Labeling for Combined Hormonal Contraceptives

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Jennifer Dao at 301-796-8189.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2017
Labeling

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations on information that should be included in the prescribing information for combined hormonal contraceptives (CHCs) that contain estrogen and progestin. CHCs include combined oral contraceptives (COCs), as well as non-oral products such as transdermal systems and vaginal rings. Many of the labeling recommendations in this guidance represent class labeling that should be included in all CHC prescribing information. General advice is provided **[within brackets in bold font]** where modifications of the prescribing information for specific products are needed.

This guidance follows the content and format requirements of the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," issued in 2006, that amended human prescription and biological product labeling (commonly referred to as the physician labeling rule (PLR)),[2,3] as well as the final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and

[1] This guidance has been prepared by the Division of Bone, Reproductive, and Urologic Products in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] 21 CFR 201.56 and 201.57; final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006); https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

[3] See the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

Lactation Labeling" (commonly referred to as the pregnancy and lactation labeling rule (PLLR)) that was issued in 2014, which amended the 2006 PLR regulations.[4,5]

This guidance does not address the content of patient labeling, which is required for COCs under 21 CFR 310.501. Applicants are advised to consider 21 CFR 310.501 and recently approved patient labeling for other contraceptive products when developing patient labeling for their products.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The content and format requirements of the PLR and the PLLR (21 CFR 201.56 and 201.57) required revisions to CHC labeling under certain circumstances. In addition, the labeling for recently approved CHCs is consistent with the labeling requirements set forth in the PLR and the PLLR. This newer CHC labeling may be different from the labeling for some older CHC products. The updates to this guidance set forth labeling recommendations that represent newer class labeling that should be included in all CHC prescribing information consistent with the labeling requirements set forth in the PLR and PLLR (21 CFR 201.56 and 201.57). We note that the specific advice provided in this guidance is not intended to cover every aspect of the PLR and PLLR requirements for CHC labeling. Accordingly, we refer the reader to 21 CFR 201.56 and 201.57, which set forth the PLR and PLLR content and format labeling requirements. We also refer the reader to the PLR Requirements for Prescribing Information web page, which lists additional guidances that address specific requirements under PLR and PLLR.[6]

III. LABELING RECOMMENDATIONS

This section provides FDA recommendations for CHC labeling other than patient labeling. Because all CHCs contain an estrogen and a progestin, FDA believes that class labeling based on information known about estrogens/progestins generally is appropriate for many sections of CHC labeling. This section provides the recommended class labeling statements. However,

[4] 21 CFR 201.56 and 201.57(c)(9); final rule "Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling" (79 FR 72064, December 4, 2014); https://federalregister.gov/a/2014-28241

[5] See the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format*. When final, this guidance will represent the FDA's current thinking on this topic.

[6] https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

there are sections in labeling that should contain product-specific information (e.g., data on the efficacy outcome or bleeding profile demonstrated in clinical trials of the specific product, or results of a drug-drug interaction study conducted with a particular CHC product). These labeling sections are identified in this section, and general guidance is provided as to the type of information that should be included.

For the Highlights of Prescribing Information, recommendations for product-specific text are listed in the appropriate footnotes directly below the labeling example. Where labeling sections are listed without any recommended language, the reader is encouraged to review approved CHC labeling in the PLR format for guidance.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[NAME (established name of progestin component, followed by established name of estrogen component)] tablets, for oral use[1]
Initial U.S. Approval: [YEAR][2]

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **[NAME] is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive (CHC) use. (5.1)**[3]

----------RECENT MAJOR CHANGES[4]**----------**

----------INDICATIONS AND USAGE----------
[NAME] is a progestin/estrogen [text][5] indicated for use by females of reproductive potential to prevent pregnancy. (1)[6],[7]

----------DOSAGE AND ADMINISTRATION----------
- One tablet by mouth at the same time every day in the order directed on the blister pack.[8] (2.1)[9]

----------DOSAGE FORMS AND STRENGTHS----------

----------CONTRAINDICATIONS----------
- High risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors, acute viral hepatitis or decompensated cirrhosis (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4, 8.1)
- Hypersensitivity reactions to components of [NAME][10] (4)

