

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022574/S-004

Trade Name: **SAFYRAL**

Generic Name: **drospirenone/ethinyl estradiol/levomefolate
calcium**

Sponsor: **Bayer HealthCare Pharmaceuticals Inc.**

Approval Date: February 13, 2012

Indications: SAFYRAL is indicated for use by women to prevent pregnancy. SAFYRAL is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 022574/S-004

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021098/S-022
NDA 021676/S-012
NDA 022532/S-004
NDA 022574/S-004

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Sharon Brown
Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Brown:

Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME	DATE OF SUBMISSION	DATE OF RECEIPT
021098	022	Yasmin (drospirenone/ethinyl estradiol) tablets	March 8, 2012	March 8, 2012
021676	012	Yaz (drospirenone/ethinyl estradiol tablets)	March 8, 2012	March 8, 2012
022532	004	Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)	March 8, 2012	March 8, 2012
022574	004	Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)	March 8, 2012	March 8, 2012

We acknowledge receipt of your amendments dated April 4 (4), 5 (5) and 9, 2012.

These "Prior Approval" supplemental new drug applications propose revisions to the **Highlights, Section 5.1 Thromboembolic Disorders and Other Vascular Problems, Section 15 References, and Section 17 Patient Counseling Information** of the package insert, and to the **FDA Approved Patient Labeling**.

The revisions update the labeling with results of a number of epidemiologic studies evaluating the comparative risk of venous thromboembolic events for drospirenone-containing oral contraceptives and oral contraceptives that contain levonorgestrel or some other progestins.

The revised language will state that combined oral contraceptives (COCs) containing drospirenone (DRSP) may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Before initiating a DRSP-containing COC in a new COC user or in a woman who is switching from a contraceptive that does not contain DRSP, the prescriber is advised to consider the risks and benefits of a DRSP-containing COC in light of the woman's risk of a VTE. The revised labeling also reports the absolute rates of VTE across various groups of reproductive-aged women.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. These waivers apply to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in these supplements, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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If you have any questions, please call Pamela Lucarelli, Regulatory Health Project Manager, at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
04/10/2012

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 022574/S-004

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SAFYRAL safely and effectively. See full prescribing information for SAFYRAL.

SAFYRAL (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets), for oral use

Initial U.S. Approval: 2010

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning

- **Women over 35 years old who smoke should not use Safyral. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

RECENT MAJOR CHANGES

Warnings and Precautions, Thromboembolic Disorders (5.1) 4/2012

INDICATIONS AND USAGE

Safyral is an estrogen/progestin COC containing a folate, indicated for use by women to:

- Prevent pregnancy. (1.1)
- Raise folate levels in women who choose to use an oral contraceptive for contraception. (1.2)

DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

DOSAGE FORMS AND STRENGTHS

Safyral consists of 28 film-coated, biconvex tablets in the following order (3):

- 21 orange tablets, each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium,
- 7 light orange tablets, each containing 0.451 mg levomefolate calcium

CONTRAINDICATIONS

- Renal impairment (4)
- Adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- **Vascular risks:** Stop Safyral if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1) COCs containing DRSP may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Before initiating Safyral 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. (5.1)
- **Hyperkalemia:** DRSP has antimineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium concentration during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium concentration. (5.2, 7.3)
- **Liver disease:** Discontinue Safyral if jaundice occurs. (5.4)
- **High blood pressure:** Do not prescribe Safyral for women with uncontrolled hypertension or hypertension with vascular disease. (5.5)
- **Carbohydrate and lipid metabolic effects:** Monitor prediabetic and diabetic women taking Safyral. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.7)
- **Headache:** Evaluate significant change in headaches and discontinue Safyral if indicated. (5.8)
- **Uterine bleeding:** Evaluate irregular bleeding or amenorrhea. (5.9)

ADVERSE REACTIONS

The most frequent adverse reactions ($\geq 2\%$) in contraception and folate clinical trials are 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/tenderness/discomfort (2.2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes (for example, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS

Nursing mothers: Not recommended; can decrease milk production. (8.3)

See [17](#) for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 4/2012

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WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke [see Contraindications (4)].

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Safyral is indicated for use by women to prevent pregnancy.

1.2 Folate Supplementation

Safyral is indicated in women who choose to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking the product or shortly after discontinuing the product.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Safyral

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive effectiveness, Safyral must be taken as directed, in the order directed on the blister pack. Single missed pills should be taken as soon as remembered.

2.2 How to Start Safyral

Instruct the patient to begin taking Safyral either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Safyral use, instruct the patient to take one orange Safyral daily, beginning on Day 1 of her menstrual cycle. (The first day of menstruation is Day 1.) She should take one orange Safyral daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Safyral should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Safyral can be taken without regard to meals. If Safyral is first taken later than the first day of the menstrual cycle, Safyral should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Safyral use, instruct the patient to take one orange Safyral daily, beginning on the first Sunday after the onset of her menstrual period. She should take one orange Safyral daily for 21 consecutive days, followed by one light orange tablet, containing levomefolate alone, daily on Days 22 through 28. Safyral should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Safyral can be taken without regard to meals. Safyral should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Safyral on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her orange tablets on the next day after ingestion of the last light orange folate tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Safyral is started later than the day following administration of the last light

orange tablet, the patient should use another method of contraception until she has taken an orange Safyral daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Safyral should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Safyral should be started when the next application would have been due. When switching from an injection, Safyral should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Safyral should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last orange tablet. If spotting or breakthrough bleeding occurs while taking Safyral, instruct the patient to continue taking Safyral by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Safyral is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Safyral if pregnancy is confirmed.

The risk of pregnancy increases with each active orange tablet missed. For additional patient instructions regarding missed pills, see the **“WHAT TO DO IF YOU MISS PILLS”** section in the **FDA-Approved Patient Labeling**. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more light orange tablets, she should still be protected against pregnancy provided she begins taking a new cycle of orange tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Safyral no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts Safyral postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Safyral for 7 consecutive days.

2.3 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, this can be regarded as a missed tablet.

2.4 Folate Supplementation

The U.S. Preventive Services Task Force recommends that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily.¹ Consider other folate supplementation that a woman may be taking before prescribing Safyral. Ensure that folate supplementation is maintained if a woman discontinues Safyral due to pregnancy.

3 DOSAGE FORMS AND STRENGTHS

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in blister packs.

Each blister pack contains 28 film-coated, round, bi-convex tablets in the following order:

- 21 orange tablets each containing 3 mg drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE) as betadex clathrate and 0.451 mg levomefolate calcium embossed with a “Y+” in a regular hexagon on one side
- 7 light orange tablets each containing 0.451 mg levomefolate calcium embossed with a “M+” in a regular hexagon on one side

4 CONTRAINDICATIONS

Do not prescribe Safyral to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35 [see *Boxed Warning and Warnings and Precautions (5.1)*]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [see *Warnings and Precautions (5.1)*]
 - Have cerebrovascular disease [see *Warnings and Precautions (5.1)*]
 - Have coronary artery disease [see *Warnings and Precautions (5.1)*]
 - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see *Warnings and Precautions (5.1)*]
 - Have inherited or acquired hypercoagulopathies [see *Warnings and Precautions (5.1)*]
 - Have uncontrolled hypertension [see *Warnings and Precautions (5.5)*]
 - Have diabetes mellitus with vascular disease [see *Warnings and Precautions (5.7)*]
 - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [see *Warnings and Precautions (5.8)*]
- Undiagnosed abnormal uterine bleeding [see *Warnings and Precautions (5.9)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [see *Warnings and Precautions (5.3)*]
- Liver tumor (benign or malignant) or liver disease [see *Warnings and Precautions (5.4)* and *Use in Specific Populations (8.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [see *Warnings and Precautions (5.10)* and *Use in Specific Populations (8.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Safyral if an arterial or venous thrombotic (VTE) event occurs.

Based on presently available information on DRSP-containing COCs with 0.03 mg ethinyl estradiol (that is, Yasmin), DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin 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. Before initiating use of Safyral 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. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs [see *Contraindications (4)*].

A number of studies have compared the risk of VTE for users of Yasmin (which contains 0.03 mg of 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.

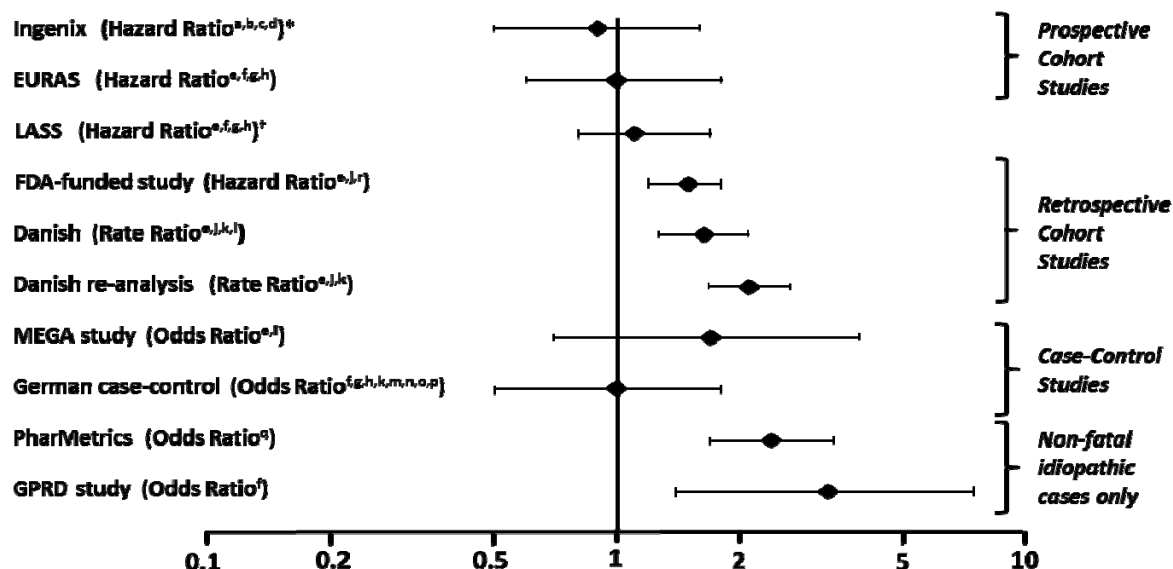
Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Current Users of Yasmin Compared to Users of Oral Contraceptives that Contain Other Progestins

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

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], the European post-approval safety study EURAS (European Active Surveillance Study) [Dinger 2007]. 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 (see Table 1), and two from Denmark [Lidegaard 2009, Lidegaard 2011]. There are two case-control studies: the Dutch MEGA study analysis [van Hylckama Vlieg 2009] and the German case-control study [Dinger 2010]. There are two nested case-control studies that evaluated the risk of non-fatal idiopathic VTE: the PharMetrics study [Jick 2011] and the GPRD study [Parkin 2011]. The results of all of these studies are presented in Figure 1.

Figure 1: VTE Risk with Yasmin Relative to LNG-Containing COCs (adjusted risk[#])



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

† LASS is an extension of the EURAS study

[#]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

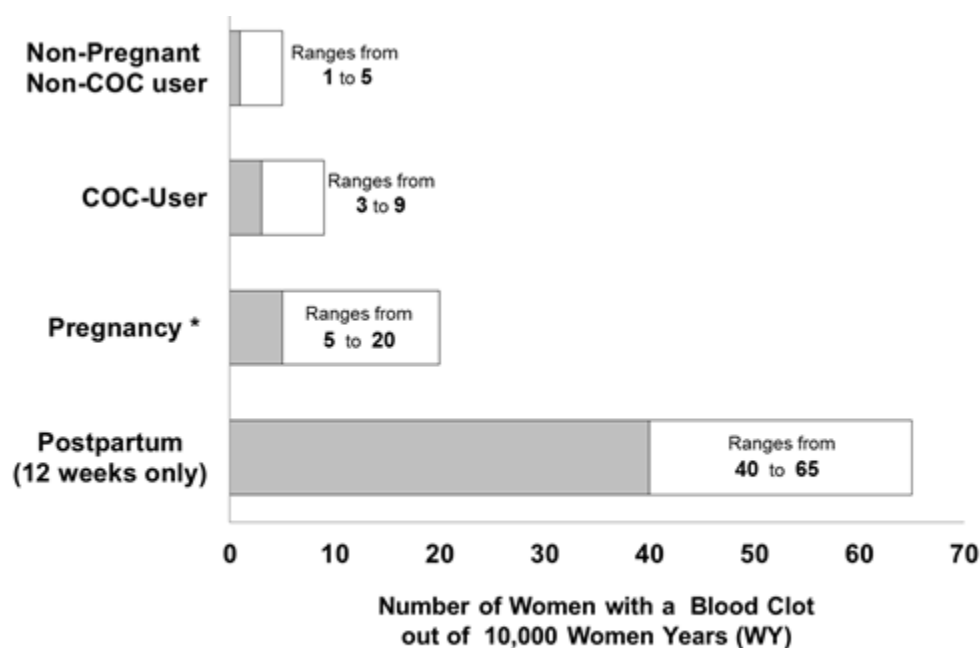
(References: Ingenix [Seeger 2007]², EURAS (European Active Surveillance Study) [Dinger 2007]³, LASS (Long-Term Active Surveillance Study) [Dinger, unpublished document on file], FDA-funded study [Sidney 2011]⁴, Danish [Lidegaard 2009]⁵, Danish re-analysis [Lidegaard 2011]⁶, MEGA study [van Hylckama Vlieg 2009]⁷, German Case-Control study [Dinger 2010]⁸, PharMetrics [Jick 2011]⁹, GPRD study [Parkin 2011]¹⁰)

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.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Figure 2 shows 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. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 2: Likelihood of Developing a 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.

If feasible, stop Safyral at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Safyral no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Safyral if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. [See Adverse Reactions (6).]

