CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022574/S-001

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

APPLICATION NUMBER:

NDA 022574/S-001

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	**X**
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022574/S-001

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceuticals Inc.
Attention: Robert J. Haydu
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Haydu:

Please refer to your Supplemental New Drug Application (sNDA) dated April 12, 2011, received April 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets).

We acknowledge receipt of your amendments dated April 27, October 6, 2011 and February 10, 2012.

This "Prior Approval" supplemental new drug application provides for the inclusion of new information regarding the risk of venous thromboembolic events (VTE) in women using combined oral contraceptives (COCs) in WARNINGS AND PRECAUTIONS, subsection Thromboembolic Disorders and Other Vascular Problems. The new information specifically concerns the temporal trend in the increased risk relative to starting a COC or restarting the same or a different COC following temporary discontinuation. The new language in this section (underlined) reads as follows:

> "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."

In addition, this supplement modifies the APPROVED PATIENT LABELING to reflect this new information.

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

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 text for the package insert, 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 this NDA, 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 this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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(s) 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.

REPORTING REQUIREMENTS

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

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

Sincerely,

{See appended electronic signature page}

Christine Nguyen, M.D.
Acting Deputy Director of Safety
Division of Reproductive and Urologic Products
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/

CHRISTINE P NGUYEN
02/13/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

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) 2/2012

----------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)
- 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 (≥ 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: 2/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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.

The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. 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.

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.

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

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.

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.

Epidemiologic studies including a DRSP-containing COC

Several studies have investigated the relative risks of thromboembolism in women using a different DRSP-containing COC (Yasmin, which contains 0.03 mg of EE and 3 mg of DRSP) compared to those in women using COCs containing other progestins. Two prospective cohort studies, both evaluating the risk of venous and arterial thromboembolism and death, were initiated at the time of Yasmin approval.[2, 3] The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in Yasmin users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC). The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in Yasmin users compared to users of other COCs, including those containing levonorgestrel. In the second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed Yasmin.

Two additional epidemiological studies, one case-control study (van Hylckama Vlieg et al.[4]) and one retrospective cohort study (Lidegaard et al.[5]) suggested that the risk of venous thromboembolism occurring in Yasmin users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so-called third generation COCs). In the case-control study, however, the number of Yasmin cases was very small (1.2% of all cases) making the risk estimates unreliable. The relative risk for Yasmin users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the product for 1 to 4 years, the relative risk was similar for users of Yasmin to that for users of other COC products.

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 (≥ 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 (≥ 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.

Interactions 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) 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 (CLcr) of 50–79 mL/min, serum DRSP concentrations were comparable to those in a control group with CLcr ≥ 80 mL/min. In subjects with CLcr 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

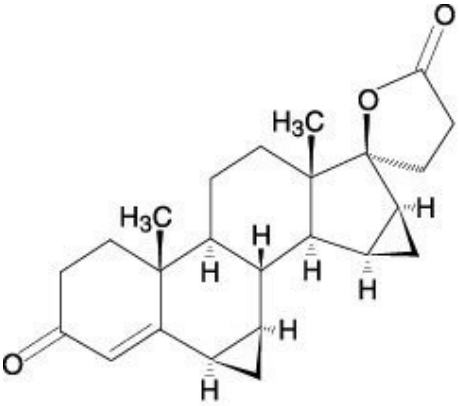
The inactive ingredients in the orange tablets are lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, yellow NF, and ferric 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 $C_{24}H_{30}O_3$.

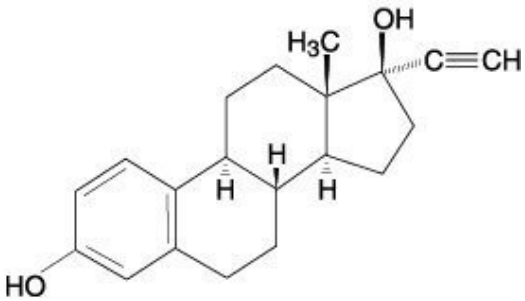
Ethinyl estradiol (19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3,17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

Levomefolate calcium (N-[4-[[(2-amino-1,4,5,6,7,8-hexahydro-5-methyl-4-oxo-(6S)-pteridinyl)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 B_9 and has a molecular weight of 497.5 and a molecular formula of $C_{20}H_{23}CaN_7O_6$

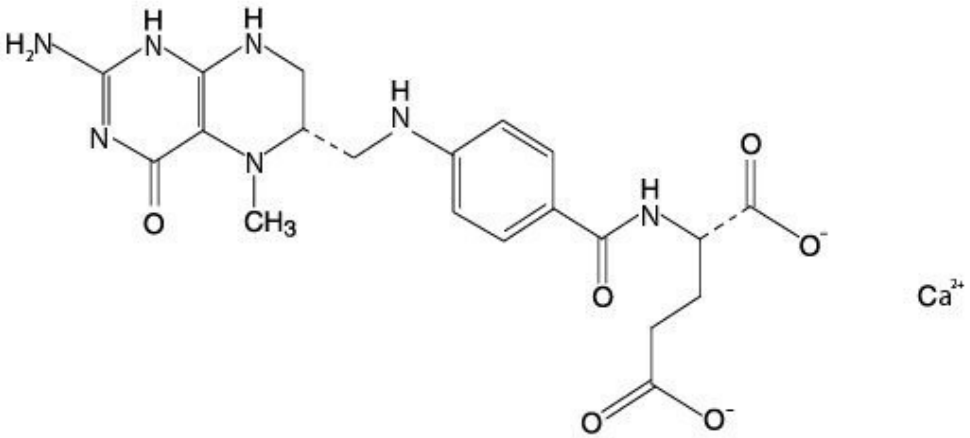
The structural formulas are as follows:



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 1).

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 1).

Levomefolate calcium is structurally identical to L-5-methyltetrahydrofolate (L-5-methyl-THF), a metabolite of vitamin B_9. 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 1: 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 CLcr of 50–79 mL/min were comparable to those in a control group with CLcr ≥ 80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CLcr 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

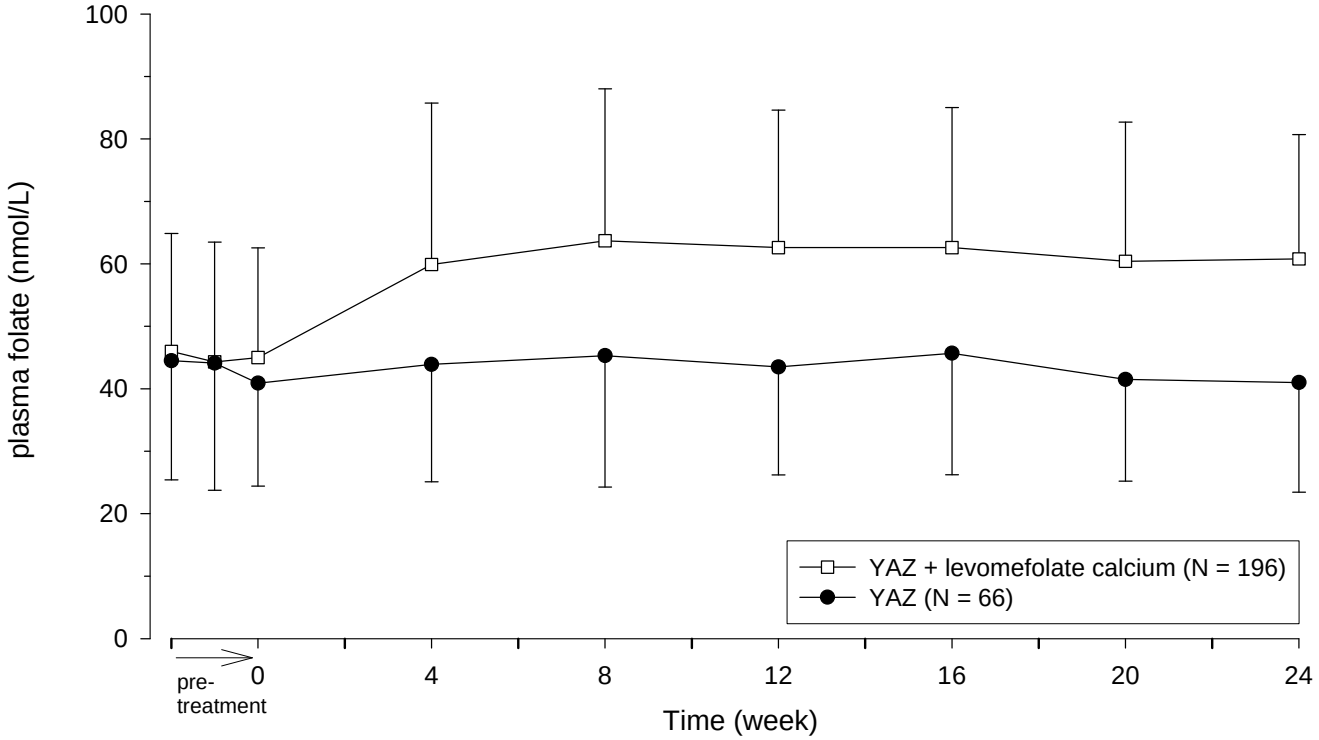
In the clinical efficacy studies of Yasmin (3 mg DRSP/0.03 mg EE) of up to 2 years duration, 2,629 subjects completed 33,160 cycles of use without any other contraception. The mean age of the subjects was 25.5 ± 4.7 years. The age range was 16 to 37 years. The racial demographic was: 83% Caucasian, 1% 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.

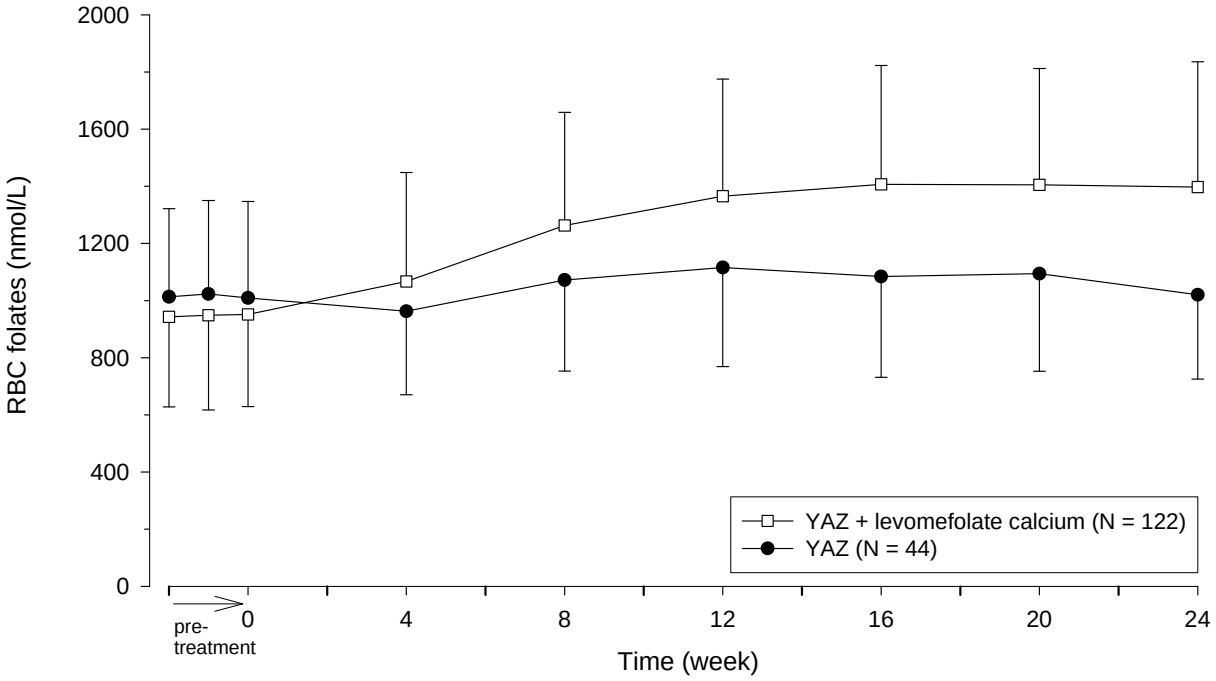
One study was a multicenter, randomized, double-blind, active-controlled, parallel group US study. Plasma folate and red blood cell folate levels were investigated during a 24-week treatment with 3 mg DRSP/0.02 mg EE (YAZ) + 0.451 mg levomefolate calcium as compared to YAZ alone in a U.S. population 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 1: 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.