----------WARNINGS AND PRECAUTIONS----------
- Vascular risks: Stop if a thrombotic or thromboembolic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in females who are not breast-feeding. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years. (5.1, 5.4)
- Liver disease: Discontinue if jaundice occurs. (5.2)
- Hypertension. If used in females with well-controlled hypertension, monitor blood pressure and stop use if blood pressure rises significantly. (5.3)
- Gallbladder disease: May cause or worsen gallbladder disease. (5.5)
- Adverse carbohydrate and lipid effect: Monitor glucose in prediabetic and diabetic females using [NAME]. Consider an alternate contraceptive method for females with uncontrolled dyslipidemia. (5.6)
- Headache. Evaluate significant change in headaches and discontinue if indicated. (5.7)
- Uterine bleeding: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist. (5.8)

----------ADVERSE REACTIONS----------
Most common adverse reactions reported in clinical trials (≥ x%)[11] are: [text].[12] (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact (MANUFACTURER) at [text][13] **or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.***

----------DRUG INTERACTIONS----------
Enzyme inducers (e.g., CYP3A4): May decrease the effectiveness of [NAME] or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with [NAME]. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Discontinue if pregnancy occurs. (8.1)
- Lactation: Advise use of another method; [NAME] can decrease milk production. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [month/year]

[1] Should be modified as appropriate for non-oral formulations.

[2] The year of the first approval of the combination of hormones should be inserted.

[3] For oral hormonal contraceptives, it is acceptable to use the term combination oral contraceptives (COCs) in place of CHCs.

[4] If applicable

[5] COC or CHC

[6] If other indications are approved, they should be provided in bullet form in the same order as in the Full Prescribing Information. Recommended language for specific secondary indications is provided as follows:

[Acne: Treat moderate acne in females who choose to use a combined hormonal contraceptive for contraception. (1.x)
Folate supplementation: Raise folate levels in females who choose to use a combined hormonal contraceptive for contraception. (1.x)
Premenstrual Dysphoric Disorder (PMDD): Treat symptoms of PMDD for females who choose to use a combined hormonal contraceptive for contraception. (1.x)]

In the case of multiple indications, the format should be:

"[NAME] is a progestin/estrogen [text][5] indicated for use by females of reproductive potential to:"

- **[then list each indication as a separate bullet, beginning with "prevent pregnancy"]**

[7] If there were entry criteria in the clinical trials that excluded females above a certain weight or body mass index (BMI), the following language should be added:

[Limitation of Use: The efficacy in females with a [weight/BMI above x] **has not been evaluated.]**

[8] This should be revised as needed if a different dispenser is used.

[9] For COCs, a bulleted format should be used to summarize if different pills are taken at different times during the cycle. It should be noted if the product must be taken with water or with respect to meals. This section should be modified as appropriate for non-oral formulations. Day 1 or Sunday start should be described as appropriate for clarity.

[10] Only if evidence of hypersensitivity reactions exists, not if hypothetical concern.

[11] The rate used as the cutoff for reporting should be specified.

[12] All at or above the frequency cutoff should be specified, with terms likely to represent the same phenomenon grouped, and listed in descending order of frequency. Frequency for individual terms should not be provided. If approved for multiple indications, applicants should discuss with FDA whether to provide separate lists or to pool the adverse reaction data.

[13] The manufacturer's phone number should be inserted.

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 combined hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including [NAME], are contraindicated in women who are over 35 years of age and smoke. ***[See Contraindications (4) and Warnings and Precautions (5.1).]***

1 INDICATIONS AND USAGE

[NAME] is indicated for use by females of reproductive potential to prevent pregnancy.

[Any important limitations of use should be added under the header "Limitations of Use:". If there were entry criteria in the clinical trials that excluded females above a certain weight or BMI, the following language should be added: "Limitation of Use: The efficacy in females with a [weight/BMI above x] **has not been evaluated."]**

[If the product has multiple indications, the section should be formatted using subsections (e.g., 1.1, 1.2). Recommended language for specific secondary indications is provided below; however, the proposed language can be discussed with the division if refinement is needed based on the specific clinical trials conducted in support of the secondary indication:

Acne: [NAME] is indicated for the treatment of moderate acne vulgaris in females who choose to use a combined hormonal contraceptive as their method of contraception.