5.2 Hyperkalemia

Safyral contains 3 mg of the progestin DRSP, which has antimineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Safyral should not be used in patients with conditions that predispose to hyperkalemia (that is, renal impairment, hepatic impairment, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration should have their serum potassium concentration checked during the first treatment cycle. Medications that may increase serum potassium concentration include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDs.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Safyral because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Safyral if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Safyral if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.7 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Safyral. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.8 Headache

If a woman taking Safyral develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Safyral if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.9 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Data from ten Yasmin contraceptive efficacy clinical trials (N=2,467) show that the percent of women who took Yasmin and experienced unscheduled bleeding decreased over time from 12% at cycle 2 to 6% (cycle 13). A total of 25 subjects out of 3,009 in the Yasmin and Safyral trials (<1%) discontinued due to bleeding complaints. These are described as metrorrhagia, vaginal hemorrhage, menorrhagia, abnormal withdrawal bleeding, and menometrorrhagia.

The average duration of scheduled bleeding episodes in the majority of subjects (86%-88%) was 4-7 days. Women who use Safyral may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from Yasmin contraceptive efficacy trials, during cycles 2 –13, 1 - 11% of women per cycle experienced no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.10 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect when COCs are taken inadvertently during early pregnancy, particularly in so far as cardiac anomalies and limb-reduction defects are concerned. Discontinue Safyral if pregnancy is confirmed and initiate a prenatal vitamin containing folate supplementation.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy [*see Use in Specific Populations (8.1)*].

5.11 Depression

Women with a history of depression should be carefully observed and Safyral discontinued if depression recurs to a serious degree.

5.12 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs [*see Drug Interactions (7.2)*].

DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

Folates may mask vitamin B12 deficiency.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke [*see Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [*see Warnings and Precautions (5.1)*]
- Liver disease [*see Warnings and Precautions (5.4)*]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Contraception and Folate Supplementation Clinical Trials

The data provided reflect the experience with the use of Yasmin (3 mg DRSP/0.03 mg EE) in the adequate and well-controlled studies for contraception (N=2,837) and folate supplementation (N=172). For contraception, the US pivotal clinical study (N=326) for the oral contraception indication for Yasmin was a multicenter, open-label trial in healthy women aged 18 -35 who were treated with Yasmin for up to 13 cycles. The second contraceptive pivotal study (N=442) was a multicenter, randomized, open-label comparative European study of Yasmin vs. 0.150 mg desogestrel/0.03 mg EE conducted in healthy women aged 17-40 who were treated for up to 26 cycles. The primary efficacy study using Safyral for folate supplementation was a randomized, single-center European trial in 172 healthy, female subjects aged 18-40 years comparing the pharmacodynamic effects of Yasmin + 0.451 mg levomefolate calcium to Yasmin co-administered with folic acid during 24 weeks of treatment followed by 20 weeks of open-label Yasmin.

The adverse reactions seen across the 2 indications overlapped and are reported using the frequencies from the pooled dataset. The most common adverse reactions ($\geq 2\%$ of users) were: premenstrual syndrome (12.4%), headache/migraine (10.3%), breast pain/tenderness/discomfort (8.1%), nausea/vomiting (4.4%), mood changes (depression, depressed mood, irritability, mood swings, mood altered and affect lability (2.3%), and abdominal pain/discomfort/tenderness (2.2%).

Adverse Reactions ($\geq 1\%$) Leading to Study Discontinuation

Contraception Clinical Trials

Of 2,837 women, 6.7% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was headache/migraine (1.5%).

Folate Clinical Trial

There were no subjects who discontinued due to an adverse reaction.

Serious Adverse Reactions:

Contraception Clinical Trials: depression, pulmonary embolism, toxic skin eruption, and uterine leiomyoma.

Folate Supplementation Clinical Trial: none reported in the clinical trial

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Yasmin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions, including fatalities, are grouped into System Organ Classes and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, intracardiac thrombosis, intracranial venous sinus thrombosis, sagittal sinus thrombosis, retinal vein occlusion, myocardial infarction and stroke), hypertension

Hepatobiliary disorders: Gallbladder disease

Immune system disorders: Hypersensitivity

Metabolism and nutrition disorders: Hyperkalemia

Skin and subcutaneous tissue disorders: Chloasma

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate and products containing St.

John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin with certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effect on DRSP: The main metabolites of DRSP in human plasma are generated without involvement of the CYP system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of DRSP.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro and clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations [see *Clinical Pharmacology* (12.3)].

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Safyral with other drugs that may increase serum potassium concentration [see *Warnings and Precautions* (5.2) and *Clinical Pharmacology* (12.3)].

7.3 Effects of Folates on Other Drugs

Folates may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs, e.g., antiepileptics (such as phenytoin), methotrexate or pyrimethamine, and may result in a decreased pharmacological effect of the antifolate drug.

7.4 Effects of Other Drugs on Folates

Several drugs have been reported to reduce folate concentrations by inhibition of the dihydrofolate reductase enzyme (e.g., methotrexate and sulfasalazine) or by reducing folate absorption (e.g., cholestyramine), or via unknown mechanisms (e.g., antiepileptics such as carbamazepine, phenytoin, phenobarbital, primidone and valproic acid).

7.5 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity. Folates may mask vitamin B12 deficiency. [See *Warnings and Precautions* (5.12) and *Drug Interactions* (7.2).]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE tablets (Yasmin), about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

Studies to date indicate there is no adverse effect of folate on nursing infants.

8.4 Pediatric Use

Safety and efficacy of Safyral has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Safyral has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Safyral is contraindicated in patients with renal impairment [*see Contraindications (4) and Warnings and Precautions (5.2)*].

In subjects with creatinine clearance (CL_{cr}) of 50–79 mL/min, serum DRSP concentrations were comparable to those in a control group with CL_{cr} ≥ 80 mL/min. In subjects with CL_{cr} of 30–49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium-sparing drugs [*see Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

Safyral is contraindicated in patients with hepatic disease [*see Contraindications (4) and Warnings and Precautions (5.4)*]. The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Safyral has not been studied in women with severe hepatic impairment.

8.8 Race

No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP is a spironolactone analogue which has antimineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

Levomefolate calcium doses of 17 mg/day (37-fold higher than the levomefolate calcium dose of Safyral) were well tolerated after long-term treatment up to 12 weeks.

11 DESCRIPTION

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) provides an oral contraceptive regimen consisting of 28 film-coated tablets that contain the active ingredients specified for each tablet below:

- 21 orange tablets each containing 3 mg DRSP, 0.03 mg EE as betadex clathrate, and 0.451 mg levomefolate calcium
- 7 light orange tablets each containing 0.451 mg levomefolate calcium

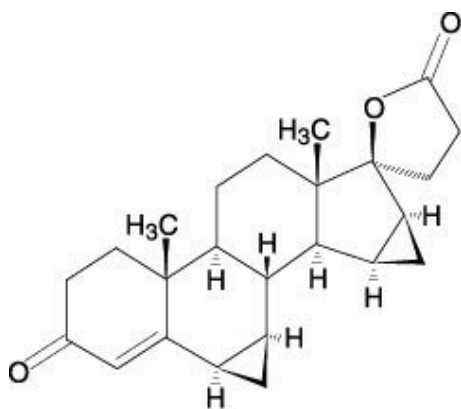
The inactive ingredients in the orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF. The light orange film-coated tablets contain 0.451 mg of levomefolate calcium. The inactive ingredients in the light orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF and ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF.

Drospirenone (6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13, 14,15,15a,16-hexadecahydro-10,13-dimethylspiro-[17H-dicyclopropa-[6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

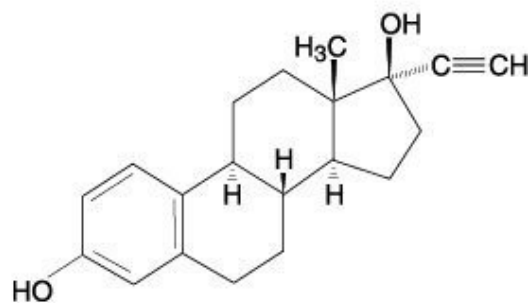
Ethinyl estradiol (19-nor-17 α -pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

Levomefolate calcium (N-[4-[[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridiny]methyl]amino]benzoyl]-L-glutamic acid, calcium salt) is a synthetic calcium salt of L-5-methyltetrahydrofolate (L-5-methyl-THF), which is a metabolite of vitamin B₉ and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$

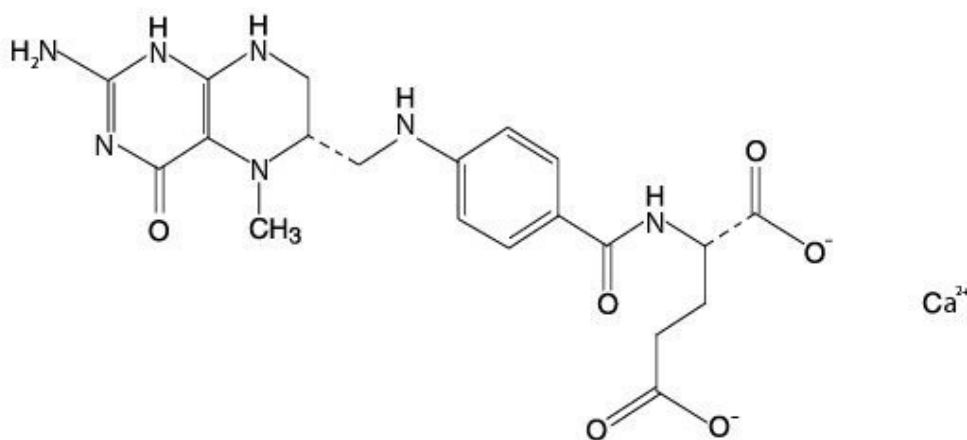
The structural formulas are as follows:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with antimineralocorticoid activity. The estrogen in Safyral is ethinyl estradiol (EE).

Contraception

No specific pharmacodynamic studies were conducted with Safyral.

Folate Supplementation

Two studies evaluated the impact of Safyral on plasma folate and red blood cell (RBC) folate levels. A randomized, double-blind, active-controlled, parallel group study compared plasma folate and RBC folate levels during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population. The pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). [See Clinical Studies (14.4).]

12.3 Pharmacokinetics

Absorption

Safyral and Yasmin are bioequivalent with respect to DRSP and EE.

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Safyral, which is a combination tablet of DRSP and EE stabilized by betadex as a clathrate (molecular inclusion complex), has not been evaluated. The bioavailability of EE is similar when dosed via a betadex clathrate formulation compared to when it is dosed as a free steroid. Serum concentrations of DRSP and EE reached peak levels within 1-2 hours after administration of Safyral.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1-10 mg. Following daily dosing of Yasmin, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum $C_{\max}$ and AUC (0-24h) values of DRSP following multiple dose administration of Yasmin (see Table 2).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Yasmin serum $C_{\max}$ and AUC (0-24h) values of EE accumulate by a factor of about 1.5 to 2 (see Table 2).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B₉. Mean baseline concentrations of about 15 nmol/L are reached in populations without folate food fortification under normal nutritional conditions. Orally administered levomefolate calcium is absorbed and is incorporated into the body folate pool. Peak plasma concentrations of about 50 nmol/L above baseline are reached within 0.5 – 1.5 hours after single oral administration of 0.451 mg levomefolate calcium.

Steady state conditions for total folate in plasma after intake of 0.451 mg levomefolate calcium are reached after about 8-16 weeks depending on the baseline levels. In red blood cells achievement of steady state is delayed due to the long life-span of red blood cells of about 120 days.

Table 2: Mean Pharmacokinetic Parameters Of YASMIN**(DRSP 3 mg and EE 0.03 mg)**

DRSP Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (ng/mL)	T_{max} (h)	AUC(0-24h) (ng•h/mL)	t_{1/2} (h)
1/1	12	36.9 (13)	1.7 (47)	288 (25)	NA
1/21	12	87.5 (59)	1.7 (20)	827 (23)	30.9 (44)
6/21	12	84.2 (19)	1.8 (19)	930 (19)	32.5 (38)
9/21	12	81.3 (19)	1.6 (38)	957 (23)	31.4 (39)
13/21	12	78.7 (18)	1.6 (26)	968 (24)	31.1 (36)
EE Mean (%CV) Values					
Cycle / Day	No. of Subjects	C_{max} (pg/mL)	T_{max} (h)	AUC(0-24h) (pg•h/mL)	t_{1/2} (h)
1/1	11	53.5 (43)	1.9 (45)	280 (87)	NA
1/21	11	92.1 (35)	1.5 (40)	461 (94)	NA
6/21	11	99.1 (45)	1.5 (47)	346 (74)	NA
9/21	11	87 (43)	1.5 (42)	485 (92)	NA
13/21	10	90.5 (45)	1.6 (38)	469 (83)	NA

NA – Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Safyral was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

The effect of food on absorption of levomefolate calcium following administration of Safyral has not been evaluated.

Distribution

DRSP and EE serum concentrations decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4–5 L/kg.

DRSP does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough concentrations). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Biphasic kinetics is reported for folates with a fast- and a slow-turnover pool. The fast-turnover pool, probably reflecting newly absorbed folate, is consistent with the terminal half-life of approximately 4-5 hours after single oral administration

of 0.451 mg levomefolate calcium. The slow-turnover pool reflecting turnover of folate polyglutamate has a mean residence time of greater than or equal to 100 days.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate. These metabolites were shown not to be pharmacologically active. In *in vitro* studies with human liver microsomes, DRSP was metabolized only to a minor extent mainly by CYP3A4.

EE has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

L-5-methyl-THF is the predominant folate transport form in blood under physiological conditions and during folic acid and levomefolate calcium administration.

Excretion

DRSP serum concentrations are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38-47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17-20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

L-5-methyl-THF is eliminated from the body by urinary excretion of intact folates and catabolic products as well as fecal excretion through a biphasic kinetics process.

Use in Specific Populations

Pediatric Use: Safety and efficacy of Safyral has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

Geriatric Use: Safyral has not been studied in postmenopausal women and is not indicated in this population.