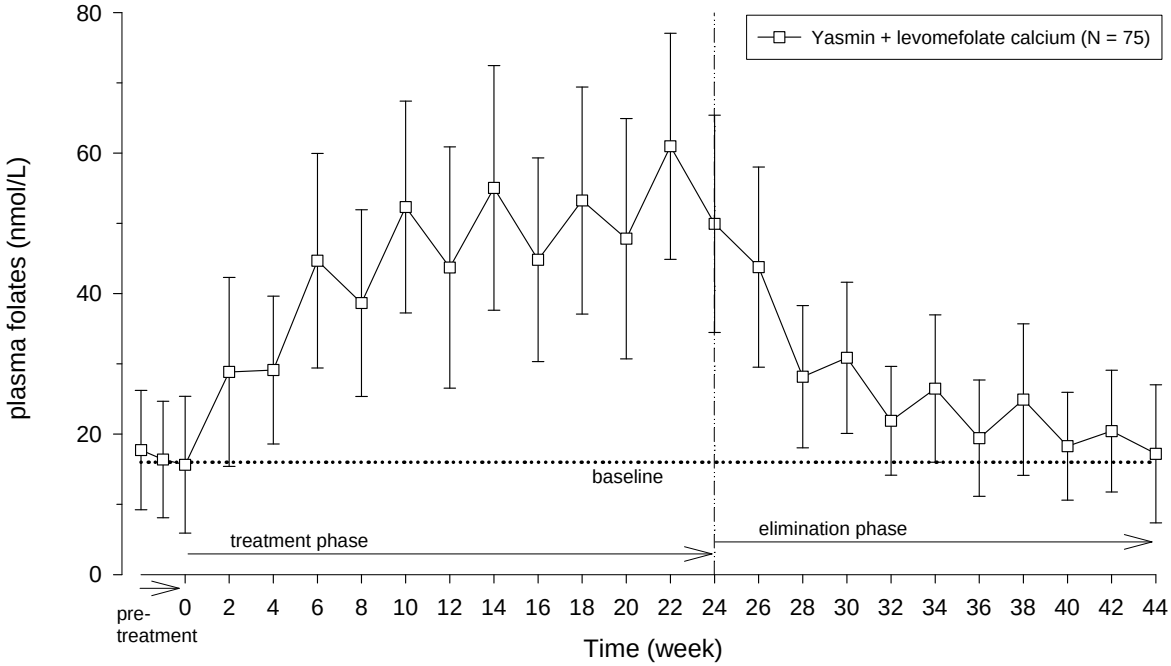
Figure 2: US Study: Mean concentration-time curves (and SD) of RBC folates after daily oral administration of YAZ + levomefolate calcium and YAZ



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.

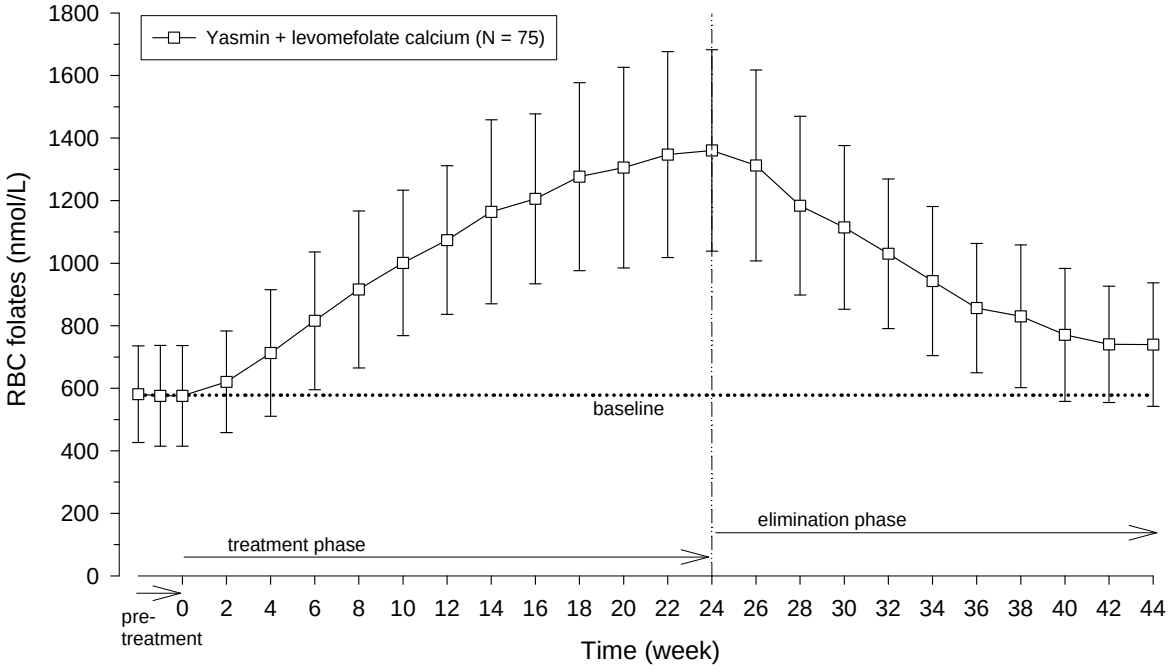
In the second study, the pharmacodynamic effect on plasma folate, RBC folate, and the profile of circulating folate metabolites was assessed during 24 weeks of treatment with 0.451 mg levomefolate calcium or with 0.4 mg folic acid (equimolar dose to 0.451 mg levomefolate calcium), both in combination 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 3: 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 4: 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].

15 REFERENCES

1. US Preventive Services Task Force. Folic Acid for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. Ann Intern Med 2009;150:626-631.

2. Dinger JC, Heinemann LAJ, et al: The safety of a drospirenone-containing oral contraceptive: final results from the European active surveillance study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344-354.

3. Seeger JD, Loughlin J, Eng PM, et al: Risk of thromboembolism in women taking ethinyl estradiol/drospirenone and other oral contraceptives. *Obstetrics & Gynecology* 2007;110(3):587-593.

4. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al: The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921.

5. Lidegaard O, Lokkegaard E, Svendsen AL, et al: Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009; 339:b2890.

6. Centers for Disease Control. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. MMWR 1992;41(No. RR-14).

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 (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 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

Bayer HealthCare Pharmaceuticals Inc.

FDA Approved Patient Labeling
Guide for Using Safyral

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.

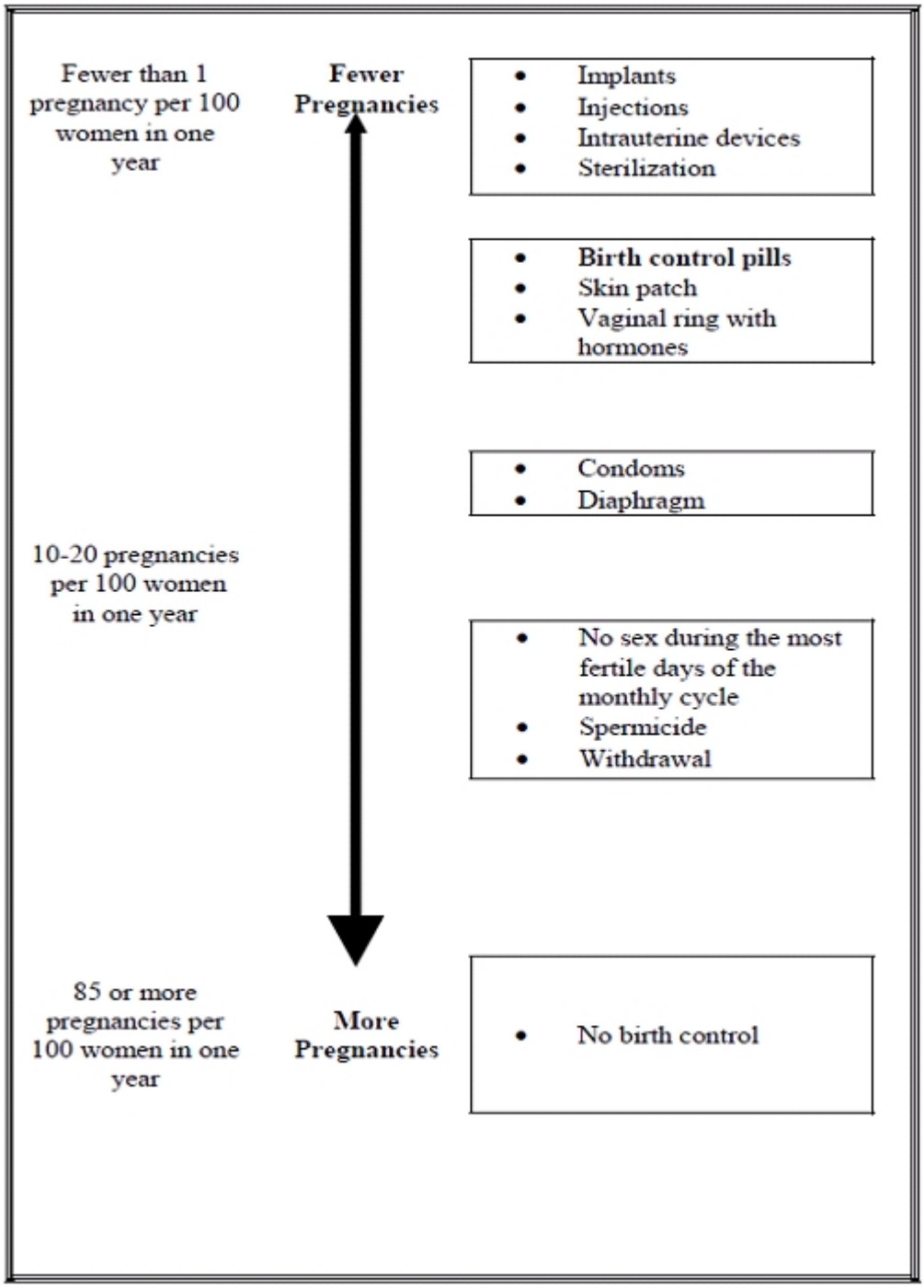
How Well Does Safyral Work?

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.

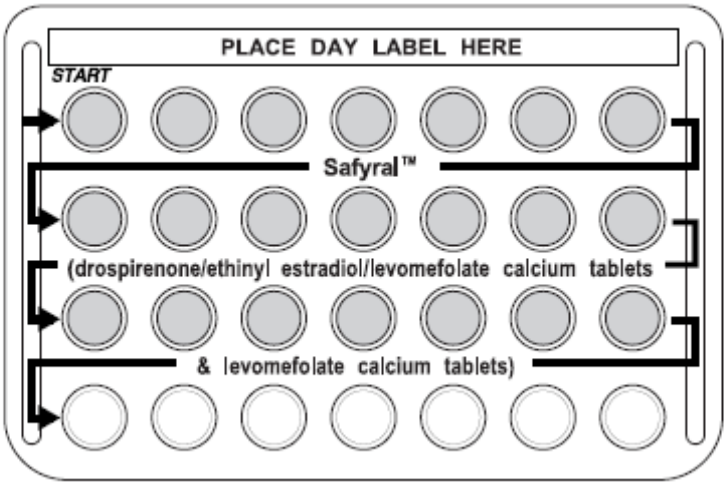
2. Look at Your Pill Pack – It has 28 Pills

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, 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.

It is possible to die 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)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

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 has 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-001

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 13, 2012
From	Christine P. Nguyen, MD
Subject	Acting Deputy Director of Safety Summary
NDA	22574/S001 (SE-8)
Applicant Name	Bayer HealthCare Pharmaceuticals Inc.
Date of Submission	April 13, 2011
PDUFA Goal Date	February 13, 2012
Proprietary Name **Established Names**	Safyral Drospirenone (DRSP)/ethinyl estradiol (EE)/levomefolate (LMF) calcium tablet
Dosage forms/Strengths	Oral tablet once daily Days 1-21: 3 mg DRSP/0.03 mg EE/ 0.451 LMF calcium per tablet Days 22-28: 0.451 mg LMF calcium per tablet
Proposed Indication	*Primary Indication:* prevention of pregnancy *Secondary Indication:* raising folate levels for the purpose of reducing the risk of a neural tube defect
Action	***Approval (see Section 5.1)***

Material Reviewed/Consulted

OND Action Package, including:	Names of Discipline Reviewers
CDTL Review	Lisa Soule, MD (also Clinical Team Lead)
Medical Officer Review	Gerald Willett, MD
Statistical Review:	Sonia Castillo, PhD Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Leslie McKinney, PhD Alexander Jordan, PhD (Lead)
CMC Review	Donna Christner, PhD Thomas Oliver, PhD (Lead)
Clinical Pharmacology Review	Li Li, PhD Chongwoo Yu PhD (Lead)
OSE/Epidemiology Consult	David Moeny, RPh, MPH Fatmatta Kuyateh, MD, MS (Lead)
Study Endpoint and Labeling Development Review	Jeanne Delasko, RN, MS Laurie Burke, RPh, MPH (Lead)

ACTING DEPUTY DIRECTOR OF SAFETY SUMMARY REVIEW

1. EXECUTIVE SUMMARY

The Applicant submitted this Efficacy Supplement (Supplement 001) to NDA 22574 (Safyral) to incorporate in the Prescribing Information new information regarding risks of venous thromboembolic events (VTEs) that was approved in Supplement 008 of NDA 21676 (Yaz). Approved under NDA 22574 in 2010, Safyral is a combination oral contraceptive (COC) that contains 3 mg of drospirenone (DRSP), 0.03 mg ethinyl estradiol (EE), and 0.451mg levomefolate calcium in each active tablet. Safyral contains the same progestin (DRSP) at the same dose (3.0 mg) as Yaz.