Premenstrual Dysphoric Disorder (PMDD): [NAME] is indicated for the treatment of symptoms of PMDD in females who choose to use a combined hormonal contraceptive as their method of contraception. The effectiveness of [NAME] when used for more than **[the duration of clinical trial(s) for this indication should be inserted]** has not been evaluated. Limitation of use: [NAME] is not indicated for treatment of premenstrual syndrome (PMS).**]**

2 DOSAGE AND ADMINISTRATION

2.1 How to Start and Take [NAME]

[Should be modified as warranted for non-oral formulations.]

[Information on Day 1 and/or Sunday start should be included, according to the method used in the registration trials. A template for providing this information with respect to COCs in tabular form is provided in Table 1. The table should be modified as necessary to reflect dosing instructions in the registration trials (e.g., if dosing with respect to meals or fed/fasted was required). Additional text may be needed to describe different dosing regimens, such as a multiphasic dosing regimen. Guidance on how to initiate use after pregnancy or childbirth should be provided (addressing use in lactating females); the general recommendation is not to start CHCs until 4 weeks postpartum. Guidance should also be provided about switching from a different method, including a different COC, a transdermal system, vaginal ring, or a progestin-only method; instructions provided in Table 1 should be modified if warranted for the specific product.]

Table 1. Instructions for Administration

Starting [NAME] in females with no current use of hormonal contraception [Instructions for Day 1 start or Sunday start based on the method(s) used in the registration clinical trial(s) should be included.]	Day 1 start • Take first tablet without regard to meals on the first day of menses • Take subsequent tablets once daily at the same time each day • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
	Sunday start • Take first tablet without regard to meals on the first Sunday after the onset of menstrual period • Take subsequent tablets once daily at the same time each day • Use additional nonhormonal contraception for the first seven days of product use • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
Switching from another contraceptive method • **A COC**	Start [NAME]: • On the day when the new pack of the previous COC would have been started
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal
• **Implant**	• On the day of removal

2.2 Dosing [NAME]

[Should be modified as warranted for non-oral formulations.]

Instruct patients to take one tablet by mouth at the same time every day. To achieve maximum contraceptive effectiveness, patients must take [NAME] as directed, in the order directed on the blister pack **[should be revised as needed if a different dispenser is used]**. The failure rate may increase when pills are missed or taken incorrectly. **[Should be revised as appropriate for non-oral CHCs.]**

[If relevant, it should be noted if the product must be taken with water or with respect to meals.]

2.3 Missed Doses

[Should be modified as warranted for non-oral formulations.]

Instruct patients about the handling of missed doses (e.g., to take single missed pills as soon as possible) and to follow the dosing instructions provided in the FDA-approved patient labeling.

[Specific instructions should be provided about handling of missed doses and the need for back-up contraception. A tabular display such as that shown in Table 2 can be helpful, but the specific recommendations should be based on instructions used in the clinical trial(s).]

Table 2. Instructions for Missed [NAME] Tablets

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional nonhormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional nonhormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

[This section is for COCs only.]

[In general, guidance provided here should reflect instructions given to subjects in the clinical trial(s).]

If vomiting occurs within **[X]** hours after taking [NAME] **[this can be individualized if the product's pharmacokinetic profile indicates faster or slower absorption]**, the patient should proceed as if she missed a tablet. In case of prolonged vomiting or diarrhea, **[if no trial instructions were provided in the case of prolonged vomiting or diarrhea (greater than 48 hours), applicants should consider referring the reader to the CDC Selected Practice Recommendations web page (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6205a1.htm#Fig5)].**

3 DOSAGE FORMS AND STRENGTHS

[The dosage of the progestin component should be described in milligrams and the estrogen component described in micrograms.]