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25-35) when 3 mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Safyral is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium concentrations were investigated in three separate groups of female subjects (n=28, age 30-65). All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP concentrations in the group with CL_{Cr} of 50–79 mL/min were comparable to those in the control group with CL_{Cr} ≥ 80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CL_{Cr} of 30–49 mL/min compared to those in the control group. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium-sparing drugs during the study, mean serum potassium concentrations increased by up to 0.33 mEq/L. [See *Contraindications (4) and Warnings and Precautions (5.2).*]

Hepatic Impairment: Safyral is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Safyral has not been studied in women with severe hepatic impairment. [See *Contraindications (4)* and *Warnings and Precautions (5.4)*.]

Drug Interactions

Consult the labeling of all concurrently used drugs to obtain further information about interactions with oral contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin with certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone concentrations.

HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing ethinyl estradiol may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

Metabolism of DRSP and potential effects of DRSP on hepatic CYP enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*.

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Interactions With Drugs That Have the Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Safyral with other drugs that may increase serum potassium concentration [see *Warnings and Precautions (5.2)*].

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium concentrations were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium concentrations in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

Effects of Folates on Other Drugs

There is a potential that folates such as folic acid and levomefolate calcium may modify the pharmacokinetics or pharmacodynamics of certain antifolate drugs (e.g., antiepileptics, methotrexate).

Effects of other Drugs on Folate

Several drugs (e.g., methotrexate, sulfasalazine, cholestyramine, antiepileptics) have been reported to reduce folate concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of levomefolate. Mutagenesis studies for levomefolate were conducted *in vitro* and *in vivo* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

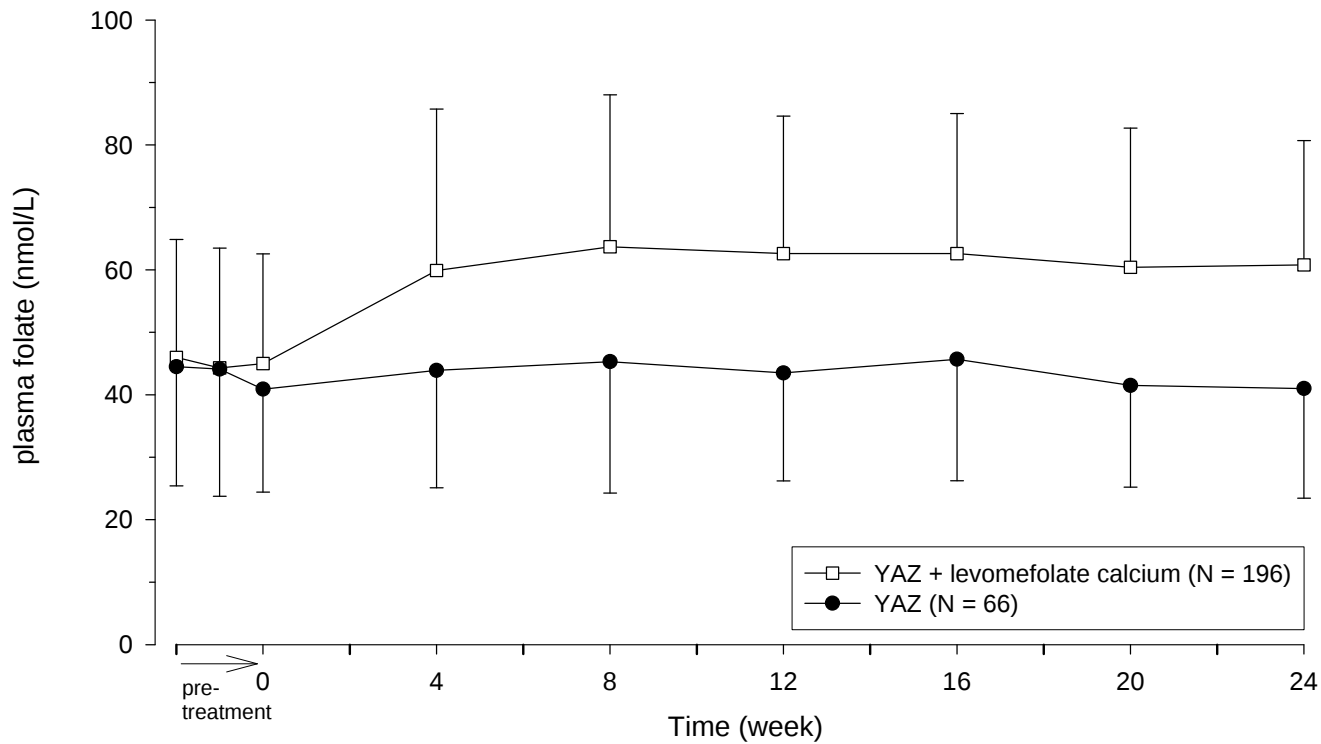
In the clinical efficacy studies of Yasmin (3 mg DRSP/0.03 mg EE) of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% Hispanic, 1% Black, <1% Asian, <1% other, <1% missing data, 14% not inquired and <1% unspecified. Pregnancy rates in the clinical trials were less than one per 100 woman-years of use.

14.2 Folate Supplementation Clinical Trials

The development program for Safyral (Yasmin + levomefolate calcium) consisted of two clinical trials.

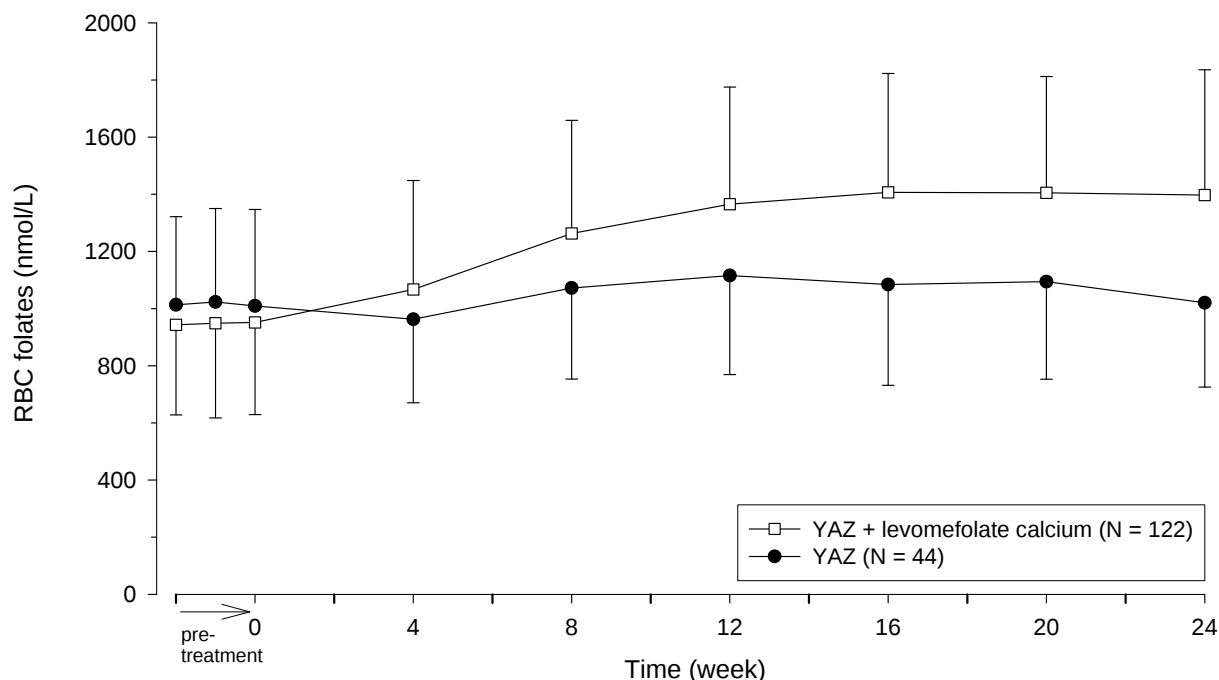
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population that consumed folate fortified food. A total of 379 healthy women between 18 and 40 years of age with no restrictions on folate supplementation received YAZ + levomefolate calcium (N= 285) or YAZ (N=94). The plasma and RBC folate concentrations at Week 24 were the co-primary endpoints. Figures 1 and 2 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in each arm of the study.

Figure 3: US Study: Mean trough concentration-time curves (and SD) of plasma folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on the per protocol analysis populations. The SD bars shown represent one SD.

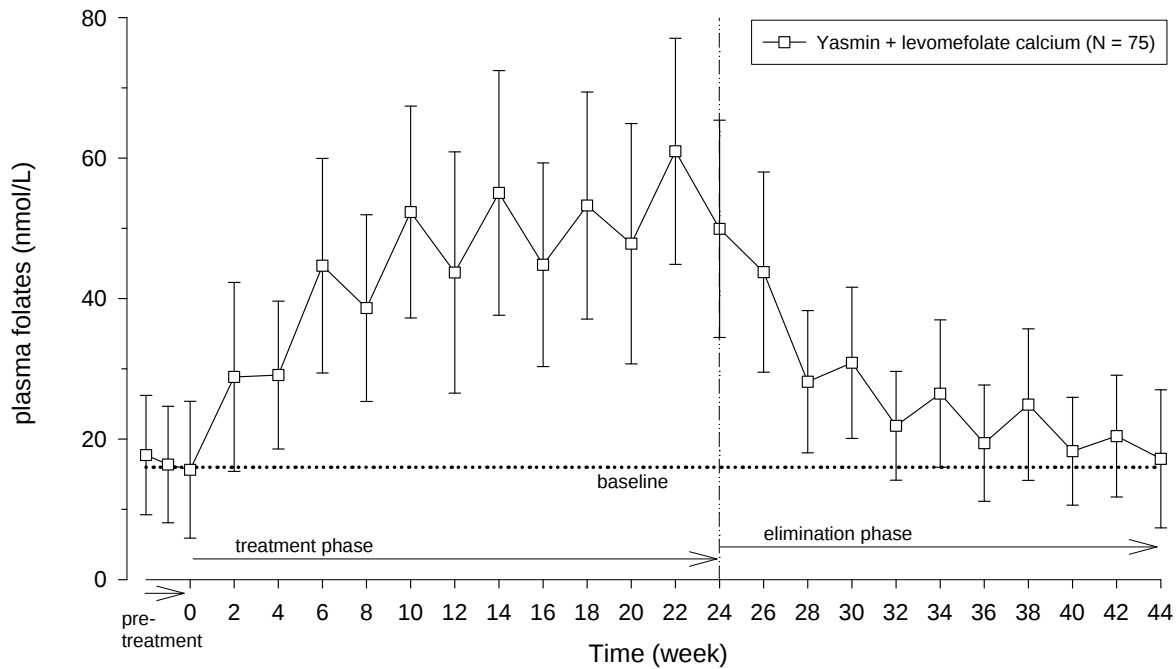
Figure 4: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



Arithmetic mean values based on 4-weekly measurements are displayed with arithmetic standard deviations which are shown in only one direction to improve readability. Data are based on the per protocol analysis populations. The SD bars shown represent one SD.

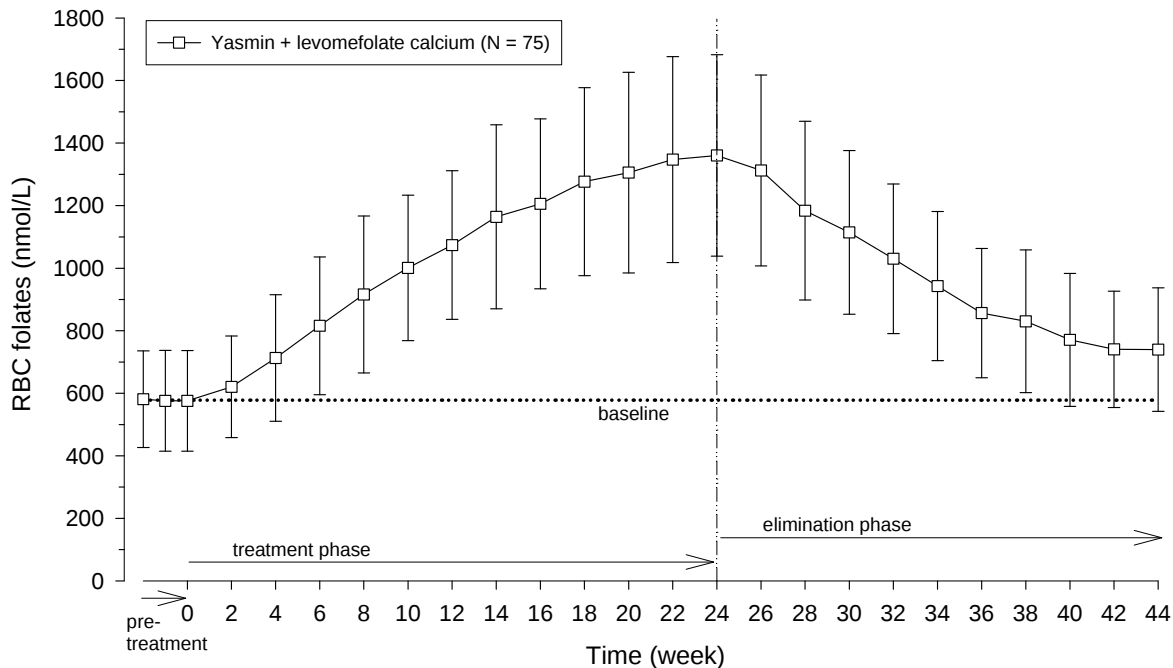
In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination with 3 mg DRSP/0.03 mg EE (Yasmin) followed by 20 weeks of open-label treatment with Yasmin only (elimination phase). One-hundred and seventy-two healthy women between 18 to 40 years of age from a German population that consumed food without folate fortification and without concomitant intake of folate supplements were randomized to one of the two treatments. Figures 3 and 4 display the results for plasma and RBC folate concentrations, respectively, among evaluable subjects in the levomefolate arm of the study.

Figure 5: German Study: Mean trough concentration-time curve (and SD) of plasma folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

Figure 6: German Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of Yasmin + levomefolate calcium



Arithmetic mean values based on biweekly measurements are displayed with arithmetic standard deviations. In the treatment phase, women received Yasmin + levomefolate calcium; in the elimination phase, all women received Yasmin only. Data are based on the per protocol analysis population. The SD bars shown represent one SD.