Supplement 008 to NDA 21676 (Yaz), which was approved on March 11, 2011, provided for new information regarding the impact of starting, restarting, and duration of current COC use on the relative increased risk of venous thromboembolic events (VTE) in women using COCs in WARNINGS AND PRECAUTIONS, subsection Thromboembolic Disorders and Other Vascular Problems. Data supporting this labeling change came from a large, multinational, European prospective cohort safety study (the European Active Surveillance Study, or EURAS) and interim data from the 5-year

extension of the EURAS Study, known as the Long-Term Active Surveillance Study for Oral Contraceptive (LASS). The EURAS/LASS study evaluated cardiovascular risks associated with COCs containing different progestins, including drosperinone (the progestin component of the COCs Yaz, Beyaz, Yasmin, and Safyral) and dienogest (the progestin component of Natazia). Current labeling for COCs, including Safyral, states that the risk of a VTE associated with the use of a COC is "highest during the first year of use of a COC." Supplement 008 of Yaz expanded upon this statement to indicate that the greatest risk of experiencing a VTE occurs:

- primarily during the first 6 months of COC use
- after starting to use a COC for the first time or after restarting (following a 4-week or greater pill-free interval) the same or a different COC

During the review cycle of this Supplement, the Applicant submitted the final study report of LASS on September 26, 2011, to NDA 21676 (Yaz). In the consult to DRUP signed November 30, 2011, the Division of Epidemiology II in the Office of Surveillance and Epidemiology (OSE/DEPI II) stated that conclusions based on the final LASS study findings remain unchanged from those based on the interim LASS data. Therefore, the approved labeling language for this Supplement, based on the final LASS study findings, is identical in scope and content to that approved in Supplement 008 of Yaz. The labeling revision states that increased risk of VTE for users of COCs, compared to non-users, is greatest in the first six months of COC use, when starting a COC, and when restarting (after a minimum of a 4-week pill free interval) the same or a different COC.

This Supplement did not contain any clinical pharmacology, chemistry, manufacturing and controls, or preclinical toxicology information. All discipline reviewers recommended approval of this Supplement, after the completion of labeling negotiations. I concur with their recommendation for approval.

Comment: The *Applicant has submitted supplements to incorporate the same labeling changes approved in Supplement 008 to NDA 21676 (Yaz) for its other DRSP-containing products (Beyaz and Yasmin) and Natazia, which contains the progestin dienogest that was also evaluated in the EURAS/LASS study. The review of these supplements relied on the same evidence (LASS study) and their approved labeling information is identical to that approved for Safyral and Yaz.*

2. FINAL LASS STUDY REPORT

The primary support for approval of this Supplement is based on data obtained from the Applicant-sponsored EURAS/LASS study. The Clinical Team, in consultation with the Division of Epidemiology II, reviewed the Applicant's final study report entitled *"Long-Term Active Surveillance Study for Oral Contraceptives (LASS) Final Study Report September 13, 2011"* submitted to NDA 21676 (Yaz) on September 26, 2011.

FDA's review of the interim data of the LASS study was previously conducted on the study report entitled "*Long-term Active Surveillance Study for Oral Contraceptives (LASS): VTE Risk and the Impact of Duration of Current OC Use*," submitted in

Supplement 008 to NDA 21676 (Yaz) in February and May, 2010. Detailed review of these interim data could be found in the DRUP Clinical Review, signed March 11, 2011, and OSE Review, signed January 7, 2011.

2.1 Background of the LASS Study

The European Active Surveillance (EURAS) Study was a multinational, prospective, noninterventional cohort study of new users of a COC or switchers to a new COC. The COCs studied included those containing DRSP (Yasmin – DRSP cohort), levonorgestrel (LNG – LNG cohort), or other progestins (other OCs cohort). The study was initiated in November 2000 and completed in December 2005. The primary focus of the study was to assess the occurrence of new cardiovascular events, in particular VTEs and arterial thrombotic events (ATEs). The study was conducted in seven European countries (Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom) and enrolled almost 59,000 women.

The Long-term Active Surveillance Study for Oral Contraceptives (LASS) was a follow up extension study on approximately 48,000 subjects who were still participating in the EURAS study at the end of 2005. No new subjects were enrolled. The objective of LASS was to extend the study period for another 5 years to better define long-term safety outcomes, including cardiovascular and neoplastic events, of OC users. LASS was the first study to examine the effect of switching and restarting therapy after treatment cessation on cardiovascular risk.

2.2 Results of Final LASS Study

The LASS study was completed in December 2010. Overall, the combined database of EURAS and LASS included 381,784 women-years of observation (WY) and 216,038 woman-years of OC exposure. The final LASS study database contained approximately 16% more women-years of exposure and 23% more women-years of observation compared to the interim data reviewed in NDA 21676/S008.

The discussion of the LASS findings is this memo is limited to temporal trend of VTE risks with the use of COCs. The analysis population was "as treated," with subjects classified into three cohorts according to the COC used upon enrollment into EURAS (DRSP, LNG, and "Other OC" users). Approximately 25% of subjects were users of DRSP-containing COC and 13% were users of dienogest-containing COCs. The distribution of users for the different progestins is shown in Table 1.

Table 1: Distribution of Users by Progestin Type

Progestin	Exposure (Women-Years)	Proportion of Total Exposure (%)
1. Drospirenone	52,278	24.2
2. Levonorgestrel	57,539	26.6
3. Other:	106,221	49.2
Desogestrel	29,490	13.7
Dienogest	27,441	12.7
Chlormadinone acetate*	19,498	9.0
Cyproterone acetate*	10,051	4.7
Gestodene*	8,498	3.9
Norgestimate	7,281	3.4
Norethisterone	2,901	1.3
Other	1,062	0.5
TOTAL (1,2,3)	216,038	100

* Not marketed in the US
Note: The Women-years reported in this table are from the as-treated (AT) group which was used as the primary analysis group for the thromboembolic adverse events
Source: Table 1, CDTL review (Lisa Soule, MD), signed 2/13/12

Comment: *The DRSP cohort in the EURAS/LASS study used Yasmin, and not the other more recently approved DRSP-containing COCs, such as Yaz. Yasmin was the first DRSP-containing COC to be approved in Europe in 2000 and the European regulatory authority requested that the EURAS study be conducted as a phase 4 commitment to evaluate the cardiovascular risks of DRSP compared to COCs containing levonorgestrel and other progestins. Safyral is identical to Yasmin with respect to the dose and dosing regimen of DRSP and EE and approved indication, with the only exception being that Safyral also contains levomefolate and has the additional indication of raising folate levels. Therefore, data from the EURAS/LASS study are directly applicable to Safyral.*

The CDTL, Lisa Soule MD, concluded that EURAS/LASS study population was adequately representative of the US population. I concur with this assessment.

The impact starting, restarting, and duration of current COC use based on the interim data of LASS was analyzed in detail by the Applicant and the FDA in NDA 21676/S008 (Yaz). DRUP Division Director's review (Scott Monroe MD) of NDA 21676/S008, signed on March 11, 2011, provided the following conclusions about the OSE's Office of Biostatistics assessment of the interim LASS data:

> *"These findings support a conclusion that (1) women who first start to use a COC are at an increased relative risk during the first 6 months of use and (2) the relative risk of experiencing a VTE is also increased after restarting the same or a different COC after not taking a COC for ≥ 4 weeks."*

The Applicant's analysis of the final LASS study findings, using a slightly larger final

LASS, database showed results that were nearly identical to those of the interim LASS data. See Table 2.

Table 2: Incidence Rate Ratios for the incidence of venous thromboembolism comparing events occurring during the 0-3 months period of use and during 4+ months period; a comparison between the May 2010 LASS report and the final LASS analysis

Patient Group (exposure)	May 2010 LASS analysis Incidence Rate Ratio 0-3 months compared to 4+ months (IRR+ point estimates and 95% CI#)	Final LASS Analysis Incidence Rate Ratio 0-3 months compared to 4+ months (IRR+ point estimates and 95% CI#)
Starters	3.7 [0.9-15.6]	3.0 [0.8-12.5]
Switchers without intake break	1.1 [0.6-2.1]	1.0 [0.6-1.7]
Recurrent users With intake break ≥4 wks *Of which*	1.9 [1.2-2.9]	2.0 [1.4-2.9]
Restarters	2.2 [1.1-4.5]	2.4 [1.4-4.3]
Switchers with intake break ≥4 wks	1.7 [1.0-3.0]	1.8 [1.1-3.0]

Source: Table 6 from OSE/DEPI review (David Moeney, RPh), signed 11/30/11, and submitted to NDA 21676 (Yaz)

Comment: *According to the OSE/DEPI II review, signed on November 30, 2011, of the final LASS study report:*

- *"The LASS study results provide additional evidence that users of drospirenone containing oral contraception may not be at an increased risk of VTE, ATE, or for the cancer outcomes of interest (primarily breast cancer). The results provided examining the period of highest risk for VTE after initiation of OC therapy continue to show the risk is highest in the first 6 months."*
- *"In the duration of use analysis, the selection of any cut-point within the first 6 months of therapy (i.e. start to 5 months compared to over 5 months use) results in an increased risk of VTE at the start of use.* (b) (4) [redacted]

Given that nearly identical point estimates of risk were observed in the analysis of the interim and final LASS datasets, the Clinical Team did not request additional Biostatistics consult and did not recommend any alteration to the language approved for NDA (b) (4) */S008 (Yaz), with the exception of removing the term "interim" when describing the LASS data. I concur with the assessments of the Clinical Team.*

3. RECOMMENDATIONS OF REVIEW DISCIPLINES

3.1 Clinical

The primary Clinical Reviewer, Gerald Willett MD, stated the following in his review, signed January 23, 2012:

> *"Approval of Safyral (NDA 22-574) Supplement 01 is recommended pending acceptable labeling."*

In the addendum, signed February 13, 2012, Dr. Willet stated that the final agreed-upon labeling was acceptable.

The Cross Discipline Team Leader, Lisa Soule MD, [who was also the Clinical Team Leader], stated the following in her review, signed February 13, 2012:

> *"I recommend approval of this efficacy supplement because acceptable labeling has been agreed upon with the Applicant.*
>
> (b) (5)
> 

Comment: *I concur with the recommendations of Drs. Willet and Soule that this Supplement be approved.*

3.2 Statistics

No new statistical data were submitted in this Supplement. The primary Statistical Reviewer, Sonia Castillo PhD, recommended the following in her review, signed July 27, 2011:

> *"There are no new changes to the efficacy section of the labeling. There are no statistical issues related to efficacy that would preclude approval*."

3.3 Clinical Pharmacology

No new clinical pharmacology data were submitted in this Supplement. The primary Clinical Pharmacology Reviewer, Li Li, Ph.D., reviewed the revisions to labeling and recommended the following in her review signed January 13, 2012:

> *"The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 finds this submission to NDA 022574 to be acceptable from the Clinical Pharmacology standpoint."*

In the addendum, signed February 13, 2012, Dr. Li stated that the final agreed-upon labeling was acceptable.

3.4 Nonclinical Pharmacology/toxicology

This Supplement did not include any nonclinical pharmacology/toxicology information. The primary Pharmacology/toxicology Reviewer, Leslie McKinney PhD, recommends approval of this Supplement from a pharmacology/toxicology perspective in her review, signed on January 12, 2012.

3.5 Chemistry, Manufacturing and Controls (CMC)

This Supplement did not include any chemistry, manufacturing and controls information. The primary CMC Reviewer, Donna Christner PhD, recommended approval of this Supplement from a CMC perspective in her review, signed April 26, 2011.

3.6 Study Endpoint and Labeling Development

The primary SEALD reviewer, Jeanne Delasko RN, recommended approval of the final agreed-upon labeling for Safyral in her review, signed February 13, 2012.

4. LABELING

The Applicant's proposed label was submitted in PLR format.

The specific wording for the new information regarding the relative increased risk of VTEs in women using COCs that will be included under **WARNINGS AND PRECAUTIONS**, subsection **Thromboembolic Disorders and Other Vascular Problems** was based on the approved language for Yaz in Supplement 008, with a minor modification to indicate that the information is based on the final, and not interim, data of LASS. The new information in the Beyaz labeling will read as follows (underlined text indicates addition):

> "….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."

Minor changes to Safyral labeling included in this Supplement involved sections related to clinical pharmacology and patient counseling information.

Final Physician and Patient Labeling submitted by the Applicant on February 10, 2012, was reviewed by all disciplines that had not previously approved earlier versions of labeling and was found to be acceptable.

5. DECISION/ACTION/RISK BENEFIT ASSESSMENT

5.1 Regulatory Action

This Supplement will be approved because acceptable Physician and Patient Labeling have been satisfactorily negotiated with the Applicant. The evidence contained in the Applicant's report entitled "Long- term Active Surveillance Study for Oral Contraceptives (LASS): VTE Risk and the Impact of Duration of Current OC Use" and the Applicant's report "Long-term Active Surveillance Study for Oral Contraceptive (LASS) Final Study

Report September 13, 2011" support the final labeling change in **WARNINGS AND PRECAUTIONS**, subsection **Thromboembolic Disorders and Other Vascular Problems**.

