<sup>7</sup>. There are two nested case-control studies that evaluated the risk of non-fatal idiopathic VTE: the PharMetrics study [Jick 2011]<sup>8</sup> and the GPRD study [Parkin 2011]<sup>9</sup>. The results of all of these studies are presented in Figure 1.

**Figure 1: VTE Risk with YASMIN® (drospirenone/ethinyl estradiol) Tablets Relative to LNG-Containing COCs (adjusted risk<sup>#</sup>)**



Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for drsp®, > 1 indicates an increased risk of VTE for drsp.

\*Comparator “Other COCs”, including LNG- containing COCs. LNG = Levonorgestrel

† LASS is an extension of the EURAS study

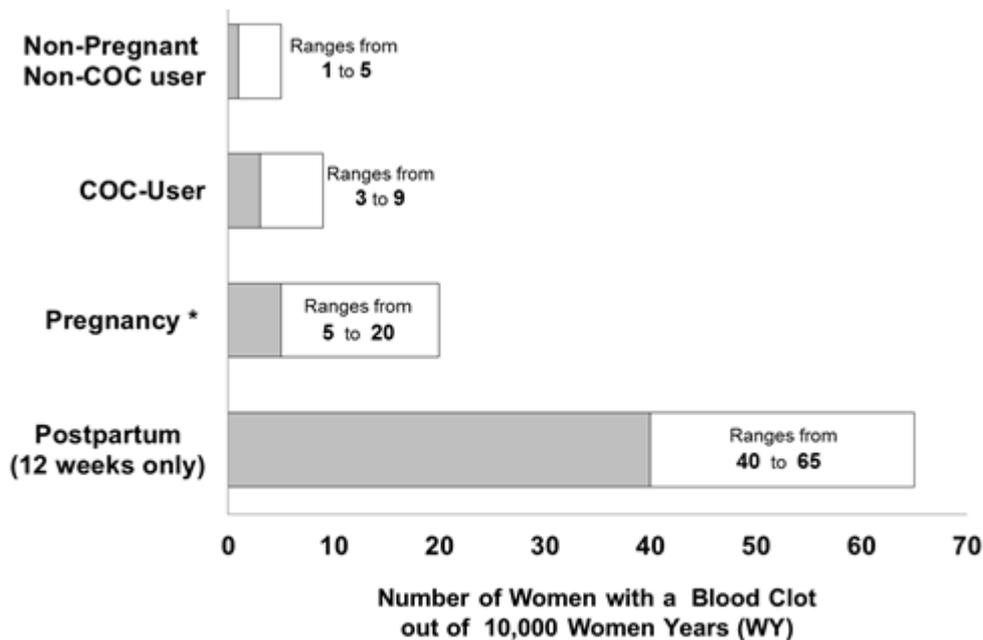
<sup>#</sup>Some adjustment factors are indicated by superscript letters: a) Current heavy smoking, b) hypertension, c) obesity, d) family history, e) age, f) BMI, g) duration of use, h) VTE history, i) period of inclusion, j) calendar year, k) education, l) length of use, m) parity, n) chronic disease, o) concomitant medication, p) smoking, q) duration of exposure, r) site



**Likelihood of Developing VTE**

The PI also provides graphic information (Figure 2) showing the risk of developing a VTE for women who are not pregnant and do not use oral contraceptives, for women who use oral contraceptives, for pregnant women, and for women in the postpartum period.

**Figure 2: Likelihood of Developing VTE**



\* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

The PI updates information stating that: “Although the absolute VTE rates are increased for users of hormonal contraceptives compared to non-users, the rates during pregnancy are even greater, especially during the post-partum period (see Figure 2). The risk of VTE in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.”