The potential to reduce the incidence of neural tube defects (NTDs) with folate supplementation is well established based on a body of evidence derived from randomized, controlled trials, nonrandomized intervention trials, and observational studies using folic acid. Therefore, the Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force recommend that women of childbearing age consume supplemental folic acid in a dose of at least 0.4 mg (400 mcg) daily^{1,6}.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets) is available in packages of three blister packs (NDC 50419-403-03).

The film-coated tablets are rounded with biconvex faces, one side is embossed with a regular hexagon shape with Y+ or M+.

Each blister pack contains 28 film-coated tablets in the following order:

- 21 round, biconvex, orange, film-coated tablets with embossed “Y+” in a regular hexagon on one side each containing 3 mg drospirenone, 0.03 mg ethinyl estradiol, and 0.451 mg levomefolate calcium
- 7 round, biconvex, light orange, film-coated tablets with embossed “M+” in a regular hexagon on one side each containing 0.451 mg levomefolate calcium

16.2 Storage

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See “FDA-approved patient labeling (Patient Information).”

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC.
- Counsel patients about the information regarding the risk of VTE with DRSP-containing COCs compared to COCs that contain levonorgestrel or some other progestins.
- Counsel patients that Safyral does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Safyral contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Safyral in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition.

- Inform patients that Safyral is not indicated during pregnancy. If pregnancy occurs during treatment with Safyral, instruct the patient to stop further intake. However, women should be advised on the continued need of sufficient folate intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See ***“What to Do if You Miss Pills”*** section in ***FDA-Approved Patient Labeling***.
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken a orange tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.
- Counsel patients to report whether they are taking folate supplements. Safyral contains the equivalent of 0.4 mg (400 mcg) of folic acid.
- Counsel patients to maintain folate supplementation if they discontinue Safyral due to pregnancy.

Manufactured for Bayer HealthCare Pharmaceuticals Inc.

Wayne, NJ 07470

Manufactured in Germany

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Bayer HealthCare Pharmaceuticals Inc.

WARNING TO WOMEN WHO SMOKE

Do not use Safyral if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What Is Safyral?

Safyral is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone. Safyral also contains levomefolate calcium, which is a B vitamin.

The progestin drospirenone may increase potassium. Therefore, you should not take Safyral if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Safyral is right for you, and during the first month that you take Safyral, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Safyral may also be taken by women who elect to use an oral contraceptive, to provide folate supplementation. It is recommended that women of reproductive age supplement their diet with 0.4 mg (400 mcg) of folic acid daily to lower their risk of having a pregnancy with a rare type of birth defect (known as a neural tube defect). The amount of folate contained in Safyral supplements folate in the diet to lower this risk should you become pregnant while taking the drug or shortly after stopping it.

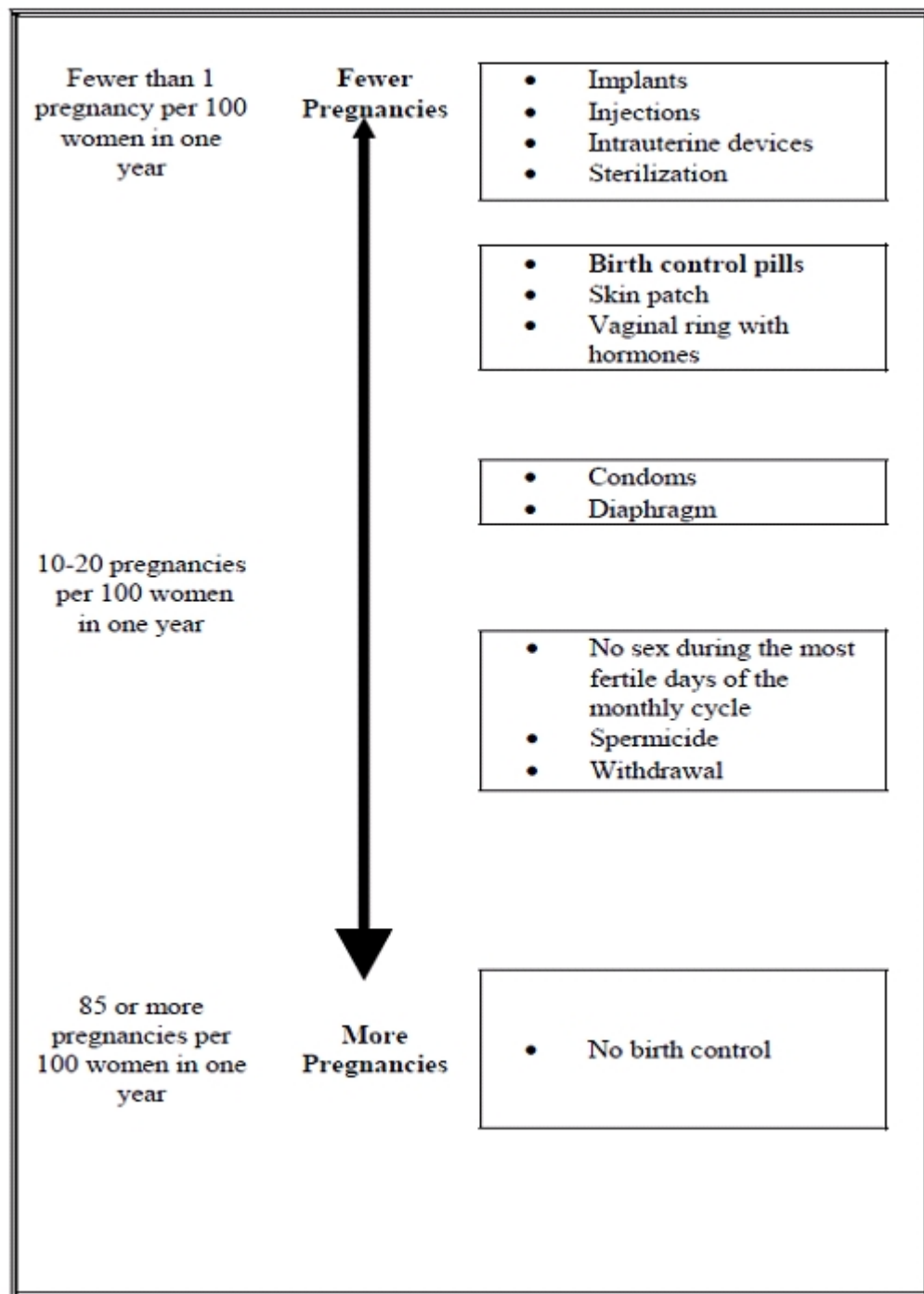
How Well Does Safyral Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of two clinical studies, about 1 woman out of 100 women may get pregnant during the first year they use Safyral.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in

effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Safyral?

1. **Be sure to read these directions** before you start taking your pills or anytime you are not sure what to do.
2. The right way to take the pill is to take one pill every day at the same time in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Safyral can be taken without regard to meals.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.

3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1-3 packs of pills.

If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.

4. Missing pills can also cause spotting or light bleeding, even when you make up these missed pills.

On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.

6. If you have trouble remembering to take the pill, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

7. If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill

It is important to take Safyral in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Safyral can be taken without regard to meals.

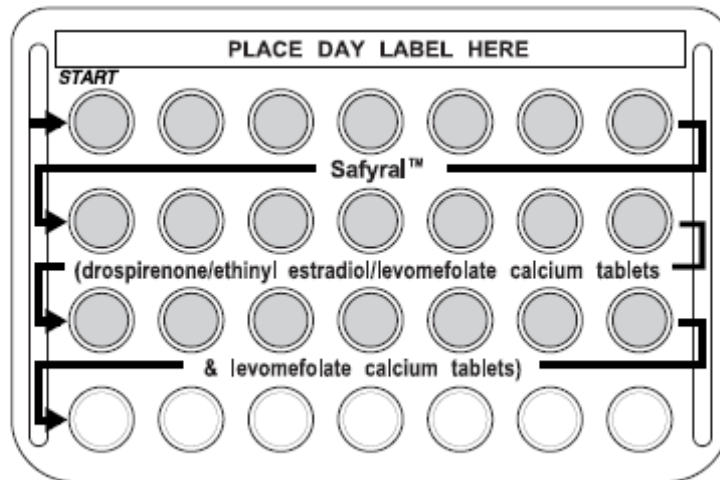
2. Look at Your Pill Pack – It has 28 Pills

The Safyral pill pack has 21 orange pills (with hormones and folate) to be taken for three weeks, followed by 7 light orange pills (without hormones, containing folate) to be taken for one week. **It is important to take the light orange pills because they contain folate.**

3. Also look for:

a) Where on the pack to start taking pills,

b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills, and (b) an extra, full pill pack.

When To Start the First Pack of Pills

You have a choice for which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.

Day 1 Start:

1. Take the first orange pill of the pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, because you are starting the Pill at the beginning of your period. However, if you start Safyral later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 orange pills.

Sunday Start:

1. Take the first orange pill of the pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Safyral after having been pregnant and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Safyral should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Safyral should be started when the next application would have been due. When switching from an injection, Safyral should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Safyral should be started on the day of removal.

What to Do During the Month

1. Take one pill at the same time every day until the pack is empty.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. When you finish a pack of pills, start the next pack on the day after your last light orange pill. **It is important to take the light orange pills because they contain folate.** Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 orange pill of your pack:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day.
2. You do not need to use a back-up birth control method if you have sex.

If you miss 2 orange pills in a row in Week 1 or Week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. **You could become pregnant** if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 orange pills in a row in Week 3 of your pack:

1. If you are a Day 1 Starter:

Throw out the rest of the pill pack and start a new pack that same day.

2. If you are a Sunday Starter:

Keep taking one pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss 3 or more orange pills in a row during any week:

1. If you are a Day 1 Starter:

Throw out the rest of the pill pack and start a new pack that same day.

2. If you are a Sunday Starter:

Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills that same day.

3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms and spermicides) as a back-up for those 7 days.

4. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss any of the 7 light orange pills in Week 4:

Throw away the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

Finally, if you are still not sure what to do about the pills you have missed:

Use a back-up method (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active orange pill each day until otherwise directed.

WHO SHOULD NOT TAKE Safyral?

Your healthcare provider will not give you Safyral if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal
- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

Tell your healthcare provider if you are already taking daily folate supplements.

What Else Should I Know about Taking Safyral?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant

- Miss one period and have not taken your birth control pills on time every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

Due to an increased risk of blood clots, you should stop Safyral at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Safyral, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you are currently on daily, long-term treatment for a chronic condition with any of the following medications, you should consult your healthcare provider before taking Safyral:

- NSAIDs (ibuprofen, naproxen and others)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (captopril, enalapril, lisinopril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Tell your healthcare provider about all medicines and herbal products that you take. Some other medicines and herbal products may make birth control pills less effective, including:

- Barbiturates
- Bosentan
- Carbamazepine
- Felbamate
- Griseofulvin
- Oxcarbazepine
- Phenytoin
- Rifampin
- St. John's wort
- Topiramate

Consider using another birth control method when you take medicines (such as the ones listed above) that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Folates may make certain drugs, including some used for epilepsy, less effective, so talk to your healthcare provider about any medicines you take.

If you have vomiting or diarrhea, your birth control pills may not work as well. Take another pill if you vomit within 3-4 hours after taking your pill, or use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your doctor you are taking birth-control pills. Certain blood tests may be affected by birth-control pills.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more. Women who use birth control pills with drospirenone (like Safyral) may have a higher risk of getting a blood clot. Some studies reported that the risk of blood clots was higher for women who use birth control pills that contain drospirenone than for women who use birth control pills that do not contain drospirenone.

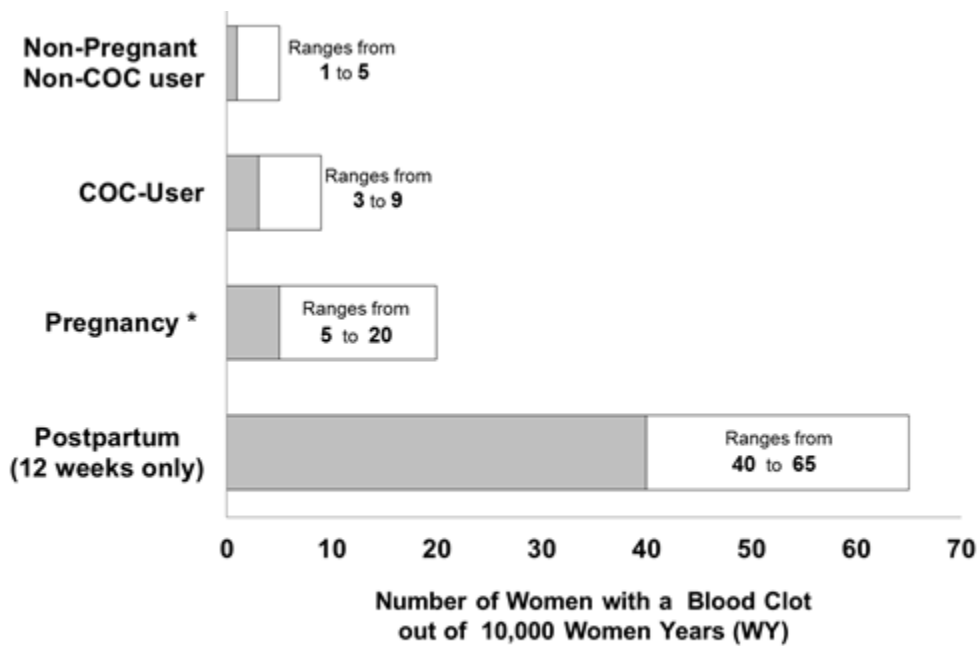
Talk with your healthcare provider about your risk of getting a blood clot before deciding which birth control pill is right for you.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (deep vein thrombosis or DVT)
- Lungs (pulmonary embolus or PE)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use birth control pills are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use birth control pills, for women who use birth control pills, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot



* 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.

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Safyral?