5.2 Risk/Benefit Assessment

The most important new information in this Supplement concerns the finding that the relative risk of a woman experiencing a venous thromboembolic event is increased when she restarts the same COC or switches to a new COC after not having used a COC for at least 4 weeks. This finding, based data from the EURAS/LASS study, appears to apply to COCs in general and not to a specific COC. Another safety finding reported in this Supplement is that the relative increased risk of a woman experiencing a venous thromboembolic event during the first year of use of a COC is greatest during the first 6 months of use. Thereafter, the risk appears to be relatively stable, although the risk remains increased while on treatment compared to the risk in a woman not using a COC. This latter safety information has already been taken into consideration in the approval of Safyral.

The overall risk/benefit profile for Safyral remains favorable. The benefits of Safyral remain unchanged from initial approval and the new information to clarify the temporal trend of the greatest increased risk of VTE appears to apply to the COCs evaluated and not unique to DRSP-containing COCs.

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

/s/

CHRISTINE P NGUYEN
02/13/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 13, 2012
From	Lisa M. Soule, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	22-574; SE-8 (Supplement # 1)
Applicant	Bayer Healthcare Pharmaceuticals
Date of Submission	April 12, 2011
PDUFA Goal Date	February 12, 2012
Proprietary Name / Established (USAN) names	Safyral Drospirenone (DRSP)/ethinyl estradiol (EE) /levomefolate calcium (LMF) tablets and LMF tablets
Dosage forms / Strength	Tablets: 28 day cycle of 3 mg DRSP/30 µg EE/0.451 mg LMF for 21 days, followed by 0.451 mg LMF for 7 days
Proposed Indication(s)	**Primary:** Prevention of pregnancy **Secondary:** 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
Recommended:	***Approval***

1. Introduction

This efficacy supplement seeks to modify labeling language regarding the risk of venous thromboembolic events (VTEs) associated with use of combined oral contraceptives (COCs). The drug product covered by this NDA is Safyral, a contraceptive containing 30 µg of ethinyl estradiol (EE), 3 mg of the progestin drospirenone (DRSP) and 0.451 mg of levomefolate calcium, which is administered in a 21/7 dosing regimen (21 days of the active combined tablets, followed by 7 days of LMF tablets). Aside from the LMF component, added to provide folate supplementation, Safyral is identical to Yasmin, the first DRSP-containing COC approved in the US.

Since the 2001 launch of Yasmin, the Applicant has conducted a large multinational (European) observational postmarketing safety study to evaluate the risk of relatively rare adverse outcomes, including VTEs and cardiovascular events, in users of Yasmin as compared to users of other COCs. This study, known as the European Active Surveillance Study (EURAS), was completed in late 2005, and was then extended in order to obtain additional long-term follow-up of the cohort of COC users for up to five more years. This extension is known as the Long Term Active Surveillance Study of Oral Contraceptives (LASS).

The Applicant has conducted an analysis of the LASS database to evaluate temporal trends in the VTE risk associated with use of COCs, including alterations in risk that occur following

temporary discontinuation and then resumption of oral hormonal contraception. On the basis of this analysis, the Applicant proposed revised labeling to indicate that

- the greatest risk of VTE associated with COC use is present after initially starting or after resuming use of the same or a different COC following a break of at least four weeks
- the greatest increase in risk relative to non-COC users is observed in the first three months of use

The Division approved this revised language for YAZ in March 2011. The Applicant has now submitted similar supplements to support the same labeling revision for its other DRSP products, Beyaz, Safyral and Yasmin, as well as for Natazia, a COC containing the progestin dienogest, which was also studied in EURAS.

2. Background

2.1 DESCRIPTION OF PRODUCT

EE and DRSP have been combined in COCs since 2001. They are found in three approved COC products in addition to Safyral: Yasmin, which contains 3 mg of DRSP and 30 µg of EE administered in a 21/7 regimen; YAZ, which contains 3 mg of DRSP and 20 µg of EE administered in a 24/4 regimen; and Beyaz, which is identical to YAZ with the addition of 0.451 mg levomefolate for folate supplementation. Safyral was approved in December 2010.

As for other COCs, the risk of arterial thrombotic (ATEs) and venous thromboembolic events (VTEs) are among the most significant safety concerns. However, as pregnancy itself is associated with even higher rates of VTEs, the risk-benefit profile of COCs for prevention of pregnancy is considered favorable. A safety issue unique to DRSP-containing COCs is that of the potential risk of hyperkalemia. DRSP has antimineralocorticoid activity, and has the potential to increase serum potassium levels, particularly in women with impaired renal function and women on other medications that may increase serum potassium. However, in postmarketing surveillance, this has not been demonstrated to be a notable safety concern. Yasmin, YAZ, Safyral and Beyaz are contraindicated in women with renal impairment, and there are labeled warnings about the potential for hyperkalemia.

2.2 REGULATORY HISTORY

COC labeling has historically included as class labeling a Warning related to the risk of VTEs associated with use of combined hormonal contraceptives. The discussion in non-PLR COC labels includes the following

> *An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease*

due to oral contraceptives is not related to length of use and disappears after Pill use is stopped.

By the time PLR labeling was implemented, the Office of Surveillance and Epidemiology (OSE) and the Division had reviewed additional literature and determined that there was an effect of duration of use, in that the excess risk of VTE in COC users compared to non-users appears to be greatest in the first year of use. In PLR COC labels, the section states

Although the use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. 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. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

As noted, the Division approved revised VTE language that reflected the LASS findings for the YAZ PLR label in 2011; the same language is now proposed for Safyral, as well as for the other DRSP-containing COCs, Yasmin and Beyaz.

During the course of this review cycle, the Applicant submitted the final study report on September 26, 2011. The clinical review is based on the final report.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Dr. Gerald Willett, stated in his review, dated January 23, 2012:

Approval of Safyral (NDA 22-574) Supplement 01 is recommended pending acceptable labeling.

Team Leader Comment:
I concur with Dr. Willett's recommendation for approval of this efficacy supplement.

Dr. Willett entered an addendum to his review on February 13, 2012, stating

This reviewer finds the final labeling (submitted 2-10-12) related to Supplement 001 for NDA 22-574 (Safyral) to be acceptable.

3. CMC/Device

No new chemistry, manufacturing and controls data were submitted in this applicant. The Chemistry reviewer, Donna Christner, Ph.D., noted that no changes had been made to CMC portions of labeling and made the following recommendation in her review dated April 26, 2011:

This Supplement is recommended for approval from CMC perspective.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in this application. The primary Toxicology reviewer, Leslie McKinney, Ph.D., reviewed the labeling and made the following

recommendation in her review dated January 12, 2012:

***Regulatory action**: The final label is acceptable.*

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology data were submitted in this application; however, minor revisions to the clinical pharmacology sections of the label were proposed by the Applicant. The primary Clinical Pharmacology reviewer, Li Li, Ph.D., reviewed the revisions to labeling, and made the following recommendations in her review dated January 13, 2012:

The Office of Clinical Pharmacology (OCP)/ Division of Clinical Pharmacology 3 finds this submission to NDA 022574 to be acceptable from the Clinical Pharmacology standpoint.

Dr. Li made several comments on labeling, which were conveyed to the Applicant. She noted that revised labeling submitted by the Applicant was acceptable, and concluded in an addendum dated February 13, 2012:

The DCP3, OCP finds NDA 022574 acceptable from the Clinical Pharmacology perspective.

No phase 4 commitments were recommended.

6. Clinical Microbiology

Clinical microbiology consultation was not requested for this application, as no changes were made to the approved formulation of the product.

7. Clinical/Statistical - Efficacy

No clinical efficacy data were submitted in this NDA.

8. Safety

This review is based on data from LASS, a five-year follow-up extension of the EURAS study, which previously ran for five years. The EURAS cohort consisted of almost 59,000 women who used Yasmin, levonorgestrel (LNG)-containing COCs or COCs with other progestins. The LASS dataset includes about 48,000 women who remained under observation (81% of the original population). LASS and EURAS together provide a total of 318,784 women-years of observation and 216,038 women-years of exposure (52,278 to Yasmin, 57,739 to LNG, and 106,221 to other COCs). Of this total, 176,309 women-years of observation came from the LASS extension, and 142,475 from the original EURAS study; 103,379 women-years of exposure came from LASS and 112,659 from EURAS.

Team Leader Comment:

The interim study report for LASS reviewed when the YAZ labeling revision was submitted included a total of 259,696 women-years of observation and 186,278 women-years of exposure. Thus, the final study report represents about a 16% increase in women-years of exposure and a 23% increase in women-years of observation compared to the interim data previously reviewed.

The Applicant obtained information from participants about body mass index, duration of COC use, hypertension and family history of VTE/ATE, and controlled for these covariates in the analysis. The analysis population was "as treated," with subjects classified according to the COC used upon entry into EURAS. Subjects were categorized into one of four use cohorts: Yasmin users, users of LNG-containing COCs, users of COCs containing other progestins (which included desogestrel, dienogest, norgestimate and norethindrone, along with a few other progestins not available in the US), and non-oral hormonal contraceptive users. The distribution of users by progestin is provided in Table 1.

Table 1 Distribution of Users by Progestin Type

Progestin	Exposure (Women-Years)	Proportion of Total Exposure (%)
1. Drospirenone	52,278	24.2
2. Levonorgestrel	57,539	26.6
3. Other:	106,221	49.2
Desogestrel	29,490	13.7
Dienogest	27,441	12.7
Chlormadinone acetate*	19,498	9.0
Cyproterone acetate*	10,051	4.7
Gestodene*	8,498	3.9
Norgestimate	7,281	3.4
Norethisterone	2,901	1.3
Other	1,062	0.5
TOTAL (1,2,3)	216,038	100

* Not marketed in the US
Note: The Women-years reported in this table are from the as-treated (AT) group which was used as the primary analysis group for the thromboembolic adverse events
Source: Table 4, Primary Medical Review by Gerald Willett, MD, dated January 23, 2012

Team Leader Comment:
Although LASS is based entirely on European data, I believe the findings remain relevant to the US population. The majority of products evaluated are available in the US market; a few products not approved in the US were included in the "other" category, but are unlikely to have a marked impact on the results.

Overall, the adjusted hazard ratios for VTE incidence in Yasmin users were 1.1 compared to LNG-containing COC users, and 0.7 compared to users of other progestin-containing COCs. The confidence intervals around both point estimates included 1, indicating no significant difference in VTE risk between the user cohorts.

The Applicant then looked at Restarters (women who resumed use of the same COC after a break of at least four weeks) and Switchers (women who switched to a different COC; this was further subdivided into those who switched after a break of at least four weeks and those who switched with no break in COC use). The analysis was based on 253 confirmed VTEs that occurred during use of COCs.

The rates reported by the Applicant by exposure class and duration of use are shown in Table 2.

Table 2 Risk of VTE by Exposure Class and Duration of Use (All Hormonal Contraceptives)

Patient Group (exposure)	0-3 Months (VTE per 10,000 WY; point estimates and 95% CI#)	4+ Months (VTE per 10,000 WY; point estimates and 95% CI#)	Incidence Rate Ratio (IRR+ point estimates and 95% CI#)
Starters	11.1 [2.3-32.4]	3.7 [1.4-8.0]	3.0 [0.8-12.5
Switchers without intake break	12.5 [7.0-20.6]	12.5 [10.0-15.5]	1.0 [0.6-1.7]
Recurrent users With intake break ≥4 wks *Of which*	23.9 [16.8-32.9]	11.8 [9.6-14.3]	2.0 [1.4-2.9]
Restarters	28.7 [16.4-46.6]	11.9 [8.7-16.0]	2.4 [1.4-4.3]
Switchers with intake break ≥4 wks	21.1 [13.1-32.3]	11.7 [8.9-15.1]	1.8 [1.1-3.0]

* VTE = Venous Thromboembolism; # 95% CI = 95% Confidence Interval; + IRR= Incidence Rate Ratio

Source: NDA 21-676, Final LASS Study Report submitted September 26, 2011, Table 30, p 55

8.1 Biometrics Consultation and Recommendation

Eric Frimpong, Ph.D., of the Division of Biometrics 7, conducted the statistical review of the interim data provided from the LASS per a consult request from OSE. He reached the following conclusion in his review dated November 15, 2010:

The analysis in the LASS provided by the sponsor (b) (4) [redacted] *verall the study showed the elevated VTE risk associated with the first year of use was more pronounced within the first 6 months. Risk patterns among the OC classes and the exposure subgroups do not show notable differences.*

Team Leader Comment:
Additional details of Dr. Frimpong's analysis are provided in his original review and in the CDTL review of NDA 21-676 dated March 11, 2011.