4 CONTRAINDICATIONS

[NAME] is contraindicated in females who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include females who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have current or history of deep vein thrombosis or pulmonary embolism *[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 or hypertension with vascular disease *[see Warnings and Precautions (5.3)]*
  - Have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease or other end-organ damage, or diabetes mellitus of > 20 years duration *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms, migraine headaches with aura, or over age 35 with any migraine headaches *[see Warnings and Precautions (5.8)]*
- Current or history of breast cancer or other estrogen- or progestin-sensitive cancer
- Liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.9)]*
- Pregnancy, because there is no reason to use CHCs during pregnancy *[see Use in Specific Populations (8.1)]*
- Hypersensitivity to any components of [NAME]. **[Only if evidence of hypersensitivity reactions exists, not if hypothetical concern; if this bullet is used, a statement should be added: "Observed reactions include…"]**

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Conditions

- Stop [NAME] if an arterial or venous thrombotic/thromboembolic event occurs.

- Stop [NAME] if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.

- Discontinue [NAME] during prolonged immobilization. If feasible, stop [NAME] at least four weeks before and through two weeks after major surgery, or other surgeries known to have an elevated risk of thromboembolism.

- Start [NAME] no earlier than four weeks after delivery in females who are not breast-feeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.

- Before starting [NAME] evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. [NAME] is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases *[see Contraindications (4)]*.

Arterial Events

CHCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

[NAME] is contraindicated in women over 35 years of age who smoke *[see Contraindications (4)]*. Cigarette smoking increases the risk of serious cardiovascular events from CHC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

Venous Events

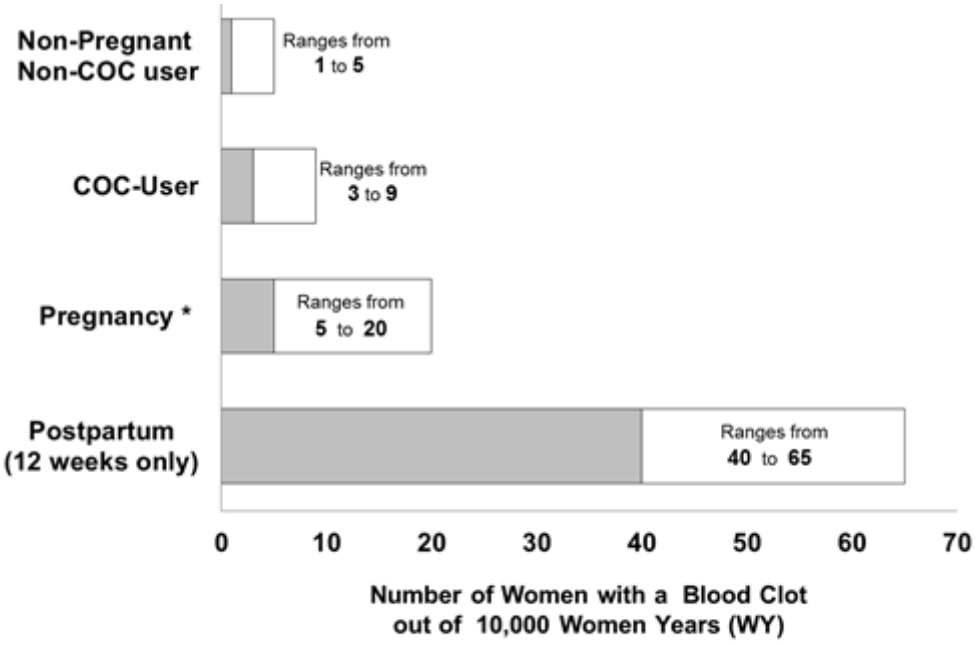
Use of CHCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs *[see Contraindications (4)]*. While the increased risk of VTE associated with use of CHCs is well-established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The rate of VTE in females using COCs **[or CHCs]** has been estimated to be **[the appropriate risk estimate should be used depending on whether the product is a COC or a non-oral CHC; either** 3 to 9 cases per 10,000 woman-years **for COCs or** 3 to 12 cases per 10,000 women-years **for non-oral CHCs]**.

The risk of VTE is highest during the first year of use of a COC and when restarting hormonal contraception after a break of four weeks or longer. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued.

[The figure and text statement of risks of users should be modified as indicated for non-oral products. The rate range for CHCs (non-oral products) is 3 to 12; *COC* should be revised to *CHC*.]

Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use oral **[or hormonal]** contraceptives, for females who use oral **[or hormonal]** contraceptives, for pregnant females, and for females in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 females who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these females will develop a VTE.

Figure 1: Likelihood of Developing a VTE



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

[For extended cycle COCs, a statement should be provided if the annual hormonal exposure is greater than that with conventional monthly COCs that contain the same strength estrogen and progestin.]

Epidemiologic Studies Pertaining to [NAME]

[If epidemiologic studies have evaluated [NAME] or progestin class, applicants should discuss with FDA whether and how the data should be presented in labeling.]

5.2 Liver Disease

Elevated Liver Enzymes

[NAME] is contraindicated in females with acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Discontinue [NAME] if jaundice develops. Acute liver test abnormalities may necessitate the discontinuation of CHC use until the liver tests return to normal and CHC causation has been excluded.

Liver Tumors

[NAME] is contraindicated in females with benign or malignant liver tumors *[see Contraindications (4)]*. CHCs increase the risk of hepatic adenomas. An estimate of the attributable risk is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death from abdominal hemorrhage.

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

5.3 Hypertension

[NAME] is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For all females, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop [NAME] if blood pressure rises significantly.

An increase in blood pressure has been reported in females using CHCs, and this increase is more likely in older women with extended duration of use. The effect of CHCs on blood pressure may vary according to the progestin in the CHC.

5.4 Age-related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Certain conditions, such as smoking and migraine headache without aura, that do not contraindicate CHC use in younger females, are contraindications to use in women over 35 years of age *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a CHC for women over 35 years, such as:

- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

5.5 Gallbladder Disease

Studies suggest an increased risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease.

A past history of CHC-related cholestasis predicts an increased risk with subsequent CHC use. Females with a history of pregnancy-related cholestasis may be at an increased risk for CHC-related cholestasis.

5.6 Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

[NAME] is contraindicated in diabetic women over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of > 20 years duration *[see Contraindications (4)]*. [NAME] may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are using [NAME]. **[Applicants should summarize here if product-specific information on the effect on carbohydrate metabolism is available.]**

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemia. [NAME] may cause adverse lipid changes. **[Applicants should summarize here if product-specific information on the effect on lipids is available.]**

Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using [NAME], which may increase the risk of pancreatitis.

5.7 Headache

[NAME] is contraindicated in females who have headaches with focal neurological symptoms or have migraine headaches with aura, and in women over age 35 years who have migraine headaches with or without aura *[see Contraindications (4)]*.

If a woman using [NAME] develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue [NAME] if indicated. Consider discontinuation of [NAME] if there is an increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Females using [NAME] may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy.

> **[The following sections should summarize data from product-specific clinical trials that describe the occurrence of unscheduled (breakthrough) bleeding, frequency of amenorrhea, and absence of scheduled (withdrawal) bleeding. The frequency of discontinuation due to bleeding complaints should be provided. Suggested language is provided below.]**

Based on subject diaries from **[number]** clinical trial(s) of [NAME], **[range of frequency, in percent of subjects, should be given]** of females experienced unscheduled bleeding per 28-day cycle **[should be modified as appropriate for extended cycle products]**. A total of **[number out of total sample size]** subjects **[percent]** discontinued due to menstrual disorders including **[Preferred Terms should be specified]**.

Amenorrhea and Oligomenorrhea

Females who use [NAME] may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. Based on subject diaries from clinical trials of [NAME] for up to **[number]** cycles, **[percent]** of females experienced cycles with no scheduled bleeding.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have **[should be modified as needed for multiphasic regimens or non-oral formulations]**), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy. **[Should be modified as needed to account for extended cycle products and/or products with a short half-life.]**

After discontinuation of a CHC, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

5.9 Depression

Carefully observe females with a history of depression and discontinue [NAME] if depression recurs to a serious degree. Data on the association of CHCs with onset of depression or exacerbation of existing depression are limited.

5.10 Cervical Cancer

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

5.11 Effect on Binding Globulins

The estrogen component of [NAME] may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.12 Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.13 Chloasma

Chloasma may occur with [NAME] use, especially in females with a history of chloasma gravidarum. Advise females with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using [NAME].