Irregular vaginal bleeding or spotting may occur while you are taking Safyral. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills regularly on time.

What if I Miss My Scheduled Period when Taking Safyral?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills regularly on time, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Safyral if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill. See your healthcare provider about appropriate folate supplementation if you stop taking Safyral, are pregnant, or plan on becoming pregnant.

General Advice about Safyral

Your healthcare provider prescribed Safyral for you. Please do not share Safyral with anyone else. Keep Safyral out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Bayer HealthCare Pharmaceuticals Inc.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 022574/S-004

MEDICAL REVIEW(S)

Clinical Review (Labeling)

(Pertaining to Drug Safety Labeling for Drospirenone-Containing Oral Contraceptives)

Application Numbers	NDA 21-098 (Yasmin) NDA 21-676 (YAZ/Contraception) NDA 21-045 (YAZ/ Acne) NDA 21-873 (YAZ/PMDD) NDA 22-532 (Beyaz) NDA 22-574 (Safyral)
Applicant	Bayer HealthCare Pharmaceuticals
Therapeutic Class	Combination oral contraceptive (COC)
Subclass	Drospirenone (DRSP)-containing combination oral contraceptives
Established Name (Yasmin & YAZ)	Ethinyl estradiol (EE) / drospirenone (DRSP)
Formulation and Regimen (Yasmin)	<u>Oral tablets</u> Cycle days 1-21 (EE 0.03 mg / DRSP 3.0 mg) Cycle days 22-28 (placebo)
Formulation and Regimen (YAZ)	<u>Oral tablets</u> Cycle days 1-24 (EE 0.02 mg / DRSP 3.0 mg) Cycle days 25-28 (placebo)
Established Name (Beyaz & Safyral)	Ethinyl estradiol (EE) / drospirenone (DRSP) / levomefolate calcium (LMF) tablets and LMF tablets
Formulation and Regimen (Beyaz)	<u>Oral tablets</u> Cycle days 1-24 (EE 0.02 mg / DRSP 3.0 mg / 0.451 mg LMF Cycle days 25-28 (0.451 mg LMF))
Formulation and Regimen (Safyral)	<u>Oral tablets</u> Cycle days 1-21 (EE 0.03 mg / DRSP 3.0 mg / 0.451 mg LMF Cycle days 22-28 (0.451 mg LMF))
Reviewer Name	Gerald Willett M.D.
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Review Completion Date	April 3, 2012

PMDD = Premenstrual dysphoric disorder

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1.0 Overview, Background Information and Regulatory Chronology

1.1 Overview

Bayer has submitted labeling supplements for its drospirenone (DRSP)-containing COCs in response to FDA-proposed labeling revisions, dated Dec 15, 2011. The product names, NDA number, and date of submission for these supplements are shown in Table 1:

Table 1: Labeling Supplement Submissions for DRSP-Containing COCs

Product	NDA(s)	Date
Yasmin	21-098	Apr 5, 2012
YAZ	21-676	
	21-045	Apr 5, 2012
	21-873	
Beyaz	22-532	Apr 5, 2012
Safyral	22-574	Apr 5, 2012

Source: Electronic document room submissions

The proposed labeling revisions are related to recent epidemiologic studies that address safety concerns regarding venous thromboembolic events (VTEs). Although VTEs represent a risk for all COCs, some postmarketing epidemiologic studies have reported an increased risk of VTEs with DRSP-containing COCs compared to COC products that contain levonorgestrel or some other progestins. These postmarketing studies and other studies that have not identified an increased risk have been reviewed by DRUP and the Office of Surveillance and Epidemiology (OSE). These postmarketing studies were also discussed at a joint advisory committee meeting that was held on Dec 8, 2011. Based on internal reviews and the perspective from the joint advisory committee, revised labeling regarding the risk for VTEs was requested for all COCs containing drospirenone.

The format of this review is as follows:

- Overview, general background and regulatory chronology (Section 1.0)
- Overview of postmarketing safety studies (Section 2.0)
- Advisory committee input (Section 3.0)
- Labeling changes (Section 4.0)
- Conclusions and recommendations (Section 5.0)
- Appendix 1 – VTE result tables (Section 6.0)
- Appendix 2 – Literature References (Section 6.0)

1.2 General Background Information

Yasmin was the first DRSP-containing COC to be approved for the U.S. market, in May 2001. Subsequent to this approval, YAZ (with a lower dose of ethinyl estradiol [EE] and a 24-day active/ 4-day placebo regimen) was approved in March 2006. The secondary indications for YAZ (acne and PMDD) were both approved within one year of the original approval for the contraceptive indication. Beyaz and Safyral have EE and drospirenone doses comparable to YAZ and Yasmin respectively but in addition contain LMF. Both of these folate-containing products were approved in 2010. The dosages for the aforementioned originator products are shown in Table 2:

Table 2: Dosing of DRSP-Containing COCs

Drug	DRSP dose	EE dose	LMF dose
Yasmin	3 mg	0.03 mg	0
YAZ	3 mg	0.02 mg	0
Beyaz	3 mg	0.02 mg	0.451 mg
Safyral	3 mg	0.03 mg	0.451 mg

DRSP = drospirenone; EE = ethinyl estradiol; LMF = levomefolate

Source: Product labels

1.3 Regulatory Chronology

The chronology of regulatory events for DRSP-containing COCs in regard to approvals and thromboembolic safety events is shown in Table 3:

Labeling Supplements for DRSP-Containing COCs
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Table 3: Chronology of Regulatory-Related Events for DRSP-Containing COCs

DATE	EVENT
2000	Approval of Yasmin in Europe
May 11, 2001	Yasmin (NDA 21-098) approved in US, with a requirement for a postmarketing safety study [Ingenix study]
December, 2005	EURAS, a postmarketing safety study requested by European regulators, is completed (the LASS extension designed to provide another 5 years of data starts). This study and extension are designed to compare Yasmin to levonorgestrel-containing and other COCs in regard to select adverse events (primarily cardiovascular events).
Mar 16, 2006	YAZ (NDA 21-676) approved (contraceptive indication) in US
Oct 4, 2006	YAZ (NDA 21-873) approved (PMDD secondary indication) in US
Jan 26, 2007	YAZ (NDA 22-045) approved (acne secondary indication) in US
May, 2007	Publication of the EURAS study in the journal <i>Contraception</i> , reporting no increased risk of VTE for Yasmin
September, 2007	Publication of the Ingenix study (study requested by US regulators to evaluate hyperkalemia and cardiovascular events) in the journal <i>Obstetrics & Gynecology</i> , reporting no increased risk of VTE for Yasmin
August 13, 2009	Publication of two studies in the <i>British Medical Journal</i> reporting a higher VTE risk for Yasmin (van Hylckama Vlieg and Lidegaard)
April 7, 2010	Labeling change is approved for Yasmin and YAZ that discusses VTE risk in light of 2 prospective studies (EURAS and Ingenix) and two epidemiologic studies in BMJ (van Hylckama Vlieg and Lidegaard)
Sept 24, 2010	Beyaz (NDA 22-532) approved (contraception and secondary indications for PMDD, acne and raising folate levels) in US
Dec 16, 2010	Safyral (NDA 22-574) approved (contraception and secondary indication for raising folate levels) in US
March 11, 2011	Labeling change is approved for YAZ that states that the risk for VTE is greatest in the first 6 months of use and is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC. This labeling change was derived from EURAS and interim data from LASS.
April 21, 2011	Publication of two additional epidemiologic studies reporting increased VTE risk for Yasmin compared to levonorgestrel-containing COCs in <i>British Medical Journal</i> (Parkin and Jick)
May 31, 2011	In a Drug Safety Communication, the FDA alerts the public of the April 21, 2011 <i>British Medical Journal</i> articles and states that these studies are under review
September 13, 2011	Final Study Report of LASS extension of EURAS, reporting non-significantly increased risk of VTE for Yasmin
September 26, 2011	Follow-up Drug Safety Communication provided preliminary results of FDA-funded study and announcement of upcoming joint Advisory Committee Meeting; FDA-funded study found an increased risk of VTE for Yasmin
December 8, 2011	Advisory Committee for Reproductive Health Drugs (ACRHD) and Drug Safety and Risk Management Advisory Committee (DSaRM) meets to discuss DRSP-containing postmarketing studies regarding VTEs
December 15, 2011	DRUP provides guidance to Bayer regarding labeling changes in the wake of the advisory committee meeting
April 5, 2012	Submission of supplements for labeling change

EURAS = European Active Surveillance Study; LASS = Long-term Active Surveillance Study;
PMDD = premenstrual dysphoric disorder; VTE = venous thromboembolism; COC = combination
oral contraceptive

Source: FDA submissions, medical literature, meeting minutes of advisory committee meeting

2.0 Overview of Postmarketing Studies for DRSP-Containing COCs

The postmarketing safety studies that evaluated cardiovascular adverse events for DRSP-containing COCs primarily assessed Yasmin, which was the first DRSP-containing COC marketed.

The following table (

Table 4) provides a high level comparison of the postmarketing safety studies in regard to:

- Study name
- Author/investigator
- Date of publication/report
- Study Design
- Overall findings with regard to VTE risk
- Date of additional reviews in DARTTS

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Table 4: Overview of Postmarketing Safety Studies for DRSP-Containing COCs

Study (name or country) Author and/or investigators Year of publication or final report Appendix location	Study Design	Findings regarding VTE risk	Additional review information in DARRTS
EURAS Dinger (author) 2007 (publication) Ref 1 Appendix 6.1.1	Prospective Observational	No increased VTE risk for DRSPCC vs. LNGCC and other COCs	DRUP (Dr. Furlong) 6-27- 2006
LASS extension of EURAS Dinger (PI) 2011 (final report) Appendix 6.1.2	Prospective Observational	Minimally increased VTE risk for DRSPCC vs. LNGCC and other COCs (HR = 1.1) – not statistically significant	OSE (CDR Moeny) 11-2- 2011
i3 Ingenix Seeger (author) 2007 (publication) Ref 2 Appendix 6.1.3	Prospective Observational	No increased VTE risk for DRSPCC vs. other COCs	DRUP (Dr. Furlong) 8-8- 2006
Danish Study Lidegaard (author) 2009 (publication) Ref 3 Appendix 6.1.4	Population- based cohort study	Increased VTE risk for DRSPCC vs. LNGCC (rate ratio = 1.6)	OSE (Dr. Ouellet- Hellstrom) 10-20-2009
Danish Study Reanalysis Lidegaard (author) 2011 (publication) Ref 8 Appendix 6.1.5	Population- based cohort study	Increased VTE risk for DRSPCC vs. LNGCC (rate ratio = 2.1)	OSE (Dr. Ouellet- Hellstrom) 9-3-2011
MEGA Study van Hylckama Vlieg (author) 2009 (publication) Ref 4 Appendix 6.1.6	Population- based case- control study	Increased VTE risk for DRSPCC vs. LNGCC (odds ratio = 1.7)	OSE (Dr. Ouellet- Hellstrom) 10-20-2009
German Case-Control Study Dinger (author) 2010 (publication) Ref 7 Appendix 6.1.7	German Community- based case- control study	No increased VTE risk for DRSPCC vs. LNGCC	OSE (Dr. Ouellet- Hellstrom) 11-16-2011 for advisory background document
PharMetrics Study Jick (author) 2011 (publication) Ref 5 Appendix 6.1.8	Population- based case- control study	Increased VTE risk for DRSPCC vs. LNGCC (odds ratio = 2.3)	OSE (Dr. Ouellet- Hellstrom) 6-6-2011
GPRD Study Parkin 2011 (publication) Ref 6 Appendix 6.1.9	Population- based case- control study	Increased VTE risk for DRSPCC vs. LNGCC (odds ratio = 3.3)	OSE (Dr. Ouellet- Hellstrom) 6-6-2011

FDA-Funded Study Sidney (principal investigator) 2011 (final report) Appendix 6.1.10	Retrospective Cohort	Increased VTE risk for DRSPCC vs. LNGCC (new user hazard ratio = 1.6; all users hazard ratio = 1.5)	OSE (Dr. Ouellet-Hellstrom) 11-4-2011
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EURAS = European Active Surveillance Study; LASS = Long-term Active Surveillance Study; DRSPCC = drospirenone-containing combination oral contraceptives; HR = hazard ratio; LNGCC = levonorgestrel-containing combination oral contraceptives; MEGA = Multiple environmental and genetic assessment of risk factors for venous thrombosis; GPRD = General Practice Research Database; DRUP = Division of Reproductive and Urologic Products; OSE = Office of Surveillance and Epidemiology;

Sources: Referenced publications and internal FDA data

The other important document that provides a review of these studies is the jointly produced (DRUP & OSE) background document that was prepared for the advisory committee meeting held on Dec 8, 2011. The date of this background document was Nov 16, 2011.

Tabular data regarding VTE risk from the postmarketing studies is included in Appendix 1 of this review. However, for more specific comments relating to the quality of the postmarketing epidemiology analysis, the reader should refer to the advisory committee background document and the OSE reviews listed in column 4 of Table 4.

3.0 Advisory Committee Meeting

An advisory committee meeting was held on December 8, 2011 to discuss the postmarketing safety findings for DRSP-containing COCs. This advisory committee was composed of members from the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

The joint committee discussed the benefits and risks of DRSP-containing COCs in light of the safety concerns that have arisen as a result of some postmarketing epidemiologic studies reporting an increased risk of VTEs for DRSP-containing COCs.

This reviewer considers the following to be key points made at the meeting:

- A number of studies showed a small increased risk in VTE for Yasmin compared to other COCs. The absolute risk is very small. All of the studies had strengths and weaknesses.
- It is difficult to determine if the increased risk is due to confounding variables. Lack of information on Body Mass Index, smoking, family history, polycystic ovarian syndrome, ethnicity, level of exercise/activity, socioeconomic status and concurrent medications could impact the

results. However some committee members questioned whether including confounding variables would actually bias toward the null.