8.2 OSE Consultation and Recommendation

David Moeny, MPH, RPh, of OSE reviewed the final LASS study report and made the following conclusions and recommendations in his review dated November 2, 2011:

The LASS study results provide additional evidence that users of drospirenone containing oral contraception may not be at an increased risk of VTE, ATE, or for the cancer outcomes of interest (primarily breast cancer). The results provided examining the period

of highest risk for VTE after initiation of OC therapy continue to show the risk is highest in the first 6 months. However the strength of this conclusion is limited by a number of weaknesses in the final report.

Limitations noted in the review include:

- Follow-up of only 80% of original EURAS participants
- Lack of information on demographics and baseline characteristics for the cohort that continued into LASS
- [redacted] (b) (4)

Mr. Moeny's review further noted that:

The conclusions from the previous OSE review remain valid in the light of these updated results: [redacted] (b) (4)

The OSE review provided a table comparing the data from the interim LASS study report to that in the final study report (Table 3).

Table 3 Incidence Rate Ratios for VTE: Interim and Final LASS Results (All Hormonal Contraceptives)

Patient Group (exposure)	May 2010 LASS analysis Incidence Rate Ratio 0-3 months compared to 4+ months (IRR+ point estimates and 95% CI#)	Final LASS Analysis Incidence Rate Ratio 0-3 months compared to 4+ months (IRR+ point estimates and 95% CI#)
Starters	3.7 [0.9-15.6]	3.0 [0.8-12.5]
Switchers without intake break	1.1 [0.6-2.1]	1.0 [0.6-1.7]
Recurrent users With intake break ≥4 wks	1.9 [1.2-2.9]	2.0 [1.4-2.9]
Of which		
Restarters	2.2 [1.1-4.5]	2.4 [1.4-4.3]
Switchers with intake break ≥4 wks	1.7 [1.0-3.0]	1.8 [1.1-3.0]

Source: Table 6, OSE Review by Dave Moeny, MPH, RPh, dated November 2, 2011

Team Leader Comments:

- **The point estimates and confidence intervals do not change in any meaningful way with the additional data accrued between the interim and final study reports. For this reason, an additional Biometrics consult was not requested for this NDA submission, and the clinical reviewers do not recommend any alteration to the language approved for YAZ beyond removing the word "interim."**

- **The OSE epidemiology reviewers were involved with the review and revision of the YAZ label proposed by the Applicant, and were in agreement with the Division's proposal to label that the increased risk is greatest within the first six months of use.**

8.3 Postmarketing Safety Findings

Periodic Adverse Drug Experience Reports (PADERs) covering the period from December 2010 through September 2011 for Safyral were reviewed by Dr. Willett. He concluded that there was no significant change in the safety profile for Safyral from the time of approval, and no findings that would impact the labeling changes related to LASS data addressed in this submission.

During this review cycle, the Division convened a joint Advisory Committee meeting on December 8, 2011 to consider conflicting data regarding an increased risk of VTE for DRSP-containing COCs (primarily from studies limited to Yasmin) as compared to COCs that contain other progestins. While the Committee agreed there was some evidence of an increased relative risk of VTE, the majority of members believed that the risk/benefit profile of these products remains favorable. Labeling revisions to address the results of the studies discussed at this Advisory Committee meeting are in preparation for the four DRSP-containing products, and are being handled separately from this supplement.

8.4 Safety Update

No specific safety update was submitted during this review cycle; as discussed in the preceding section, the Division reviewed all relevant PADERs and publications that related to VTE risk for DRSP-containing COCs.

8.5 Overall Assessment of Safety Findings

This efficacy supplement primarily addresses the temporal trends in the increased risk of VTE associated with use of COCs. The extended follow-up provided in LASS, consistent with the findings of EURAS, does not suggest any increased risk of VTE for DRSP-containing contraceptives as compared to COCs that contain different progestins.

The fact that COC users have an increased risk of VTE compared to non-users has been known and described in labeling for years, as has the fact that the increased risk is greatest in the first year of use. (b) (4) Rather, it appears that risk is variable, but remains particularly elevated for at least the first six months of use, stabilizing thereafter.

Of particular value in this analysis is the evaluation of VTE risk by exposure status, classifying COC users as new Starters, Switchers (with or without a break in COC use) or Restarters (following a break in use). The finding that VTE risk is elevated not only in new users, but also in women who resume use following a break of four weeks or greater, is new and important safety information that should be described in labeling.

9. Advisory Committee Meeting

The Division determined that an Advisory Committee was not needed to review this efficacy supplement. As discussed in Section 8.3, an Advisory Committee was convened in December 2011 to discuss other aspects of the VTE risk attributable to DRSP-containing COCs.

10. Pediatrics

Review by the Pediatric Review Committee (PeRC) was not needed for this efficacy supplement, as no changes in indication or population were proposed.

11. Other Relevant Regulatory Issues

No DSI inspection was requested for the LASS; the study was conducted through a network of over 1100 European physicians.

12. Labeling

The Safyral label is already in PLR format; changes in labeling were focused on Section 5.1 of Warnings and Precautions. The labeling in that section is identical to that approved for YAZ, with deletion of the word "interim" in describing the LASS findings.

Agreement with the Applicant on labeling was reached on February 10, 2012. The agreed-upon labeling with respect to VTEs is

> *The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism 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.*

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend approval of this efficacy supplement because acceptable labeling has been agreed upon with the Applicant.

The Division will need to consider whether this labeling should be extended to all COCs currently marketed. Some of the most widely used progestin components in US-marketed COCs were minimally represented in the EURAS/LASS dataset. Therefore, I do not recommend that the labeling revisions approved here for DRSP-containing COCs should be required in all currently marketed COCs. (b) (5) [redacted]

13.2 Risk Benefit Assessment

The risk/benefit profile for the DRSP-containing COCs used for prevention of pregnancy and various additional, secondary, indications has been determined to be acceptable on the basis of previous NDA reviews, formal postmarketing surveillance, a recent Advisory Committee and experience in millions of women over a number of years. This is also true for the overall risk/benefit profile for combination hormonal contraceptives generally. I do not find that the data in this supplement changes that overall assessment. However, I do believe the new information, in particular that relating to the increase in VTE risk noted upon resumption of COC use following a break of four weeks or longer, to be important new information that should be clearly conveyed in labeling for these DRSP-containing COCs.

13.3 Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk management activities beyond labeling are recommended.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

No postmarketing studies are recommended.

13.5 Recommended Comments to Applicant

None

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

/s/

LISA M SOULE
02/13/2012

CHRISTINE P NGUYEN
02/13/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Application Type	NDA (Supplement)
Application No.	22-574
Supplement No.	S-001
Priority or Standard	Standard
Submit Date	April 12, 2011
PDUFA Goal Date	February 13, 2012
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Gerald Willett M.D.
Addendum Date	February 13, 2012
Established Name	Drospirenone (DRSP) /Ethinyl estradiol (EE) /levomefolate calcium (LMF) tablets and levomefolate calcium tablets
Trade Name	Safyral
Therapeutic Class	Oral contraceptive (OC)
Applicant	Bayer HealthCare Pharmaceuticals Inc
Formulation	Oral tablets
Dosing Regimen - Cycle Days (dose)	Days 1-21 (DRSP 3 mg/EE 0.03 mg/ LMF 0.451 mg) Days 22-28 (LMF 0.451 mg)
Primary Indication	Contraception
Secondary Indication	Raise folate levels
Intended Population	Women of childbearing age

Addendum

This reviewer finds the final labeling (submitted 2-10-12) related to Supplement 001 for NDA 22-574 (Safyral) to be acceptable.

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

/s/

GERALD D WILLETT
02/13/2012

LISA M SOULE
02/13/2012
I concur with Dr. Willett's conclusion and recommendation for approval

CLINICAL REVIEW

Application Type	NDA (Supplement)
Application No.	22-574
Supplement No.	S-001
Priority or Standard	Standard
Submit Date	April 12, 2011
PDUFA Goal Date	February 13, 2012
Division / Office	Division of Reproductive and Urologic Products (DRUP) / Office of Drug Evaluation III (ODE III)
Reviewer Name	Gerald Willett M.D.
Review Completion Date	January 11, 2012
Established Name	Drospirenone (DRSP) /Ethinyl estradiol (EE) /levomefolate calcium (LMF) tablets and levomefolate calcium tablets
Trade Name	Safyral
Therapeutic Class	Oral contraceptive (OC)
Applicant	Bayer HealthCare Pharmaceuticals Inc
Formulation	Oral tablets
Dosing Regimen - Cycle Days (dose)	Days 1-21 (DRSP 3 mg/EE 0.03 mg/ LMF 0.451 mg) Days 22-28 (LMF 0.451 mg)
Primary Indication	Contraception
Secondary Indication	Raise folate levels
Intended Population	Women of childbearing age

Table of Contents

Table of Tables

List of Abbreviations

AE	Adverse event
AMI	Acute myocardial infarction
BMI	Body mass index
CI	Confidence interval
CMC	Chemistry, Manufacturing and Controls
COC	Combination oral contraceptive
CHF	Congestive heart failure
CT	Computed tomography
CVA	Cerebrovascular accident
DRUP	Division of Reproductive and Urologic Products
DRSP	Drospirenone
DVT	Deep venous thrombosis
ECG	Electrocardiogram
EE	Ethinyl estradiol
EURAS	European Active Surveillance
FDA	Food and Drug Administration
INAS	International Active Surveillance
IND	Investigational New Drug (application)
IRB	Institutional review board
LASS	Long-Term Active Surveillance Study
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NDA	New Drug Application
OB	Office of Biostatistics
OC	Oral contraceptive
ODE III	Office of Drug Evaluation III
OSE	Office of Surveillance and Epidemiology
PADER	Periodic adverse drug experience report
PE	Pulmonary embolism
PMDD	Premenstrual dysphoric disorder
PSUR	Periodic safety update report
SAE	Serious adverse event
SD	Standard deviation
VTE	Venous thromboembolism
WY	Women-years

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval of Safyral (NDA 22-574) Supplement 01 is recommended pending acceptable labeling.

1.2 Risk Benefit Assessment

In this supplement, the Applicant is seeking to add new information regarding the risk of venous thromboembolic events to the labeling for Safyral. This information is identical to that recently added to the YAZ (NDA 21-676) label (approved March 11, 2011), aside from removing the descriptor “interim” in characterizing the data to reflect the issuance of the final report of the study supporting this change.

This new information specifically focuses on the risk of VTE based on duration of use and also on risk with resumption of COC use following a break of 4 weeks or greater. The data supporting this addition to the label are derived from a 5-year extension of a large European postmarketing study called the European Active Surveillance (EURAS) study. The extension phase is separately called the Long-Term Active Surveillance Study (LASS).

The EURAS study (a postmarketing study initiated in Europe) originally focused on the safety of the first drospirenone-containing COC (brand name Yasmin) compared to levonorgestrel-containing COCs and other COCs. In EURAS 58,674 women were followed for 142,475 women-years (WY) of observation. The overall findings of EURAS indicated that cardiovascular risks were similar for drospirenone-containing COCs compared to levonorgestrel-containing OCs and other COCs.

With the LASS extension of the EURAS study, the Applicant had sufficient data available to focus on VTE risk related to duration of use within the first year of use and the risk of starting the same or a different COC after a 4 week or greater pill-free interval. Based on this LASS data, the YAZ label now contains information indicating that the VTE risk is highest in the first 6 months of COC use and that there is an increased VTE risk after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC.

Review of this supplemental information for the YAZ label was performed not only by the Division of Reproductive and Urologic Products (DRUP), but also by the Office of Surveillance and Epidemiology (OSE) and by the Office of

Biostatistics (OB). OSE and OB analyzed the interim LASS data (b) (4) [redacted] OSE and OB concurred with the Applicant's labeling in regard to the increased VTE risk after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC.

These data (although not derived from a study that specifically evaluated Safyral) are applicable to the Safyral label because they are from a study that evaluated Yasmin (a DRSP-containing COC with the same hormonal components as Safyral).

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for postmarketing risk evaluation or mitigation strategies based on this submission.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no additional recommendations for postmarketing requirements or commitments base on this submission. A prior postmarketing commitment for drospirenone-containing COCs with folate (called INAS-FOCUS) is ongoing.

2 Introduction and Regulatory Background

2.1 Product Information

Safyral is a combination oral contraceptive (COC) that contains 0.03 mg of ethinyl estradiol and 3 mg of drospirenone as the active contraceptive hormones. Safyral also contains levomefolate that is designed to raise folate levels in the women taking this product. Safyral is designed to be taken daily for 21 days, similar to Yasmin.

Ethinyl estradiol is the estrogen found in nearly all COCs. The progestin drospirenone is found in 4 originator COC products (Yasmin, YAZ, Beyaz and Safyral) as well as some generic products. Drospirenone has antimineralocorticoid properties, like spironolactone. There is a theoretical safety risk of hyperkalemia with drospirenone. This has not proven to be of significant clinical concern based on the clinical studies and postmarketing safety analyses to date, but it is listed as a warning in the product labels.

Safyral carries the same primary indication(contraception) as Yasmin. It additionally carries the secondary indication of raising folate due to its levomefolate component.