6 ADVERSE REACTIONS

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

- Serious cardiovascular events *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

[Clinical trials experience: See the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* for detailed instructions. The following should be provided: (1) common adverse reactions; (2) adverse reactions leading to study discontinuation; and (3) serious adverse reactions, in a text list or tables, sorted by decreasing order of frequency. The frequency cutoff should be noted and should be appropriate for the safety database. Terms that may represent the same phenomenon before calculating frequency (e.g., disorders of menstrual frequency/volume, nausea/vomiting) should be grouped.]

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of [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 product exposure.

[Postmarketing experience: See the guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* for detailed instructions. Typically, adverse reactions already described elsewhere in labeling should not be repeated in subsection 6.2. However, if a serious adverse reaction (such as a pulmonary embolus) is described in class labeling for CHCs and there are no such events that occurred in the clinical trial(s) of the product but such events have occurred in the postmarketing setting with the product, then those postmarketing events should be included here.]

7 DRUG INTERACTIONS

The sections below provide information on substances for which data on drug interactions with CHCs are available. There is little information available about the clinical effect of most drug interactions that may affect CHCs. However, based on the known pharmacokinetic effects of these drugs, clinical strategies to minimize any potential adverse effect on contraceptive effectiveness or safety are suggested.

Consult the approved product labeling of all concurrently used drugs to obtain further information about interactions with CHCs or the potential for metabolic enzyme or transporter system alterations**.**

[If no studies were conducted with the product, this fact should be indicated as shown below; the general class labeling provided in the following sections should still be included.]

No drug-drug interaction studies were conducted with [NAME].

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances Decreasing the Plasma Concentrations of CHCs and Potentially Diminishing the Efficacy of CHCs:

Table 3 includes substances that demonstrated an important drug interaction with [NAME].

Table 3. Significant Drug Interactions Involving Substances That Affect CHCs

Metabolic Enzyme Inducers	
Clinical effect	• Concomitant use of CHCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of CHCs *[see Clinical Pharmacology (12.3)]*. • Decreased exposure of the estrogen and/or progestin component of CHCs may potentially diminish the effectiveness of CHCs and may lead to contraceptive failure or an increase in breakthrough bleeding.
Prevention or management	• Counsel females to use an alternative method of contraception or a backup method when enzyme inducers are used with CHCs. • Continue backup contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability.
Examples	Aprepitant, barbiturates, bosentan, carbamazepine, efavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, rufinamide, topiramate, products containing St. John's wort,[a] and certain protease inhibitors (see separate section on protease inhibitors below).
Colesevelam	
Clinical effect	• Concomitant use of CHCs with colesevelam significantly decreases systemic exposure of ethinyl estradiol *[see Clinical Pharmacology (12.3)]*. • Decreased exposure of the estrogen component of CHCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the CHC.
Prevention or management	Administer 4 or more hours apart to attenuate this drug interaction.

[a] Induction potency of St. John's wort may vary widely based on preparation.

Substances increasing the systemic exposure of CHCs:
Co-administration of atorvastatin or rosuvastatin and CHCs containing ethinyl estradiol increase systemic exposure of ethinyl estradiol by approximately 20 to 25 percent. Ascorbic acid and acetaminophen may increase systemic exposure of ethinyl estradiol, possibly by inhibition of conjugation. CYP3A inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice,[7] or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of CHCs.

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:
Significant decreases in systemic exposure of the estrogen and/or progestin have been noted when CHCs are co-administered with some HIV protease inhibitors (e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir), some HCV protease inhibitors (e.g., boceprevir and telaprevir), and some non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine).

In contrast, significant increases in systemic exposure of the estrogen and/or progestin have been noted when CHCs are co-administered with certain other HIV protease inhibitors (e.g., indinavir and atazanavir/ritonavir) and with other non-nucleoside reverse transcriptase inhibitors (e.g., etravirine).

7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

Table 4 provides significant drug interaction information for drugs co-administered with [NAME].