**As a reminder, Important Safety Information about the products mentioned earlier is provided on the following pages.**



## Indications

The following products are indicated for use by women to prevent pregnancy:

- **Beyaz<sup>®</sup>** (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- **SAFYRAL<sup>®</sup>** (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- **YASMIN<sup>®</sup>** (drospirenone/ethinyl estradiol) tablets
- **YAZ<sup>®</sup>** (drospirenone/ethinyl estradiol tablets)

For women who choose a COC for contraception, Beyaz and SAFYRAL are also indicated to:

- Raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the products or shortly after discontinuing the products

In addition, for women who choose a COC for contraception, Beyaz and YAZ are indicated to:

- Treat the emotional and physical symptoms of premenstrual dysphoric disorder (PMDD)
  - The effectiveness of Beyaz and YAZ for PMDD when used for more than 3 menstrual cycles has not been evaluated. Beyaz and YAZ have not been evaluated for the treatment of premenstrual syndrome
- Treat moderate acne for women at least 14 years of age who have achieved menarche

## Important Safety Information about Beyaz, SAFYRAL, YASMIN, and YAZ

### Patients who should not take Beyaz, SAFYRAL, YASMIN, or YAZ

**Women over 35 years old who smoke should not use Beyaz, SAFYRAL, YASMIN, or YAZ. Smoking increases the risk of serious cardiovascular side effects from Beyaz, SAFYRAL, YASMIN, or YAZ use. This risk increases with age and the number of cigarettes smoked.**

- Beyaz, SAFYRAL, YASMIN, and YAZ are contraindicated in women with a high risk of arterial or venous thrombotic diseases, undiagnosed abnormal uterine bleeding, breast cancer or other hormone-sensitive cancer, liver tumors (benign or malignant) or liver disease, conditions that predispose to hyperkalemia (ie, renal impairment, hepatic dysfunction, and adrenal insufficiency), or who are pregnant

### Know serious risks with Beyaz, SAFYRAL, YASMIN, and YAZ

- **Thromboembolic and Other Vascular Events:** Stop Beyaz, SAFYRAL, YASMIN, or YAZ if an arterial or venous thrombotic event occurs. The risk of venous thromboembolism (VTE) is highest during the first year of combination oral contraceptive (COC) use. This increased risk is greatest after initially starting a COC or restarting the same or a different COC following a 4 week or greater Pill-free interval. Epidemiologic studies suggest drospirenone (drsp<sup>®</sup>)-containing COCs may be associated with a higher risk of VTE than COCs containing levonorgestrel or some other progestins; other studies do not support this finding. These studies reported the risk of VTE ranged from no increase to a 3-fold increase. Before initiating Beyaz, SAFYRAL, YASMIN, or YAZ in a new COC user or in a woman switching from a contraceptive not containing drsp, consider the risks and benefits of Beyaz, SAFYRAL, YASMIN, or YAZ in light of her VTE risk (eg, smoking, obesity, family history of VTE)

COC use also increases risk of arterial thromboses (eg, stroke and myocardial infarction), especially in women with risk factors for these events. Use COCs with caution in women with cardiovascular disease risk factors. If feasible, stop Beyaz, SAFYRAL, YASMIN, or YAZ at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism. Start Beyaz, SAFYRAL, YASMIN, or YAZ no earlier than 4 weeks after delivery in women not breastfeeding

**Additional Warnings & Precautions follow, as well as Serious and Most Common Adverse Reactions.**



**Important Safety Information continued for:**

- **Beyaz<sup>®</sup>** (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- **SAFYRAL<sup>®</sup>** (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- **YASMIN<sup>®</sup>** (drospirenone/ethinyl estradiol) tablets
- **YAZ<sup>®</sup>** (drospirenone/ethinyl estradiol tablets)
  