2.2 Currently Available Treatments for Proposed Indication

Contraceptive methods for females include:

- Barrier methods (condom, diaphragm, cervical cap)
- COCs
- Progestin-only oral contraceptives
- Intrauterine devices (levonorgestrel-containing and copper-containing)
- Injectable contraceptives
- Contraceptive implants
- Contraceptive vaginal rings
- Surgical sterilization (tubal ligation, intratubal obstructive devices)

Approved COCs (originators and generics) containing DRSP and EE include the following dosage combinations:

- Yasmin = drospirenone 3 mg / ethinyl estradiol 0.03 mg – 21 days active, 7 days placebo [Generics = Barr (ANDA 77527) and Watson (ANDA 90081)]
- YAZ = drospirenone 3 mg / ethinyl estradiol 0.02 mg – 24 days active, 4 days placebo [Generic = Barr (ANDA 78515)]
- Beyaz = drospirenone 3 mg / ethinyl estradiol 0.02 mg / levomefolate calcium 0.451 mg– 24 days, levomefolate calcium 0.451 mg – 4 days
- Safyral = drospirenone 3 mg / ethinyl estradiol 0.03 mg / levomefolate calcium 0.451 mg – 21 days, levomefolate calcium 0.451 mg – 7 days

2.3 Availability of Proposed Active Ingredients in the United States

Ethinyl estradiol is used in nearly all combination oral contraceptives in the US. One exception is the recently approved Natazia product that incorporates estradiol valerate as the estrogenic component. Drospirenone is found in the products listed in Section 2.2; it has been marketed in the US since 2001.

2.4 Important Safety Issues with Consideration to Related Drugs

COCs as a general class have a number of safety issues that have been well recognized since their introduction in the 1960s. The following adverse events represent the major concerns described in contraceptive labeling:

- Vascular events, which may rarely be fatal, including:

    - Deep venous thrombosis, pulmonary embolism, other venous thromboses
    - Myocardial infarction (especially in women >35 years who smoke)
    - Stroke (both ischemic and hemorrhagic types reported)
- Hepatic adenomas, hepatic nodular hyperplasia, cholestasis
- Blood pressure increase
- Gallbladder disease
- Headaches
- Irregular uterine bleeding, amenorrhea, oligomenorrhea
- Nausea
- Breast tenderness
- Mood changes
- Hypertriglyceridemia

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There was no presubmission regulatory activity related to this supplement.

2.6 Other Relevant Background Information

All of the relevant background information was conveyed in the preceding sections.

3 Ethics

In the EURAS study, the primary ethical approval of the study was granted by the Berlin Chamber of Physician's Ethics Committee. Adverse events were fully monitored and reviewed by both the investigator and Advisory Council at least twice a year.

The LASS extension was to begin after all relevant legal, administrative and ethical requirements were fulfilled. All relevant national data protection laws were to be followed. The LASS protocol was submitted to the relevant Ethics Committees and Institutional Review Boards for approval.

Financial disclosure information was not required for these postmarketing safety studies that form the basis for labeling changes sought in this supplement.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The submitted data do not require CMC review.

4.2 Clinical Microbiology

Microbiology was not required for this application.

4.3 Preclinical Pharmacology/Toxicology

The submitted data do not require a Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

The submitted data do not require a Clinical Pharmacology review.

4.5 Biostatistics

See Section 4.6 for biostatistics review relating to the labeling change for YAZ based on interim LASS data.

4.6 Office of Surveillance and Epidemiology (OSE)

OSE was originally consulted regarding the Applicant's submission of this labeling for YAZ on May 10, 2010. They reviewed the submission and pertinent medical literature. They also utilized the Office of Biostatistics (OB) for confirmation and reanalysis of the LASS data.

<u>OSE Summary and Recommendations Regarding LASS Interim Results</u>

In the OSE consult their Summary and Recommendations state:

"Literature review, the applicant's analysis of the data, and the OB reanalysis show that there is an increased risk of VTE early in therapy although the elevated risk never really disappears during use. (b) (4) [redacted]

(b) (4) [redacted]

(b) (4)

OB Conclusions and Recommendations Regarding LASS Interim Results

In the OB consult their Conclusions and Recommendations state:

"The Office of Surveillance and Epidemiology (OSE) requested an assessment of the statistical methodology implemented in the Long-term Active Surveillance Study (LASS) report. This review addresses the validity of the analysis the sponsor is using to support its request for a revised label in the warnings section regarding the occurrence of venous thromboembolism.

This review addresses the time pattern in the risk for venous thromboembolism (VTE) for oral contraceptives (OCs) based on the Long-term Active Surveillance Study (LASS) for Oral Contraceptives, (b) (4)

(b) (4)

Overall, the study supports that the elevated VTE risk associated with the first year of use was more pronounced within the first 6 months."

OSE Summary and Recommendations Regarding Final LASS Study Report

The labeling for YAZ was based on interim results from LASS. DRUP received the final LASS report on September 26, 2011 from Bayer. DRUP asked OSE to review the final report.

OSE had the following statement in their consult review that is pertinent to the requested labeling for Safyral:

"The results examining the period of highest risk for VTE after initiation of OC therapy continue to show the risk is highest in the first 6 months."

5 Sources of Clinical Data

5.1 Summary Table

The study on which this supplement submission is based is shown in Table 1

Table 1: Long-term Active Surveillance Study for Oral Contraceptive (LASS):

EURAS/LASS	Study design	COC Treatment groups	Number of subjects
Study dates: a) EURAS study = 2001 - 2005 b) LASS extension: 2006 - 2010 Countries: 1) Austria 2) Belgium 3) Denmark 4) France 5) Germany 6) Netherlands 7) United Kingdom	Prospective multinational, controlled, non-interventional cohort study	1) Yasmin 2) Levonorgestrel-containing OCs 3) Other OCs	EURAS 59,510 subjects enrolled LASS 47,799 oral contraceptive users remained from EURAS to participate in LASS

Source: Submission 57 to NDA 21-676; Final LASS Report.

5.2 Review Strategy

The clinical review strategy was to review the following:

- LASS final study report and compare to interim results
- Periodic adverse drug experience reports (PADERs) for Safyral.

5.3 Discussion of Study- Long-term Active Surveillance Study for Oral Contraceptive (LASS) Protocol

5.3.1 Study Title

"Long-term Active Surveillance Study for Oral Contraceptives"

5.3.1.2 Ethics

The Protocol stated that:

"The study will only start after all relevant legal, administrative and ethical requirements have been fulfilled. Information on the identity of the patients and treating physicians will be kept separated from the clinical information throughout the study. All relevant national data protection laws will be followed. The study protocol will be submitted to the relevant Ethics Committees and Institutional Review Boards for comments and approval."

5.3.3 Study Sites

LASS was an extension of the EURAS Study, which was conducted via a network of 1,113 physicians in 7 European countries (Austria, Belgium, Denmark, France, Germany, Netherlands and United Kingdom).

5.3.4 Study Objectives

The LASS protocol stated that:

The primary objective of LASS is to assess the risks of long-term use of DRSP-containing COCs and other established COCs in a study population that is representative of the actual users of the individual preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes.

The main clinical outcomes of interest for the long-term follow-up were:

- Death or hospitalization due to cardiovascular events; in particular, arterial thromboembolism (e.g., acute myocardial infarction and stroke) and venous thromboembolism (e.g., deep venous thrombosis and pulmonary embolism)
- Breast cancer

Secondary objectives were to:

- Analyze the long-term drug utilization pattern of DRSP-containing OCs and established OCs in a study population that is representative for typical use of the individual preparations under routine medical conditions
- Investigate the number of women who start treatment with antihypertensive drugs during the follow-up period
- Evaluate other serious gynecological diseases such as ovarian or endometrial cancer

5.3.5 Study Design

LASS was a large, multinational, prospective, controlled, non-interventional, long-term cohort extension of the existing EURAS Study that followed OC users for up to 5 years.

The cohort definitions were the following:

- Starter = woman who used an OC for the first time in her life
- Re-starter = woman who used the same OC after a break of at least 4 weeks

- Switcher = woman who switched from one OC preparation to another OC preparation. Use of the latter preparation may start after a break or immediately after stopping the first preparation
- Recurrent user = woman who was a re-starter or switcher

The oral contraceptives were divided into three major groups for analysis:

- OCs containing drospirenone
- OCs containing levonorgestrel
- OCs containing other progestins

Scheduled contact with all cohort members occurred every twelve months via mailed questionnaires.

The follow-up questionnaires addressed the occurrence of adverse events particularly with regard to cardiovascular outcomes (e.g., AMI, stroke, VTE), breast cancer and treated hypertension. Reasons for switching to another OC or discontinuation were requested if applicable.

If there was no response to the mailed questionnaires a four level process to minimize “lost to follow-up” consisted of (in sequence):

- Two reminder letters
- Further direct attempts to contact the woman, friends, relatives and her Gynecologist/ Primary Care Physician via phone calls
- Search in national and international phone and address directories
- Official address search via national databases (including death)

5.3.6 Efficacy Variables

EURAS and LASS were primarily postmarketing safety analyses.

5.3.1.12 Analysis of Safety

Validation of self-reported events was performed through contacts with the diagnosing and/or treating physician. This procedure was mandatory for all serious clinical outcomes (e.g., VTEs, ATEs and cancer).

The clinical outcomes were validated according to pre-defined algorithms and the VTE results were verified in a blinded adjudication process. Reported serious events were categorized as confirmed (subdivided into definite and probable) and not confirmed according to the following predefined algorithm:

Definite event:

Confirmed by diagnostic measures with high specificity (e.g., phlebography for DVT, spiral CT for pulmonary embolism, cerebral MRI for cerebrovascular accidents, ECG with typical ST segment elevation for acute myocardial infarction, tumor histology for cancer, two-sided blood pressure measurement with diastolic blood pressure of more than 120 mm Hg for hypertensive crisis)

Probable event:

Absence of confirmation by a diagnostic measure with high specificity, but a clinical diagnosis was confirmed by a health professional or supported by diagnostic tests with low specificity (such as D-dimer for VTE or typical ECG/blood gas tests for PE).

These cases were usually characterized by a subsequent specific therapy (such as fibrinolysis or long-term anticoagulant therapy). However, if the attending physician confirmed that the diagnosis is correct, the event was classified as a probable event even if a specific treatment was not given.

Event not confirmed:

- Reported event excluded by a diagnostic measure with high sensitivity
- Other medical condition diagnosed by attending physician
- Woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could clarify the diagnosis

5.3.1.13 Protocol Amendments

There were no protocol amendments.

6 Review of Efficacy

The data in this supplement relate only to safety. The clinical data being reviewed to support revision of labeling language for Safyral will be reviewed in Section 7.

7 Review of Safety

7.1 Components of NDAs 21-676 (YAZ) and 22-574 (Safyral) Used to Evaluate Safety and Labeling Changes in this Supplement Review

The key submission to NDA 21-676 was:

- Submission No. 57 (9/26/2011) – Final LASS report

The key submissions to the current NDA (22-574) were:

- Submission No. 17 (4/12/2011) – Labeling Supplement for LASS changes
- Submissions No. 18 (4/14/2011); No. 21 (7/15/2011); No. 24 (8/26/2011) and No. 28 (10/14/2011) – Periodic Adverse Drug Experience Reports (PADERs)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure

The overall exposure in LASS was adequate to evaluate duration of use and recurrent use (after a 4 week or greater pill free interval) for the selected populations. Because Safyral has the same hormonal doses and dose regimen as Yasmin (which was studied in LASS) we would expect the safety findings relating to VTE risk for Safyral to be similar to those observed for Yasmin.

7.2.2 Explorations for Dose Response

Not applicable for this submission.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable for this submission.

7.2.4 Routine Clinical Lab Testing

Not applicable for this submission.

7.2.5 Metabolic, Clearance, and Interaction Workup

Not applicable for this submission.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

LASS evaluated a multitude of drug products in the oral contraceptive drug class (see **Error! Reference source not found.** for a list of progestin components evaluated).

7.3 Safety Results from LASS Pertaining to this Supplement

7.3.1 Enrollment Data

The LASS extension was conducted in seven European countries where Yasmin is marketed; i.e., Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom. More than 112,000 WY of COC exposure was obtained by the end of the EURAS study in December 2005. At the end of the EURAS study, a total of 47,799 out of 58,674 study participants who had been in follow-up since study entry into EURAS were willing to continue follow-up into LASS.

The LASS study follow-up yielded another 176,309 WY of observation and 103,379 WY of OC exposure to the combined EURAS/LASS database. Overall, the combined database includes 318,784 WY of observation and 216,038 WY of OC exposure. At the time of the submission of the interim analysis (May 2009), there was a total of 259,696 WY of observation and 186,278 WY of COC exposure.

7.3.2 Incidence and Incidence Rate Ratios for VTEs occurring in Starters, Switchers and Recurrent Users (LASS results)

The LASS data that is critical to the proposed labeling change is presented in the following in this section of the review. Table 2 shows the results derived from the interim LASS results and which supported the YAZ labeling change. Table 3 shows the results from the final LASS report and supports the labeling change for this Safyral submission.