- When asked in a voting question whether the benefits of the DRSP-containing COCs for prevention of pregnancy outweighed their risks, the committee voted:
 - Yes = 15
 - No = 11
 - Abstained = 0
- When asked in a voting question whether current DRSP labels adequately reflected the risk/benefit profile for these products the committee voted:
 - Yes = 5
 - No = 21
 - Abstained = 0
- Committee suggestions for improvement of the labels included:
 - Inclusion of results of all studies
 - Simplification and presentation of safety data results in a tabular or graphic format

4.0 Labeling Changes

The proposed labeling changes for the four Bayer originator DRSP-containing COCs (Yasmin, YAZ, Beyaz, Safyral) contains the following (by labeling section) The table and figures numbers in this section are the numbers found in the label; the particular label cited here is Beyaz; the appropriate drug names are substituted in the other labels.

Highlights

The statement in *Warnings and Precautions*:

“COCs containing DRSP may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Before initiating Beyaz 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. (5.1)”

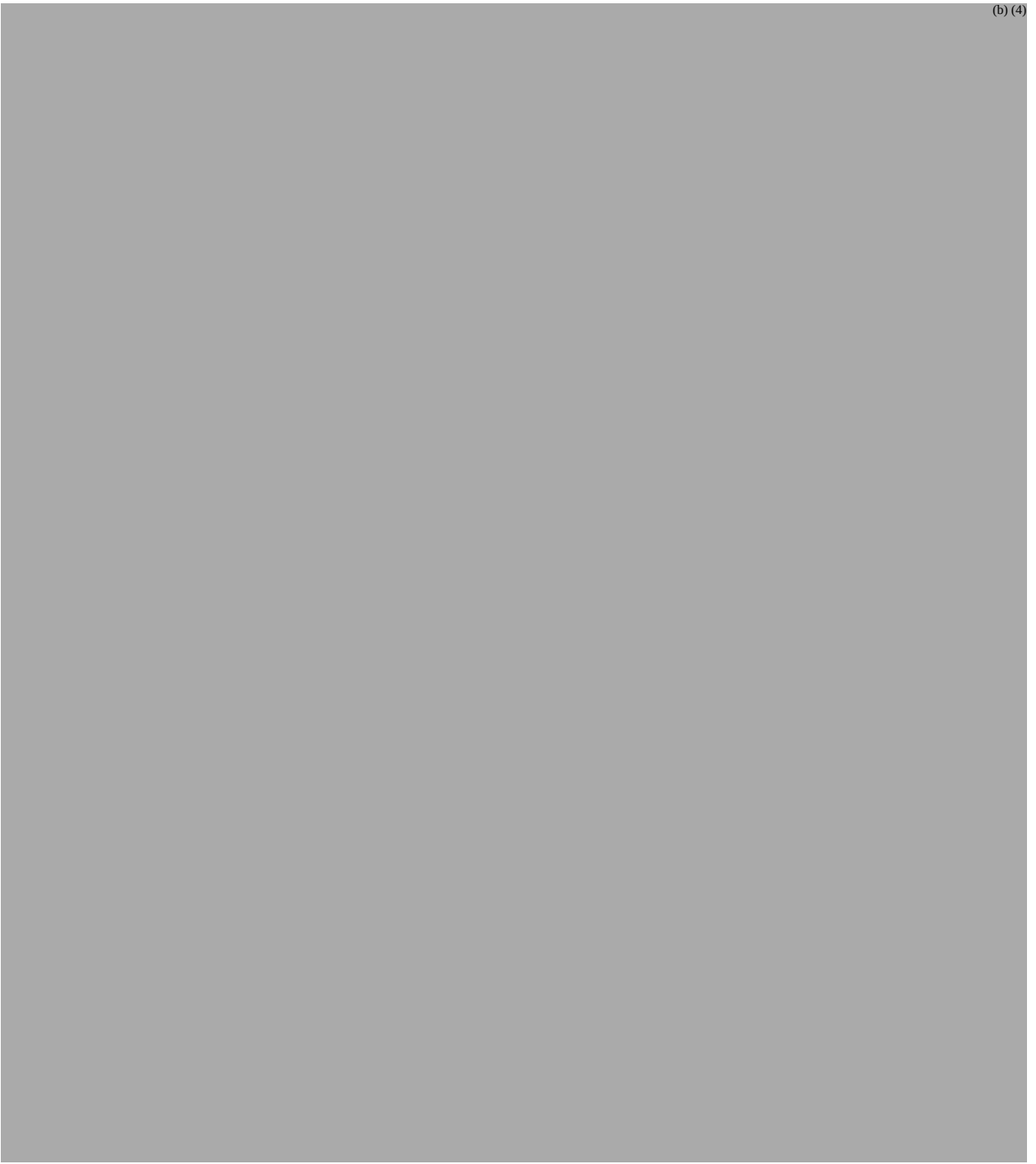
Section 5.1 Thromboembolic Disorders and Other Vascular Problems

“Based on presently available information on DRSP-containing COCs with 0.03 mg ethinyl estradiol (that is, Yasmin), DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin 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. Before initiating use of Beyaz 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. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs”

This statement is followed by a new table that lists the 3 studies that were either required by regulatory authorities or were funded by the FDA. The table includes the comparator product(s) and the hazard ratio as shown below:

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(b) (4)



Following the table there is text that discusses all of the reviewed postmarketing studies. This text is as follows:

(b) (4)



The other addition to Section 5.1 is a new graphic comparison of absolute VTE risks for the following four populations:

- Non-pregnant / Non-COC user
- COC-user
- Pregnancy

- Postpartum

The figure portrayed in the label is shown below:



Medical Officer's Comment:

The lowest risk is for non-pregnant/non-COC users; each succeeding category has a higher risk. The most important information conveyed in this figure is that pregnancy/postpartum presents a higher risk of VTE than does COC use.

Section 17 Patient Counseling Information

A bullet was added, stating:

- “Counsel patients about the information regarding the risk of VTE with DRSP-containing COCs compared to COCs that contain levonorgestrel or some other progestins. “

Patient Labeling

The revised patient labeling states that

“Women who use birth control pills with drospirenone (like Beyaz) may have a higher risk of getting a blood clot. Some studies reported that the risk of blood clots was higher for women who use birth control pills that contain drospirenone than for women who use birth control pills that do not contain drospirenone.

Talk with your healthcare provider about your risk of getting a blood clot before deciding which birth control pill is right for you.”

The patient label also has the graphic comparison of VTE risk of the four populations previously mentioned:

- Non-pregnant / Non-COC user
- COC-user
- Pregnancy
- Postpartum

5.0 Conclusions and Recommendations

This reviewer concurs with the proposed labeling changes for Yasmin, YAZ, Beyaz and Safyral that were submitted on April 5, 2012.

This reviewer finds the following:

- In light of the postmarketing epidemiologic findings, the labeling changes in these supplements convey to health care providers and users information regarding the potential increased risk of VTE with DRSP-containing COCs compared to other COCs, including LNG-containing COCs.
- The label conveys the important message that healthcare providers and patients should consider the woman's specific risk of VTE before deciding which birth control method is the best option.
- The overall VTE risk for women (baseline, COC-use, pregnancy and postpartum) is accurately portrayed based on published literature.
- The use of tabular, graphic and forest plot presentations in the revised label will aid in communicating the VTE safety data.

6.0 Appendices

6.1 Appendix 1 – Compilation of Tables Illustrating VTE Risk in Postmarketing Studies of DRSP-Containing COCs

This section includes the pertinent tables from the postmarketing epidemiologic studies that present VTE safety risk information. The table numbers refer to the numbering in the original studies and are not separately listed in the Table of Tables of this review. Risk estimates highlighted in yellow are those included in the revised labeling.

6.1.1 EURAS Study

This is the pertinent table from the EURAS publication (2007). The incidence rates and adjusted hazard ratios for VTE are highlighted.

Table 3
Incidences, crude and HR_{adj}'s, and confidence limits for main clinical outcomes of interest

Clinical outcome	Cohort	Incidence ^a		HR (DRSP vs. comparators)			
		PE	95% CI	PE _{crude}	95% CI	PE _{adj}	95% CI
TE ^b	DRSP	9.8	6.5–14.1	–	–	–	–
	LNG and other OCs	11.3	9.1–13.8	0.9	0.6–1.3	0.8	0.5–1.2
	LNG	10.8	7.5–15.1	0.9	0.5–1.5	0.9	0.5–1.4
	Other OCs	11.6	8.9–14.9	0.8	0.5–1.3	0.7	0.4–1.1
VTE	DRSP	9.1	5.9–13.3	–	–	–	–
	LNG and other OCs	9.2	7.2–11.5	1.0	0.6–1.6	0.9	0.6–1.4
	LNG	8.0	5.2–11.7	1.1	0.7–2.0	1.0	0.6–1.8
	Other OCs	9.9	7.4–13.0	0.9	0.6–1.5	0.8	0.5–1.3
ATE ^b	DRSP	0.7	0.1–2.5	–	–	–	–
	LNG and other OCs	2.1	1.3–3.4	0.3	0.1–1.4	0.3	0.1–1.3
	LNG	2.9	1.3–5.4	0.3	0.1–1.2	0.3	0.1–1.2
	Other OCs	1.7	0.8–3.2	0.4	0.2–1.9	0.3	0.1–1.5
Treated Arrhythmia	DRSP	2.8	1.2–5.5	–	–	–	–
	LNG and other OCs	3.9	2.7–5.5	0.7	0.3–1.6	0.7	0.3–1.4
	LNG	5.1	2.9–8.3	0.6	0.2–1.3	0.5	0.2–1.2
	Other OCs	3.2	1.9–5.2	0.9	0.4–2.0	0.8	0.3–1.8
Death	DRSP	1.4	0.4–3.6	–	–	–	–
	LNG and other OCs	2.0	1.2–3.2	0.7	0.2–2.1	0.7	0.2–2.0
	LNG	2.5	1.1–5.0	0.6	0.2–1.8	0.5	0.2–1.7
	Other OCs	1.7	0.8–3.2	0.8	0.3–2.6	0.8	0.3–2.6

TE indicates thromboembolism (VTE/ATE combined); PE, point estimate.

^a Events per 10,000 WY.

^b Without transient ischemic attacks.

DRSP = drospirenone; LNG = levonorgestrel; VTE = venous thromboembolism; ATE = arterial thromboembolism; HR = hazard ratio

Source; Table 3; EURAS publication (2007) (Reference #1 Dinger)

6.1.2 LASS Extension of EURAS Study

Tables 23 and 24 from the final report are included in this section. The incidence rates and hazard ratios for VTE are highlighted for Yasmin and LNG.

Table 23 Thromboembolic events: Number, incidence and 95% confidence intervals per cohort (AT analysis)

Category	Yasmin (52,278 WY)		LNG (57,539 WY)		Other OCs (106,221 WY)		NOHC (15,177 WY)		No use (87,570 WY)		Total Nos.
	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	
All TE	63	12.1 (9.3-15.4)	75	13.0 (10.3-16.3)	178	16.8 (14.4-19.4)	18	11.9 (7.0-18.7)	56	6.4 (4.8-8.3)	390
of which Fatal	0	0.0 (0.0-0.7)	5	0.9 (0.3-2.0)	2	0.2 (0.0-0.7)	0	0.0 (0.0-2.4)	3	0.3 (0.1-1.0)	10
All VTE	56	10.7 (8.1-13.9)	53	9.2 (6.9-12.0)	144	13.6 (11.4-16.0)	14	9.2 (5.0-15.5)	39	4.5 (3.2-6.1)	306
of which PE	14	2.7 (1.5-4.5)	14	2.4 (1.3-4.1)	23	2.2 (1.4-3.2)	3	2.0 (0.4-5.8)	7	0.8 (0.3-1.6)	61
VST	1	0.2 (0.0-1.1)	0	0.0 (0.0-0.6)	7	0.7 (0.0-1.4)	1	0.7 (0.0-3.7)	3	0.3 (0.1-1.0)	12
All ATE	7	1.3 (0.5-2.8)	22	3.8 (2.4-5.8)	34	3.2 (2.2-4.5)	4	2.6 (0.7-6.7)	17	1.9 (1.1-3.1)	84
of which AMI	1	0.2 (0.0-1.1)	6	1.0 (0.4-2.3)	5	0.5 (0.2-1.1)	0	0.0 (0.0-2.4)	5	0.6 (0.2-1.3)	17
Stroke	4	0.8 (0.2-2.0)	7	1.2 (0.5-2.5)	22	2.1 (1.3-3.1)	4	2.6 (0.7-6.7)	9	1.0 (0.5-2.0)	46
TIA	1	0.2 (0.0-1.1)	5	0.9 (0.3-2.0)	6	0.6 (0.2-1.2)	0	0.0 (0.0-6.7)	3	0.3 (0.1-1.0)	15
Other ATE	1	0.2 (0.0-1.1)	4	0.7 (0.2-1.8)	1	0.1 (0.0-0.5)	0	0.0 (0.0-6.7)	0	0.0 (0.0-0.4)	6

* incidence rates are given in events per 10⁴ WY

LNG = levonorgestrel; OC = oral contraceptive; NOHC = non-oral hormonal contraceptive; TE Thromboembolism (venous and arterial); CI = confidence interval; PE = pulmonary embolism VST = venous sinus thrombosis; VTE = venous thromboembolism; ATE = arterial thromboembolism; AMI = acute myocardial infarction; TIA = transient ischemic attack
Source: Table 23 from LASS final report page 50 of 127

Table 24 Adjusted hazard ratios (HR) and confidence limits for VTE, ATE and TE

	Yasmin vs.					
	LNG		Other OCs		LNG & Other OCs	
	HR	95% CI	HR	95% CI	HR	95% CI
VTE	1.1	0.8 - 1.7	0.7	0.5 - 1.0	0.8	0.6 - 1.1
ATE	0.4	0.2 - 0.9	0.4	0.2 - 0.9	0.4	0.2 - 0.8
TE	0.9	0.7 - 1.3	0.7	0.5 - 0.9	0.8	0.6 - 1.1

LNG = levonorgestrel; OC = oral contraceptive; HR = hazard ratio; CI = confidence interval; PE = pulmonary embolism; VTE = venous thromboembolism; ATE = arterial thromboembolism; TE = Thromboembolism (venous and arterial)

Source: Table 23 from LASS final report page 50 of 127

6.1.3 i3 Ingenix Study

Table 3 from the journal article is included in this section

Table 3. As-Matched Incidence Rates and Rate Ratios for Thromboembolism

Outcome*	EE/DSRP Initiators (N=22,429; PY=14,081)			Other Oral Contraceptive Initiators (N=44,858; PY=27,575)			Rate Ratio [§]	95% CI
	Events (n) [†]	IR [‡]	95% CI	Events (n) [†]	IR [‡]	95% CI		
Thromboembolism	18	1.3	0.8-2.0	39	1.4	1.0-1.9	0.9	0.5-1.6
DVT only	12	0.8	0.5-1.5	25	0.9	0.6-1.3	0.9	0.4-1.9
PE only	5	0.3	0.1-0.8	12	0.4	0.2-0.7	0.8	0.2-2.5
DVT and PE	1	0.1	0.0-0.3	2	0.1	0.0-0.2	1.0	0.2-18.6

EE/DSRP, ethinylestradiol/drospirenone; PY, person-years; IR, incidence rate; CI confidence interval; DVT, deep vein thrombosis; PE, pulmonary embolism.