- **Hyperkalemia:** Beyaz, SAFYRAL, YASMIN, and YAZ contain drospirenone that has the potential for hyperkalemia in high-risk patients and are contraindicated in patients with conditions that predispose to hyperkalemia. Check serum potassium level during the first treatment cycle in women who receive long-term treatment with medications that may increase serum potassium (eg, ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs)
- **Liver Disease:** Discontinue Beyaz, SAFYRAL, YASMIN or YAZ if jaundice develops
- **High Blood Pressure (BP):** Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs. Monitor BP in women with well-controlled hypertension and stop Beyaz, SAFYRAL, YASMIN or YAZ if BP rises significantly. BP may increase in COC users, more likely occurring in older women and with extended use
- **Gallbladder Disease:** Studies suggest a small increased relative risk of developing gallbladder disease among COC users
- **Carbohydrate and Lipid Metabolic Effects:** Monitor prediabetic and diabetic COC users. Consider alternative contraception for women with uncontrolled dyslipidemia
- **Headache:** If a Beyaz, SAFYRAL, YASMIN or YAZ user develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Beyaz, SAFYRAL, YASMIN or YAZ if indicated
- **Bleeding Irregularities:** Evaluate irregular bleeding or amenorrhea; check for causes such as pregnancy or malignancy
- **For Beyaz and SAFYRAL, folates may mask vitamin B12 deficiency**
- **Counsel patients that Beyaz, SAFYRAL, YASMIN and YAZ do not protect against HIV infection and other sexually transmitted diseases**

**Serious adverse reactions in Beyaz and YAZ clinical trials:**

- Cervix carcinoma stage 0, cervical dysplasia, and migraine

**Most common adverse reactions (≥2%) in Beyaz and YAZ clinical trials:**

- In Beyaz contraception, moderate acne and folate clinical trials: headache/migraine (5.9%), menstrual irregularities (4.1%), nausea/vomiting (3.5%), and breast pain/tenderness (3.2%)
- In YAZ contraception and moderate acne clinical trials: headache/migraine (6.7%), menstrual irregularities (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4.0%), and mood changes 2.2%)
- In Beyaz and YAZ PMDD clinical trials: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%)

**Additional Serious and Most Common Adverse Reactions follow.**



**Important Safety Information continued for:**

- **SAFYRAL<sup>®</sup>** (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)
- **YASMIN<sup>®</sup>** (drospirenone/ethinyl estradiol) tablets

**Serious adverse reactions in SAFYRAL and YASMIN clinical trials:**

- Depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma

**Most common adverse reactions (≥2%) in SAFYRAL and YASMIN clinical trials:**

- In SAFYRAL clinical trials: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), mood changes (2.3%), and abdominal pain/discomfort/tenderness (2.2%)
- In YASMIN clinical trials: premenstrual syndrome (13.2%), headache/migraine (10.7%), breast pain/tenderness/discomfort (8.3%), nausea/vomiting (4.5%), mood changes (2.3%), and abdominal pain/discomfort/tenderness (2.3%)

**Please see enclosed full Prescribing Information for Beyaz<sup>®</sup> (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets), SAFYRAL, YASMIN, and YAZ<sup>®</sup> (drospirenone/ethinyl estradiol tablets).**

**References:** 1. Seeger, J.D., Loughlin, J., Eng, P.M., Clifford, C.R., Cutone, J., and Walker, A.M. (2007). Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 110, 587-593. 2. Dinger, J.C., Heinemann, L.A., and Kuhl-Habich, D. (2007). 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* 75, 344-354. 3. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author) <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>, accessed April 10, 2012. 4. Lidegaard, O., Lokkegaard, E., Svendsen, A.L., and Agger, C. (2009). Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 339, b2890. 5. Lidegaard, O., Nielsen, L.H., Skovlund, C.W., Skjeldstad, F.E., and Lokkegaard, E. (2011). Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ* 343, d6423. 6. van Hylckama Vlieg, A., Helmerhorst, F.M., Vandenbroucke, J.P., Doggen, C.J., and Rosendaal, F.R. (2009). The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 339, b2921. 7. Dinger, J., Assmann, A., Mohner, S., and Minh, T.D. (2010). Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 36, 123-129. 8. Jick, S.S., and Hernandez, R.K. (2011). Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 342, d2151. 9. Parkin, L., Sharples, K., Hernandez, R.K., and Jick, S.S. (2011). Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 342, d2139.