Table 2: Risk of VTE for Various Subgroups by Duration of Use Categories: Incidence Rates by Time to Event Categories and Incidence Rate Ratios with Their 95% Confidence Intervals

Patient Group (exposure)	0-3 Months (VTE per 10,000 WY; point estimates and 95% CI)	4+ Months (VTE per 10,000 WY; point estimates and 95% CI)	Incidence Rate Ratio comparing 0-3 to 4+ months of use (IRR point estimates and 95% CI)
Starters (17,798 WY)	12.1 [2.5-35.3]	3.3 [1.1-7.6]	3.7 [0.9-15.6]
Switchers without intake break (65,983 WY)	11.3 [5.8-19.7]	10.1 [7.6-13.1]	1.1 [0.6-2.1]
Recurrent users with intake break ≥ 4 weeks	19.7 [13.0-28.6]	10.4 [8.2-13.0]	1.9 [1.2-2.9]
Of which:			
Restarters (33,952 WY)	21.2 [10.2-38.9]	9.6 [6.4-13.8]	2.2 [1.1-4.5]
Switchers with intake break ≥ 4 weeks (55,777 WY)	18.9 [11.0-30.2]	10.9 [8.1-14.3]	1.7 [1.0-3.0]

VTE = venous thromboembolism; WY = women years; CI = confidence interval; IRR = incidence rate ratio
Source: NDA 21-676; Submission #41; Report by Dinger; page 6 of 18.

Table 3: Final Report: Risk of VTE for Various Subgroups by Duration of Use Categories: Incidence Rates by Time to Event Categories and Incidence Rate Ratios with Their 95% Confidence Intervals

Patient Group (exposure)	0-3 Months (VTE per 10,000 WY; point estimates and 95% CI)	4+ Months (VTE per 10,000 WY; point estimates and 95% CI)	Incidence Rate Ratio comparing 0-3 to 4+ months of use (IRR point estimates and 95% CI)
Starters	11.1 [2.3-32.4]	3.7 [1.4-8.0]	3.0 [0.8-12.5]
Switchers without intake break	12.5 [7.0-20.6]	12.5 [10.0-15.5]	1.0 [0.6-1.7]
Recurrent users with intake break ≥ 4 weeks	23.9 [16.8-32.9]	11.8 [9.6-14.3]	2.0 [1.4-2.9]
Of which:			
Restarters	28.7 [16.4-46.6]	11.9 [8.7-16.0]	2.4 [1.4-4.3]
Switchers with intake break ≥ 4 weeks	21.1 [13.1-32.3]	11.7 [8.9-15.1]	1.8 [1.1-3.0]

VTE = venous thromboembolism; WY = women years; CI = confidence interval; IRR = incidence rate ratio
Source: NDA 21-676; Submission #57; Page 55 of 127

Medical Officer's Comment:
The incidence rates from the final report are similar to those seen with the interim results that supported the LASS-related YAZ labeling change. Based on these results, this reviewer feels that the final LASS results supports the same labeling language for Safyral that the interim LASS results supported for YAZ labeling.

7.3.4 Progestin Distribution in EURAS/LASS

The distribution of the progestin components of the COCs included in EURAS/LASS is shown in Table 4

Table 4: Progestin Distribution in EURAS/LASS (AT)

Progestin	Exposure [WY]	Proportion [%]
1.Drospirenone	52,278	24.2%
2.Levonorgestrel	57,539	26.6%
3.Other:	106,221	49.2%
Desogestrel	29,490	13.7%
Dienogest	27,441	12.7%
Chlormadinone acetate	19,498	9.0%
Cyproterone acetate	10,051	4.7%
Gestodene	8,498	3.9%
Norgestimate	7,281	3.4%
Norethethisterone	2,901	1.3%
Other	1,062	0.5%
TOTAL (1,2,3)	216,038	100%

WY – Women-years
Note: The Women-years reported in this table are from the as-treated (AT) group which was used as the primary analysis group for the thromboembolic adverse events.
Source: NDA 21-676; Submission #57; Page 28-9 of 127

Medical Officer's Comment:
The progestins in the prior table that are not approved in the U.S. included chlormadinone acetate, cyproterone acetate and gestodene.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Not applicable for this application

7.4.2 Laboratory Findings

Not applicable for this application

7.4.3 Vital Signs / Body Weight

Not applicable for this application

7.4.4 Electrocardiograms (ECGs)

Not applicable for this application

7.4.5 Special Safety Studies/Clinical Trials

LASS, which is the subject of this review, could be described as a special postmarketing safety study because of its focus on cardiovascular and oncology safety evaluation.

7.4.6 Immunogenicity

Not applicable for this application

7.5 Other Safety Explorations

Not applicable for this application

7.5.2 Time Dependency for Adverse Events

See Section 7.3.2, which deals with duration of use and VTE incidence

7.5.3 Drug-Demographic Interactions

Not applicable for this application

7.5.4 Drug-Disease Interactions

Not applicable for this application

7.5.5 Drug-Drug Interactions

Not applicable for this application

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable for this application

7.6.2 Human Reproduction and Pregnancy Data

Not applicable for this application

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable for this application

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable for this application

7.7 4-Month Safety Update

A separate 4-month safety report was not required because the Division had adequate up to date safety reporting (PADERs)..

8 Postmarketing Experience

8.1 Periodic Adverse Drug Experience Reports (PADERs) – Safyral

The following tables (Table 5) provide information on thromboembolic adverse drug experiences in recent PADERs for Safyral.

Table 5: Periodic Adverse Drug Experience Reports for Safyral – Thromboembolic Events (Dec 2010 through Sep 2011)

Time Period	Submission No. / Date of submission	US labeling changes	Number of thromboembolic events reported per time period
12-16-2010 thru 3-15-2011	18 & 24 / 4-14-2011 & 8-26-2011	No	No thromboembolic case events reported in this initial period
3-16-2011 thru 6-15-2011	21 / 7-15-2011	No	No thromboembolic case events reported in this period
6-16-2011 thru 9-15-2011	28 / 10-14-2011	No	No thromboembolic case events reported in this period

Note: Submission 18 was found to have a corrupted file and was replaced in submission 24
Source: NDA 22-532; Submissions 18, 21, 24 and 28

Medical Officer's Comment:
These recent postmarketing safety results do not represent any significant change in the safety profile and do not impact the labeling changes related to LASS data in this submission.

9 Appendices

9.1 Labeling Recommendations

Section 5.1 of the Safyral label (specifically the underlined section in the following paragraph) will be revised based on the data from LASS.

The use of COCs increases the risk of venous thromboembolism. However, pregnancy increases the risk of venous thromboembolism as much or more than

the use of COCs. The risk of venous thromboembolism 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. ~~Interim~~ 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. Interim 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.

Medical Officer's Comment:
Because LASS is now finalized, the term "Interim" is no longer needed.

9.2 Advisory Committee Meeting

An advisory committee meeting was not required for this supplement.

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

/s/

GERALD D WILLETT
01/23/2012

LISA M SOULE
01/23/2012
I concur with Dr. Willett's conclusions and recommendations.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

CHEMISTRY REVIEW(S)

Chemistry Review: 1	**Division:** HFD-580	**NDA Number:** **22-574**

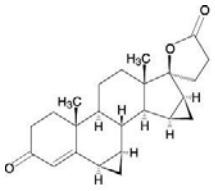
Name and Address of Applicant:	**4. Supplement(s): 1 (Prior Approval)**
Bayer HealthCare Pharmaceuticals Inc. PO Box 1000 Montville, NJ 07045-1000	**Number:** 0017/SDN 18 **Date(s): 13-Apr-2011**
5. Name of Drug: Safyral	**6. Nonproprietary name:** Drospirenone/ethinyl estradiol/levomefolate calcium and levomefolate calcium

7.Supplement Provides for	**8. Amendment(s):**
Incorporate recently approved changes from NDA 21-676 PAS-008 concerning venous thromboembolic events into WARNINGS AND PRECAUTIONS section of label	NA

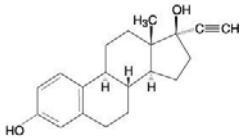
9. Pharmacological Category:	**10. How Dispensed:**	**11. Related Documents:**
Oral contraceptive	R_x	NDA 21-676 PAS-008 approval letter dated 11-Mar-2011.

12. Dosage Form:	**13. Potency:**
Tablet	**3 mg drospirenone/0.03 mg ethinyl estradiol /0.451 mg levomefolate calcium and 0.451 mg levomefolate calcium**

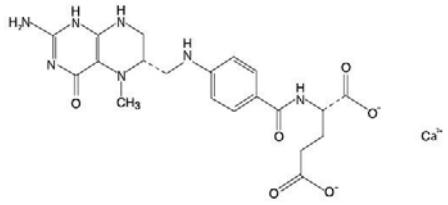
14. Chemical Name and Structure:



Drospirenone



Ethinyl estradiol



Levomefolate Calcium

15. Comments

This labeling supplement incorporates recently approved changes from NDA 21-676 PAS-008 concerning venous thromboembolic events into WARNINGS AND PRECAUTIONS section of label. No changes have been made to the CMC portions of the label.

16. Conclusion:

This Supplement is recommended for approval from CMC perspective. Since this is an OND-managed supplement, any correspondence will be made by the OND PM.

17. Name: **Donna F. Christner, Ph.D.** **Signature:** **Date:**

18. Concurrence: **Thomas Oliver, Ph.D.** **Signature:** **Date:**


APPEARS THIS WAY ON
ORIGINAL

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

/s/

DONNA F CHRISTNER
04/26/2011

THOMAS F OLIVER
04/26/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

PHARMACOLOGY REVIEW(S)

Review memo

Date: 7-18-2011

NDA #: 22574 Supplement 1, Supporting document #18, Sequence #0017

Date of submission: 4-12-2011

Sponsor: Bayer Healthcare Pharmaceuticals, Inc

Drug Product: drospirenone 3 mg, ethinyl estradiol 0.03 mg, levomefolate calcium 0.451 mg

Drug Name: Safyral®

Approval date: 12-16-2010

Indication: prevention of pregnancy

Recommendation: No new nonclinical information has been submitted to this supplement. There are no nonclinical issues that would preclude approval.

Leslie McKinney
PharmTox reviewer
DRUP

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

/s/

LESLIE C MCKINNEY
07/20/2011

ALEXANDER W JORDAN
07/20/2011

Memo to file

Date: 6-15-2011

NDA #: 22574 Supplement 1, Supporting document #18, Sequence #0017

Date of submission: 4-12-2011

Sponsor: Bayer Healthcare Pharmaceuticals, Inc

Drug Product: drospirenone 3 mg, ethinyl estradiol 0.03 mg, levomefolate calcium 0.451 mg

Drug Name: Safyral®

Approval date: 12-16-2010

Indication: prevention of pregnancy

Subject: This application concerns labeling revisions, but is being reviewed as an efficacy supplement due to pending revision of clinical data.

Regulatory action: This submission is fileable from a PharmTox perspective.

Leslie McKinney
PharmTox reviewer
DRUP

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

/s/

LESLIE C MCKINNEY
06/15/2011

ALEXANDER W JORDAN
06/16/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

STATISTICAL REVIEW(S)

Memorandum of Statistical Review

NDA/Supporting Document Number:	22-574 Supplement 001 / 018 / SE8
Drug Name:	Safyral (0.03 mg ethinylestradiol + 3.0 mg drospirenone + 0.451 mg levomefolate calcium)
Indication(s):	Prevention of pregnancy
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.
Date(s):	Letter Date: April 12, 2011 PDUFA Date: February 13, 2012
Review Priority:	1 Standard
Biometrics Division:	Division of Biometrics 3
Biometrics Reviewer:	Sonia Castillo, Ph.D.
Biometrics Team Leader:	Mahboob Sobhan, Ph.D.
Medical Division:	Division of Reproductive and Urologic Drug Products
Clinical Team:	Gerald Willett, M.D., Medical Reviewer Lisa Soule, M.D., Team Leader
Project Manager:	Pamela Lucarelli
Key Words:	Language for Labeling

This submission applies changes to the safety portion of the label regarding thrombotic events. There are no new changes to the efficacy section of the labeling. There are no statistical issues related to efficacy that would preclude approval.

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

/s/

SONIA CASTILLO
07/27/2011

STATISTICS FILING CHECKLIST FOR A NEW NDA

NDA Number: 22-574 / Supp. Doc. 018

Applicant: Bayer HealthCare Phamaceuticals, Inc.