* Some of these outcomes may be continuations of preexisting conditions.

[†] Hospitalizations not related to trauma, infection, or preexisting conditions and evidence of hyperkalemia or hypokalemia.

[‡] Incidence rates expressed as events per 1,000 person-years.

[§] From a proportional hazards model.

Source: Table 3; i3 Ingenix publication (2007) (Reference #2 Seeger)

6.1.4 Danish Study

There are 2 tables from the publication selected for this section. In the author's Table 1 incidence rates and adjusted rate ratios for DRSP and LNG are compared to non-use. In the author's Table 3 an adjusted rate ratio comparing DRSP to LNG is presented. The key VTE risk results are highlighted.

Labeling Supplements for DRSP-Containing COCs

Clinical Review

Gerald Willett MD

Table 1| Crude incidence rates and adjusted rate ratios of venous thrombosis in women using different types of hormonal contraception

Characteristics	Woman years	% of woman years	No of women with venous thrombosis	Rate per 10 000 woman years	Adjusted rate ratio (95% CI)
Age group					
15-19	1 359 821	13.0	250	1.84	0.39 (0.33 to 0.45)*
20-24	1 491 764	14.3	444	2.98	0.62 (0.54 to 0.70)*
25-29	1 491 959	14.3	537	3.60	0.86 (0.76 to 0.96)*
30-34	1 587 896	15.2	598	3.77	Reference
35-39	1 628 852	15.6	685	4.21	1.18 (1.05 to 1.32)*
40-44	1 518 172	14.5	797	5.25	1.57 (1.41 to 1.74)*
45-49	1 368 909	13.1	902	6.59	2.09 (1.88 to 2.32)*
Total	10 447 373	100.0	4213	4.03	—
Previous use					
Never	4 813 053	46.1	1467	3.05	Reference
Former	2 278 576	21.8	667	2.93	1.08 (0.98 to 1.18)†
Current use					
Non-use (never or former use of oral contraceptives)	7 194 242	67.9	2168	3.01	Reference
Current use of oral contraceptives	3 253 131	31.1	2045	6.29	2.83 (2.65 to 3.01)†
Use of combined pill:					
<1 year	684 061	21.6	443	6.48	4.17 (3.73 to 4.66)†
1-4 years	1 449 000	45.8	787	5.43	2.98 (2.73 to 3.26)†
>4 years	1 031 953	32.6	793	7.68	2.76 (2.53 to 3.02)†
Oral contraceptives with 50 µg oestrogen	82 902	2.5	65	7.84	2.67 (2.09 to 3.42)†
Oral contraceptives with 20-40 µg oestrogen and:					
Levonorgestrel	367 408	10.9	201	5.47	2.02 (1.75 to 2.34)†
Desogestrel or gestodene	2 008 262	59.8	1370	6.82	3.55 (3.30 to 3.83)†
Drospirenone	131 541	3.9	103	7.83	4.00 (3.26 to 4.91)†
Progestogen only:					
Levonorgestrel 30 µg or norethisterone 350 µg	65 820	0.6	12	1.82	0.59 (0.33 to 1.04)†
Desogestrel 75 µg	9044	0.1	3	3.32	1.10 (0.35 to 3.41)†
Hormone releasing intrauterine device	101 351	1.0	34	3.35	0.89 (0.64 to 1.26)

*Adjusted for current use of oral contraceptives, calendar year, and educational level.

†Adjusted for age, calendar year, and educational level.

Source: Table1; Danish Study publication (2009) (Reference #3 Lidegaard)

Table 3| Adjusted rate ratios (95% confidence intervals) of venous thromboembolism in current users of combined oral contraceptives according to oestrogen dose and progestogen type after adjustment for length of use

Variables	Progestogen						
	Norethisterone	Levonorgestrel	Norgestimate	Desogestrel	Gestodene	Drospirenone	Cyproterone
Oestrogen 50 µg:	1.44 (0.97 to 2.14)	1.20 (0.85 to 1.71)	—	—	—	—	—
Woman years	39 211	43 691	—	—	—	—	—
Venous thromboembolism	28	37	—	—	—	—	—
Oestrogen 30-40 µg:	0.98 (0.71 to 1.37)	1 (reference)	1.19 (0.96 to 1.47)	1.82 (1.49 to 2.22)	1.86 (1.59 to 2.18)	1.64 (1.27 to 2.10)	1.88 (1.47 to 2.42)
Woman years	118 751	367 408	329 463	233 883	1 012 977	131 541	126 687
Venous thromboembolism	43	201	151	191	744	103	90
Oestrogen 20 µg:	—	—	—	1.51 (1.25 to 1.82)	1.51 (1.22 to 1.86)	—	—
Woman years	—	—	—	442 223	319 180	—	—
Venous thromboembolism	—	—	—	251	184	—	—

Rate ratios adjusted for age, calendar year, education, and length of use.

Source: Table 3; Danish Study publication (2009) (Reference #3 Lidegaard)

6.1.5 Danish Study Re-Analysis

Tables 2 and 5 from this publication are shown in this section. DRSP results are highlighted. Table 2 compares VTE risk for Yasmin against non-use of COCs; Table 5 compares against LNG-containing COCs with 30-40 mcg of EE.

Labeling Supplements for DRSP-Containing COCs

Clinical Review

Gerald Willett MD

Table 2| Exposure time, number of events of venous thromboembolism, crude incidence per 10 000 user years, and adjusted relative risk of venous thromboembolism in current users of different oral contraceptives and hormone releasing intrauterine device with non-users as reference group

Group	Women years	No of events*	Crude incidence per 10 000 user years*	Adjusted relative risk† (95% CI)
Non-use	4 960 730	1812	3.7	1 (reference)
Progestogen with 50 µg ethinylestradiol:				
Norethisterone	6848	11	16.1	5.66 (3.12 to 10.3)
Levonorgestrel	23 691	31	13.1	3.54 (2.48 to 5.05)
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	10	3.7	1.57 (0.84 to 2.92)
Phasic levonorgestrel	105 970	89	8.4	2.28 (1.85 to 2.83)
Levonorgestrel combined	104 251	78	7.5	2.19 (1.74 to 2.75)
Norgestimate	267 664	165	6.2	2.56 (2.18 to 3.01)
Desogestrel	170 249	201	11.8	4.21 (3.63 to 4.87)
Gestodene	668 355	738	11.0	4.23 (3.87 to 4.63)
Drospirenone	286 859	266	9.3	4.47 (3.91 to 5.11)
Cyproterone	120 934	109	9.0	4.10 (3.37 to 4.99)
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	322	6.8	3.26 (2.88 to 3.69)
Gestodene	472 118	321	6.8	3.50 (3.09 to 3.97)
Drospirenone	23 055	23	10.0	4.84 (3.19 to 7.33)
Progestogen only:				
Norethisterone	44 168	9	2.0	0.56 (0.29 to 1.07)
Desogestrel	29 187	6	2.1	0.64 (0.29 to 1.42)
Levonorgestrel releasing intrauterine device	155 149	55	3.5	0.83 (0.63 to 1.08)

*Events are venous thromboembolisms.

†Adjusted for age, year, and level of education.

Source: Table 2; Danish Study Re-Analysis publication (2011) (Reference #8 Lidegaard)

Table 5| Rate ratio of confirmed venous thromboembolism between different combined oral contraceptives with adjustment for length of use

Product group	Women years	No of events*	Adjusted rate ratio† (95% CI)	P value
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	8	0.76 (0.36 to 1.60)	0.47
Levonorgestrel phasic	105 970	66	1.07 (0.75 to 1.52)	0.71
Levonorgestrel combined	104 251	57	1 (reference)	—
Norgestimate	267 664	119	1.18 (0.86 to 1.62)	0.30
Desogestrel	170 249	168	2.24 (1.65 to 3.02)	<0.001
Gestodene	668 355	575	2.12 (1.61 to 2.78)	<0.001
Drospirenone	286 859	196	2.09 (1.55 to 2.82)	<0.001
Cyproterone	120 934	88	2.11 (1.51 to 2.95)	<0.001
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	246	1.60 (1.20 to 2.14)	0.0015
Gestodene	472 118	240	1.70 (1.27 to 2.27)	0.0004
Drospirenone	23 055	16	2.22 (1.27 to 3.89)	0.005

*Events are venous thromboembolisms.

†Adjusted for age, calendar year, level of education, and length of use.

Source: Table 5; Danish Study Re-Analysis publication (2011) (Reference #8 Lidegaard)

6.1.6 MEGA Study

Table 3 from the publication of this study is selected for this section. The odds ratios from DRSP and LNG are highlighted.

Table 3 | Risk of venous thrombosis associated with different types of progestogens in combined oral preparations. Data are numbers (percentages) unless stated otherwise

Type of progestogen	Thrombosis patients (n=1524)	Controls (n=1760)	Odds ratio (95% CI)*
Levonorgestrel†	485 (31.9)	373 (21.2)	3.6 (2.9 to 4.6)
Gestodene†	119 (7.8)	67 (3.8)	5.6 (3.7 to 8.4)
Desogestrel†	289 (19.0)	108 (6.2)	7.3 (5.3 to 10.0)
Lynestrenol†	44 (2.9)	19 (1.1)	5.6 (3.0 to 10.2)
Norethisterone	11 (0.7)	7 (0.4)	3.9 (1.4 to 10.6)
Cyproterone acetate	125 (8.2)	62 (3.5)	6.8 (4.7 to 10.0)
Norgestimate	9 (0.6)	4 (0.2)	5.9 (1.7 to 21.0)
Drospirenone	19 (1.2)	14 (0.8)	6.3 (2.9 to 13.7)
No oral contraceptive (reference)	421 (27.7)	1102 (62.8)	1

*Odds ratio adjusted for age and period of inclusion (categorical; divided per 6 calendar months).

†Analysis restricted to preparation with most commonly used dose of oestrogen: for levonorgestrel, gestodene, and desogestrel, 30 µg (645 patients and 385 controls); for lynestrenol 37.5 µg (42 patients and 19 controls).

Source: Table 3; MEGA Study publication (2009) (Reference #4 van Hylckama Vlieg)

6.1.7 German Case-Control Study

Table 6 from this publication is included in this section. The comparison of DRSP/EE vs. low dose LNG/EE is highlighted.

Table 6 Crude and adjusted odds ratios for venous thromboembolism cases among users of dienogest/ethinylestradiol and drospirenone/ethinylestradiol in comparison to any other low-dose combined oral contraceptive, and low-dose levonorgestrel/ethinylestradiol

Comparison	Point estimate	95% CI
(a) COC use vs no use		
OR _{crude}	1.9	1.5–2.5
OR _{adj9}	2.4	1.8–3.2
(b) DNG/EE vs other low-dose COCs		
OR _{crude}	0.9	0.6–1.6
OR _{adj9}	0.9	0.6–1.4
(c) DNG/EE vs low-dose LNG/EE		
OR _{crude}	1.1	0.7–1.8
OR _{adj9}	1.0	0.6–1.8
(d) DRSP/EE vs low-dose LNG/EE		
OR _{crude}	1.0	0.6–1.6
OR _{adj9}	1.0	0.5–1.8

adj9, Adjusted for personal history of venous thromboembolism (VTE), family history of VTE, body mass index, duration of combined oral contraceptive use, parity, educational level, chronic disease, concomitant medication and smoking; CI, confidence interval; COC, combined oral contraceptive; DNG, dienogest; DRSP, drospirenone; EE, ethinylestradiol; LNG, levonorgestrel; OR, odds ratio.

Source: Table 6; German Case-Control Study publication (2010) (Reference #7 Dinger)

6.1.8 PharMetrics Study

Tables 2 and 3 from this study are presented in this section. It should be noted that only idiopathic case of VTE were evaluated in this study.

Table 2 | Odds ratios for venous thromboembolism in users of oral contraceptives containing drospirenone compared with those containing levonorgestrel

Exposure	No (%) cases	No (%) controls	Crude* odds ratio (95% CI)	Adjusted† odds ratio (95% CI)
Overall				
Levonorgestrel	65 (15)	368 (85)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.3 (1.6 to 3.2)	2.4 (1.7 to 3.4)
Levonorgestrel 20 users only				
Levonorgestrel-20	20 (13)	131 (87)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.7 (1.6 to 4.7)	3.2 (1.8 to 5.5)
Levonorgestrel 30 users only				
Levonorgestrel-30	45 (16)	237 (84)	1.0	1.0
Drospirenone	121 (28)	313 (72)	2.1 (1.4 to 3.1)	2.2 (1.5 to 3.4)
New episodes of use only				
Levonorgestrel	42 (14)	253 (86)	1.0	1.0
Drospirenone	102 (28)	264 (72)	2.5 (1.7 to 3.8)	2.7 (1.7 to 4.1)
Users of unknown duration only				
Levonorgestrel	23 (17)	115 (83)	1.0	1.0
Drospirenone	19 (28)	49 (72)	2.0 (0.91 to 4.3)	2.1 (0.96 to 4.7)
New episodes of use with no previous episode				
Levonorgestrel	20 (17)	97 (83)	1.0	1.0
Drospirenone	52 (33)	106 (67)	2.7 (1.5 to 5.1)	2.8 (1.5 to 5.2)
New episodes of use with previous episode				
Levonorgestrel	22 (12)	156 (88)	1.0	1.0
Drospirenone	50 (24)	158 (76)	2.3 (1.3 to 4.0)	2.6 (1.4 to 4.6)

*For overall analysis, crude odds ratio is a conditional odds ratio; for stratified analyses, crude odds ratios are adjusted for age and index year.

†Also adjusted for duration.

Source: Table 2; PharMetrics Study publication (2011) (Reference #5 Jick)

Table 3 | Incidence rates and incidence rate ratios for venous thromboembolism in users of drospirenone and levonorgestrel oral contraceptives

Exposure	Cases (n=186)	Person years	Incidence rate (95% CI) per 100 000 person years	Incidence rate ratio (95% CI)
Drospirenone/ethinylestradiol				
Age <30	63	253 895	24.8 (19.1 to 31.7)	4.6 (2.6 to 8.2)
Age 30-39	42	107 701	39.0 (28.1 to 52.7)	2.1 (1.3 to 3.3)
Age 40-44	16	31 248	51.2 (29.3 to 83.2)	2.4 (1.2 to 4.8)
Levonorgestrel/ethinylestradiol 20 µg or 30 µg				
Age <30	14	259 522	5.39 (2.94 to 9.05)	1.0
Age 30-39	35	187 017	18.7 (13.0 to 26.0)	1.0
Age 40-44	16	75 284	21.3 (12.1 to 34.5)	1.0

Crude incidence rate ratio=2.5 (95% CI 1.8 to 3.3).

Incidence rate ratio adjusted for age=2.8 (95% CI 2.1 to 3.8).

Source: Table 3; PharMetrics Study publication (2011) (Reference #5 Jick)

6.1.9 GPRD Study

Table 2 from this study is included in this section. This study also only evaluated idiopathic VTE cases.

Table 2 | Current use of oral contraceptives and venous thromboembolism

Progestogen in oral contraceptive	Cases (n=61)	Controls (n=215)	Unadjusted matched odds ratio (95% CI)	Adjusted matched odds ratio (95% CI)*
Multiple imputation analysis†:				
Levonorgestrel	44	189	1.0	1.0
Drospirenone	17	26	3.2 (1.5 to 7.0)	3.3 (1.4 to 7.6)
Complete case analysis‡:				
Levonorgestrel	42	154	–	1.0
Drospirenone	15	22	–	2.9 (1.1 to 7.4)

*Adjusted for body mass index as continuous variable.

†Missing values for body mass index and smoking are imputed.

‡Effect of multiple imputation is illustrated by presentation of complete case analysis adjusted for body mass index; cases and controls with missing body mass index are excluded from complete case analysis, as are controls of excluded cases.

Source: Table 3; GPRD Study publication (2011) (Reference #6 Parkin)

6.1.10 FDA-Funded Study

Table 12b from the final report of the FDA-funded study is included.

Table 12b. Relative hazard of study endpoints associated with study exposure CHCs relative to LNG2

	ATE	VTE	VTE hospitalized	CVD mortality	Total mortality
All users					
DRSP	0.81 (0.45, 1.44)	1.45 (1.15, 1.83)	1.49 (1.11, 2.01)	0.33 (0.09, 1.18)	0.66 (0.45, 0.99)
NGNM	1.14 (0.52, 24.8)	1.34 (0.97, 1.83)	1.35 (0.92, 1.99)	0.21 (0.03, 1.67)	0.73 (0.45, 1.19)
ETON	1.43 (0.50, 4.12)	1.28 (0.83, 1.99)	1.33 (0.77, 2.30)	0.58 (0.07, 4.67)	1.08 (0.58, 2.04)
New users					
DRSP	1.64 (0.79, 3.40)	1.57 (1.13, 2.18)	1.72 (1.14, 2.59)	0.57 (0.05, 6.35)	0.57 (0.32, 1.02)
NGNM	0.90 (0.28, 2.91)	1.19 (0.75, 1.87)	1.12 (0.63, 2.00)	0	0.84 (0.41, 1.71)
ETON	1.34 (0.30, 6.05)	0.96 (0.47, 1.95)	0.72 (0.25, 2.03)	0	0.67 (0.20, 2.23)

DRSP = drospirenone; LNG2 = levonorgestrel; NGNM = norelgestromin; ETON = Etonogestrel

Source: Final Report; FDA-funded study

6.2 Literature References

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Clinical Review
Gerald Willett MD

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/s/

GERALD D WILLETT
04/09/2012

LISA M SOULE
04/09/2012

I concur with Dr. Willett's recommendation for approval of the four labeling supplements submitted April 5, 2012 for drospirenone-containing oral contraceptives.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 022574/S-004

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research**

**Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Date: April 6, 2012

Reviewer(s): Rita Ouellet-Hellstrom, Ph.D, M.P.H.,
Associate Director
Division of Epidemiology II (DEPI-II)

Division Director Judy Staffa, Ph.D., R.Ph., Director
Division of Epidemiology II (DEPI-II)

Drug Name(s): 3mg drospirenone/20-30 mcg ethinyl estradiol
(Beyaz, Yaz, Yasmin, Safyral)

Application Type/Number: NDA 21-098 (Yasmin)
NDA 21-676 (Yaz/Contraception)
NDA 21-045 (Yaz/Acne)
NDA 21-873 (Yaz/PMDD)
NDA 22-532 (Beyaz)
NDA 22-574 (Safyral)

Applicant/sponsor: Bayer Healthcare

OSE RCM #: 2011-3296

TSI #: 770

1 INTRODUCTION

Several drospirenone-containing products have been approved by the FDA since 2001. Yasmin [3.0 mg drospirenone (DRSP), 30 µg ethinyl estradiol (EE)], was approved for contraception in May 2001; Safyral (3 mg drospirenone, 30 µg EE, 0.45 mg levomefolate calcium) was approved for contraception and folate supplementation in December 2010.

YAZ (3.0 mg DRSP, 20 µg EE) was approved for contraception in March 2006, for premenstrual dysphoric disorder (PMDD) in October 2006, and acne in January 2007; Beyaz (3.0 mg drospirenone, 20 µg EE, 0.45 mg levomefolate calcium) was approved for contraception, PMDD, Acne, and folate supplementation in September 2010.

Two post marketing studies, initiated at the time of approval in 2001 and referred to as the regulatory studies, compared thrombotic and thromboembolic events for Yasmin with other combined hormonal contraceptives. The first was a European/German Study (EURAS)¹ was requested by the European Medical Authorities and the other^{2,3}, requested by the Agency, was US based. EURAS included users of the oral contraceptive containing 3 mg of drospirenone with 30 µg ethinyl estradiol (Yasmin) and two groups of comparators: levonorgestrel-containing contraceptives (LNG) and other contraceptives. The US-based study identified Yasmin initiators every quarter for the length of the study then matched each DRSP initiator to two other contraceptive initiators based on their respective propensity scores or probability of being prescribed Yasmin. Neither of these two studies showed an increased risk for venous thromboembolic events (VTE) or arterial thrombotic events (ATE) associated with use of Yasmin compared to the comparator groups. Since then, however, several observational studies, two in 2009^{4,5} and two more recently in 2011^{6,7}, in addition to the FDA-funded study, most using claims data with or without medical record confirmation, have consistently reported an increased VTE relative risk associated with Yasmin use compared to use of levonorgestrel (LNG)-containing or other progestin-containing combined oral contraceptives (COC).

On December 8, 2011, the FDA convened an Advisory Committee Meeting to request advice on interpreting the differences in relative risk reported by these studies.

As a result, the Division of Reproductive and Urologic Products (DRUP) is proposing labeling change and has requested the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology (DEPI-II) to review the proposed language relating to the epidemiology studies.

2 METHODS AND MATERIALS

OSE DEPI-II reviewed the final agreed upon labeling submitted April 5, 2012 (April 4 for Yaz) focusing mostly on the language pertaining to the epidemiologic studies completed and published during the postmarketing period.

Although only the language in the Beyaz label is referenced in this review, the same language is included in the Yasmin, Yaz, and Safyral labels and will be included in all the labels for the drospirenone-containing oral contraceptives products listed below.

Approved Oral Contraceptives Containing Drospirenone

Brand name	Generic name
Beyaz	Drospirenone 3 mg, ethinyl estradiol 0.02 mg and levomefolate calcium 0.451 mg
Drospirenone and ethinyl estradiol	Drospirenone 3 mg and ethinyl estradiol 0.03 mg
Drospirenone and ethinyl estradiol	Drospirenone 3 mg and ethinyl estradiol 0.02 mg
Gianvi	Drospirenone 3 mg and ethinyl estradiol 0.02 mg
Loryna	Drospirenone 3 mg and ethinyl estradiol 0.02 mg
Ocella	Drospirenone 3 mg and ethinyl estradiol 0.03 mg
Safyral	Drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levomefolate calcium 0.451 mg
Syeda	Drospirenone 3 mg and ethinyl estradiol 0.03 mg
Yasmin	Drospirenone 3 mg and ethinyl estradiol 0.03 mg
Yaz	Drospirenone 3 mg and ethinyl estradiol 0.02 mg
Zarah	Drospirenone 3 mg and ethinyl estradiol 0.03 mg

3 REVIEW RESULTS

The regulatory epidemiologic studies are summarized and their results presented in the label's Table 1 below. The additional studies completed and published in 2009 and 2011 are summarized in text and Figure 1.

(b) (4)





These results are then placed in context with the available information on VTE risks for women of reproductive age.

4 CONCLUSIONS

OSE DEPI-II has reviewed all of these studies including the FDA-funded^{8,9} study and agrees that the proposed language and graphics presented in the label adequately characterize the epidemiologic studies despite the many methodological issues that make interpretation of the results complex. The cumulative evidence in the post marketing studies cannot be ignored and need to be communicated to prescribers and consumers. The differences seen in study results, however, need further characterization to confirm or allay the possible increased VTE risks associated with the drospirenone-containing oral contraceptive products. The studies reviewed did not all account for important known confounders and none accounted for suspected but unproven patient characteristics that may influence prescribing and likely affect the risk of VTE. For these reasons, it is unclear whether the increased relative VTE risk reported in some of the epidemiologic studies is actually due to use of drospirenone-containing birth control pills.

Overall, OSE DEPI II agrees that, to date, the risk appears to be higher for drospirenone-containing pills when compared to other COCs. However, the risk of VTE, although higher when using any combined hormonal contraceptives than not using them, still remains lower than the VTE risk in pregnancy and the postpartum period.

5 RECOMMENDATIONS

OSE DEPI-II supports the labeling change as proposed.

REFERENCES

- ¹ Dinger JC, Heinemann LAJ, Kühl-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.
- ² Eng PM, Seeger JD, Loughlin J, Clifford CR, Mentor S, and Walker AM. 2008. *Supplementary data collection with case-cohort analysis to address potential confounding in a cohort study of thromboembolism in oral contraceptive initiators matched on claims-base propensity scores*. Pharmacoepidemiology and Drug Safety, 17:297-305.
- ³ Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutome J, and Walker AM. 2007. *Risk of Thromboembolism in Women Taking Ethinyl estradiol/Drospirenone and Other Oral Contraceptives*. Obstetrics & Gynecology, 110(3): 587-593.
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- ⁵ van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. 2009. *The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study*. BMJ. 2009 Aug 13;339: b2921. doi: 10.1136/ bmj.b2921.
- ⁶ Parkin L, Sharples K, Hernandez RK, Jick SS. 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. Apr 21;342:d2139. doi: 10.1136/bmj.d2139.
- ⁷ Jick SS, Hernandez RK. 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. Apr 21;342:d2151. doi: 10.1136/bmj.d2151.
- ⁸ Sidney S, Cheeatham TC, Cooper WO, Connell F. 2011. *Combined Hormonal Contraceptives (CHCs) and the Risk of Cardiovascular Disease Endpoints*. <http://www.fda.gov/Drugs/DrugSafety/ucm277346.htm>
- ⁹ Ouellet-Hellstrom R. 2011. *Review of the FDA-funded Study: Combined Hormonal Contraceptive (CHC) and the Risk of Cardiovascular Disease Endpoints*; October 22, 2011 v2. RCM: 2008-1629; TSI 770. Nov 3, 2011.

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/s/

RITA P OUELLET-HELLSTROM
04/09/2012

TAREK A HAMMAD
04/10/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 022574/S-004

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



NDA 021098/S-022
NDA 021676/S-012
NDA 022532/S-004
NDA 022574/S-004

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Bayer HealthCare Pharmaceuticals Inc.
Attention: Sharon Brown
Director, Global Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Ms. Brown:

We have received your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER	SUPPLEMENT NUMBER	PRODUCT NAME	DATE OF SUBMISSION	DATE OF RECEIPT
021098	022	Yasmin (drospirenone/ethinyl estradiol) tablets	March 8, 2012	March 8, 2012
021676	012	YAZ (drospirenone/ethinyl estradiol tablets)	March 8, 2012	March 8, 2012
022532	004	Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)	March 8, 2012	March 8, 2012
022574	004	Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)	March 8, 2012	March 8, 2012

These supplemental applications propose changes to **Section 5.1 Thromboembolic Disorders and Other Vascular Problems** based on information discussed at the Reproductive Health Drugs Advisory Committee held on December 8, 2011.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on May 7, 2012, in accordance with 21 CFR 314.101(a).

If the applications are filed, the goal date will be September 8, 2012.

NDA 021098/S-022
NDA 021676/S-012
NDA 022532/S-004
NDA 022574/S-004
Page 2

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application numbers listed above at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-3961.

Sincerely,

{See appended electronic signature page}

Pamela Lucarelli
Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

PAMELA LUCARELLI
03/20/2012