Letter Date: 4-12-2011

Drug Name: Safyral (0.03 mg ethinylestradiol + 3.0 mg drospirenone + 0.451 mg levomefolate calcium)

NDA Type: Supplement 001 / SE8

Indication: Prevention of pregnancy

On **initial** overview of the NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	This submission applies changes to the safety portion of the label regarding thrombotic events. There are no new changes to the efficacy section of the labeling.
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.			X	
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			X	
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).			X	

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE____YES____

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	This submission applies changes to the safety portion of the label regarding thrombotic events. There are no new changes to the efficacy section of the labeling.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.			X	
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			X	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	

Sonia Castillo, Ph.D. 6-9-2011

Reviewing Statistician Date

Mahboob Sobhan, Ph.D. 6-9-2011

Supervisor/Team Leader Date

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

/s/

SONIA CASTILLO
06/29/2011

MAHBOOB SOBHAN
06/29/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY ADDENDUM

NDA 022574	Submission Dates: 4/12/2011 (SDN 018; Supplement 001)
Brand Name	Safyral®
Generic Name	Drospirenone (DRSP) /ethinyl estradiol (EE) / levomefolate calcium
Primary Reviewer	Li Li, Ph.D.
Secondary Reviewer	Chongwoo Yu, Ph.D.
OCP Division	Division of Clinical Pharmacology 3 (DCP3)
OND division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Bayer HealthCare Pharmaceuticals, Inc.
Submission Type	Efficacy Supplement
Formulation; Strength(s)	Oral tablet containing either 1) drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levomefolate calcium 0.451 mg or 2) levomefolate calcium 0.451 mg only
Indications	• Prevention of pregnancy • Raise folate levels in women who choose to use an oral contraceptive for contraception

The purpose of this addendum is to address the Office of Clinical Pharmacology (OCP)'s recommendation on the Sponsor's proposed product labeling that was not addressed in the original Clinical Pharmacology review of this submission under NDA 022574 (DARRTS, 1/13/2012).

1. OCP's Recommendations on the Product Labeling

7.2 Effects of Combined Oral Contraceptives on Other Drugs

The following statement from Section 5.12 was also added to Section 7.2: "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."

Reviewer's Comment: *This was placed in Section 7.2 as concomitant use of COCs may affect the necessary dose of thyroid hormone therapy.*

8.6 Patients with Renal Impairment

The creatinine clearance (CLcr) ranges used in the section 8.6 was modified from 50 – 80 mL/min to 50 – 79 mL/min, AND from 30 – 50 mL/min to 30 – 49 mL/min.

Reviewer's Comment: *This modification is to provide the clear distinction of the different renal impairment stages. The same changes were applied to Section 12.3 Pharmacokinetics under Renal Impairment.*

8.8 Race

The following statement was added to Section 8.8 based on information regarding race available in section 12.3: "No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women".

The final agreed upon product label between the Sponsor and the DRUP will be attached to the Approval Letter. There are no pending Clinical Pharmacology labeling issues.

2. Recommendation

The DCP3, OCP finds NDA 022574 acceptable from the Clinical Pharmacology perspective.

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

/s/

LI LI
02/13/2012

CHONGWOO YU
02/13/2012

CLINICAL PHARMACOLOGY REVIEW

NDA 022574	Submission Dates: 4/12/2011 (SDN 018; Supplement 001)
Brand Name	Safyral®
Generic Name	Drospirenone (DRSP) /ethinyl estradiol (EE) / levomefolate calcium
Primary Reviewer	Li Li, Ph.D.
Secondary Reviewer	Chongwoo Yu, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Bayer HealthCare Pharmaceuticals, Inc.
Submission Type	Efficacy Supplement
Formulation; Strength(s)	Oral tablet containing either 1) drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levomefolate calcium 0.451 mg or 2) levomefolate calcium 0.451 mg only
Indications	• Prevention of pregnancy • Raise folate levels in women who choose to use an oral contraceptive for contraception

Table of Contents

1 Executive Summary

This review addresses the submission of Efficacy supplement submitted on April 12, 2011 to NDA 022574. There was no new Clinical Pharmacology information submitted for review.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 finds this submission to NDA 022574 to be acceptable from the Clinical Pharmacology standpoint.

1.2 Summary of Important Clinical Pharmacology Findings

Background

Safyral® was approved under NDA 022574 on December 16, 2010. Safyral® consists of 24 hormone containing tablets containing 3 mg of drosperinone (DRSP), 0.03 mg of ethinyl estradiol (EE),0.451 mg of levomefolate calcium (metafolin), and 4 tablets containing 0.451 mg of metafolin only (metafolin mono). The dosage regimen of Safyral® is one hormone-containing tablet daily for 24 consecutive days followed by one metafolin mono tablet daily for 4 days per treatment cycle.

Regulatory History

The efficacy supplement for YAZ® (NDA 021676, SDN134), approved on March 11, 2011, included new information in the Warning and Precaution section regarding the increased risk of the venous thromboembolism (VTE) in women using combined oral contraceptive (COCs). In the current submission, the Sponsor submitted a new efficacy supplement to add the same language to the labels for Safyral® (NDA 022574). No new clinical pharmacology related document is submitted.

The currently approved label is already in Physician Labeling Rule (PLR) format. The Sponsor has proposed some editorial labeling changes. Please refer to the detailed recommendations of the OCP regarding the proposed labeling changes located in Section1.3 of this review.

1.3 Labeling Recommendations

The Sponsor proposed changes to the following Clinical Pharmacology related parts of theproduct label in this NDA supplement. ~~Strikes~~ are used for deletion and double underline isused for addition for the OCP response to the Sponsor's proposal.

Full Prescribing Information

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 Hormonal Contraceptives

HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels 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.

Reviewer's Comment: *This reviewer recommends "HCV" to be added as some HCV protease inhibitors such as boceprevir and telaprevir have been reported for drug interactions with combined oral contraceptives. The same recommendation regarding adding "HCV" protease inhibitors also applies to Section 12.3 Pharmacokinetics under Clinical Pharmacology.*

The table below is originally from boceprevir label showing the drug interaction of boceprevir with yaz®.

administered Drug	***Co-administered Drug Dose/Schedule***	***Boceprevir Dose/Schedule***	***Ratio Estimate of Co-administered Pharmacokinetic Parameters (in Combination vs. Alone) (90% CI of the Ratio Estimate) ****	
			Change in mean C_{max}	***Change in mean AUC(τ)***
Drospirenone/ Ethinyl estradiol	*Drospirenone 3 mg + Ethinyl estradiol 0.02 mg daily x 14 days*	*800 mg three times daily x 7 days*	*Drospirenone 1.57 (1.46-1.70)* *Ethinyl estradiol 1.00 (0.91-1.10)*	*Drospirenone 1.99 (1.87-2.11)* *Ethinyl estradiol 0.76 (0.73-0.79)*

7.6 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests. 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. 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 (5.12).]*

Reviewer's Comment: *According to 21 CFR §201.57(c)(8)(ii), the DRUG INTERACTIONS Section of the Full prescribing information is required to contain practical guidance on known interference of the drug with laboratory tests. Therefore, the text with the double underline should be added.*

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 (b) (4) creatinine clearance (CLcr)~~,~~ = 50–80 mL/min~~)~~, serum DRSP levels were comparable to those in subjects with (b) (4) CLcr~~,~~ > 80 mL/min~~)~~. In subjects with (b) (4) CLcr~~,~~ = 30–50 mL/min~~)~~, serum DRSP levels were on average 37% higher than those in the group with (b) (4) CLcr ≥ 80 mL/min. 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)]*.

12.3 Pharmacokinetics

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 levels were investigated in three separate groups of female subjects (n=28, age 30-65) with creatinine clearance (CLcr) >80 mL/min (b) (4) (b) (4), CLcr = 50-80 mL/min and CLcr = 30-50 mL/min, respectively (b) (4). 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 levels in the group with (b) (4) CLcr = 50-80 mL/min were comparable to those in the group with (b) (4) (CLcr >80 mL/min). The serum DRSP levels were on average 37% higher in the group with (b) (4) (CLcr = 30-50 mL/min) compared to those in the group with CLcr > 80 mL/min. (b) (4). 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 levels increased by up to 0.33 mEq/L. *[See Contraindications (4), Warnings and Precautions (5.2) and Use in Specific Populations (8.6).]*

Reviewer's Comment: (b) (4)

(b) (4)

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

/s/

LI LI
01/13/2012

CHONGWOO YU
01/13/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 022574 **Applicant: Bayer Health Care Pharmaceuticals, Inc** **Stamp Date: 04/13/2011**

SDN: 18

Drug Name: Safyral **NDA/BLA Type: Efficacy supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√
2	Has the applicant provided metabolism and drug-drug interaction information?			√
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			√
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			√
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			√
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√
11	Is the appropriate pharmacokinetic information submitted?			√
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			√
General				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA/BLA or Supplement

13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			√
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?			√
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?			√
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			√
17	Was the translation from another language important or needed for publication?			√

*Abbreviation: N/A = Not Applicable

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Background:

The efficacy supplement for YAZ® (NDA 021676, SDN134), approved on March 11th, 2011, provided for the inclusion of new information regarding the increased risk of the venous thromboembolism (VTE) in women using combined oral contraceptive (COCs) in the Warning and Precaution section, subsection thromboembolic disorders and other vascular problems. In the current submission, Beyer has submitted a new supplement to add the same language to the labels for Safyral® (NDA 022574).

No new clinical pharmacology related document is submitted. The currently approved label is already in Physician Labeling Rule (PLR) format. Therefore, there is no pending review from clinical pharmacology standpoint.

Li Li

Reviewing Pharmacologist Date

Myong-Jin Kim

Team Leader/Supervisor Date

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

/s/

LI LI
06/20/2011

MYONG JIN KIM
06/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

OTHER REVIEW(S)

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	**SAFYRAL (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets), for oral use**
Application Number/Supplement Number	NDA 22574, supplement 001
Type of Application	Clinical Efficacy
Indication	For use by women to: • Prevent pregnancy • Raise folate levels in women who choose to use an oral contraceptive for contraception.
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Office/Division	ODE III/DRUP
Division Project Manager	Pamela Lucarelli
Submission Date	April 13, 2011
PDUFA Goal Date	February 13, 2012
SEALD Review Date	February 13, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko, RN, MS
SEALD Director	Laurie B. Burke, RhP, MPH

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). 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."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for "peds only" indications) are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling …

    (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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

/s/

JEANNE M DELASKO
02/13/2012

LAURIE B BURKE
02/13/2012

Labeling Review Memo

Date: 1-12-2012

NDA #: 22574 Supplement 1, Supporting document #18, Sequence #0017

Date of submission: 4-12-2011

Sponsor: Bayer Healthcare Pharmaceuticals, Inc

Drug Product: drospirenone 3 mg, ethinyl estradiol 0.03 mg, levomefolate calcium 0.451 mg

Drug Name: Safyral®

Approval date: 12-16-2010

Indication: prevention of pregnancy

Regulatory action: The final label is acceptable.

Leslie McKinney
PharmTox reviewer
DRUP

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

/s/

LESLIE C MCKINNEY
01/12/2012

ALEXANDER W JORDAN
01/12/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022574/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022574 SUPPL # 001 HFD # 580

Trade Name Safyral

Generic Name drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets

Applicant Name Bayer HealthCare Pharmaceuticals Inc.

Approval Date, If Known February 10, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

New clinical data was supplied to re-evaluate the temporal relationship of the risk of venous thromboembolic events in women using combined oral contraceptives.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 021676 drospirenone/ethinyl estradiol

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Long-term Active Surveillance Study for Oral Contraceptives (LASS)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Long-term Active Surveillance Study for Oral Contraceptives (LASS)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☒
		! Explain: Study was conducted in Europe, IND not required.

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☒	! NO ☐

Explain: The applicant provided support for the study.	! Explain:
Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Pamela Lucarelli
Title: Regulatory Health Project Manager
Date: February 17, 2012

Name of Office/Division Director signing form: Christine Nguyen
Title: Acting Deputy Director of Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

PAMELA LUCARELLI
02/21/2012

CHRISTINE P NGUYEN
02/21/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22574/S-001

FILING COMMUNICATION

Bayer HealthCare Pharmaceuticals Inc.
Attention: Robert J. Haydu
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Haydu:

Please refer to your Supplemental New Drug Application (sNDA) dated April 12, 2011, received April 13, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets).

We also refer to your submission dated April 27, 2011.

This supplemental application proposes changes to the WARNINGS and PRECAUTIONS section to include language regarding venous thromboembolic events in combined oral contraceptive users.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is February 13, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by January 13, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

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(s) 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.

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

Sincerely,

{See appended electronic signature page}

Scott Monroe, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

SCOTT E MONROE
06/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022574/S-001

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Bayer HealthCare Pharmaceuticals Inc.
Attention: Robert J. Haydu
Deputy Director, Regulatory Affairs
P.O. Box 1000
Montville, NJ 07045-1000

Dear Mr. Haydu:

We have received your April 12, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 022574

SUPPLEMENT NUMBER: 001

PRODUCT NAME: Safyral (drospirenone/ethinyl estradiol/levomefolate calcium tablets and levomefolate calcium tablets)

DATE OF SUBMISSION: April 12, 2011

DATE OF RECEIPT: April 13, 2011

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes changes to the WARNINGS and PRECAUTIONS sections to include language regarding venous thrombosis events in combined oral contraceptive users. Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product made with this change.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 12, 2011, in accordance with 21 CFR 314.101(a).

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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 022574/S-001** submitted on April 12, 2011, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. 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, 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

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

/s/

PAMELA LUCARELLI
04/15/2011