[7] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it could be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double-strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

Table 4. Significant Drug Interaction Information for Drugs Co-Administered With CHCs

Lamotrigine	
Clinical effect	• Concomitant use of CHCs with lamotrigine may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation *[see Clinical Pharmacology (12.3)]*. • Decreased systemic exposure of lamotrigine may reduce seizure control.
Prevention or management	Dose adjustment may be necessary. Consult the approved product labeling for lamotrigine.
Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy	
Clinical effect	Concomitant use of CHCs with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-binding and cortisol-binding globulin *[see Warnings and Precautions (5.11)]*.
Prevention or management	The dose of replacement thyroid hormone or cortisol therapy may need to be increased. Consult the approved product labeling for the therapy in use. *[See Warnings and Precautions (5.11)]*.
Other Drugs	
Clinical effect	Concomitant use of CHCs may decrease systemic exposure of acetaminophen, morphine, salicylic acid, and temazepam. Concomitant use with ethinyl estradiol-containing CHCs may increase systemic exposure of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).
Prevention or management	The dosage of drugs that can be affected by this interaction may need to be increased. Consult the approved product labeling for the concomitantly used drug.

[If available, specific clinical pharmacology data should be added here concerning the effects of the product on human CYP enzymes at clinically relevant concentrations (see Clinical Pharmacology (12.3)).]

7.3 Effect on Laboratory Tests

The use of CHCs may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS

[Certain subsections and headings described in the PLLR may not be pertinent to the labeling for CHCs. For example, it is not anticipated that this section would include a description of a pregnancy registry or would have information included under the Clinical Considerations heading. When information is clearly not applicable, such headings and subsections are omitted. See 21 CFR 201.56, 201.57(c)(9)(i)-(iii), and the draft guidance for industry *Pregnancy,*

Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format **for complete details on content for PLLR labeling.]**

8.1 Pregnancy

Risk Summary

[This section should summarize the human, animal, and pharmacologic data and identify the source of the data. If the product contains a new progestin or estrogen, applicants should provide a risk statement(s) that describes, for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug's pharmacology. If there are no human data, then a statement that there are no human data must be made in the Risk Summary (21 CFR 201.57(c)(9)(i)(B)) and the human data section should not be included. If embryo/fetal studies were conducted, then a sentence summarizing those studies should be included here with details under "Animal Data." If no studies were done, then a statement should be made in the Risk summary and the animal data section should not be included.

If the product contains a well-characterized progestin and estrogen, the class language provided below should be used.]

[NAME] is contraindicated in pregnancy because there is no reason to use CHCs in pregnancy. Discontinue [NAME] if pregnancy occurs. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to CHCs before conception or during early pregnancy. In animal reproduction studies in **[species]**, **[results should be summarized]**. **[OR]** Animal studies to evaluate embryo/fetal toxicity were not conducted.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Data

Human Data

[Applicants should describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, including information about the data source, number of subjects, study duration, exposure time, and limitations of the data.]

Animal Data

[Embryo/fetal (Segment II and III) studies should be reported here. If no studies were done, this heading should not be included.]

8.2 Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. **[The concentration in human milk and the actual or estimated infant dose, if available, should be described, as well as the effects on the breast-fed infant.]** CHCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. *[See also Dosage and Administration (2.2).]* The developmental

and health benefits of breast-feeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breast-fed child from (name of drug) or from the underlying maternal condition.

Data

[If available, specific pharmacologic data should be added here concerning the percentage of the product that is present in the breast milk of postpartum females.]

8.4 Pediatric Use

Safety and efficacy of [NAME] have been established in females of reproductive potential. **[Unique efficacy or safety information relevant to patients younger than 18 years of age should be provided here.]** Use of [NAME] before menarche is not indicated.

8.5 Geriatric Use

[NAME] has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

[Contraindication and any other statements that are relevant to this heading should be included with appropriate cross-references [*see Contraindications (4) and Warnings and Precautions (5.4)]*. This section should be omitted if there are no relevant data.]

8.7 Renal Impairment

[Any statements that are relevant to this heading should be added with appropriate cross-references. This section should be omitted if there are no relevant data.]

8.8 Race/Ethnicity

[Any statements that are relevant to this heading should be added and cross-referenced to other sections if appropriate. This section should be omitted if there are no relevant data.]

8.9 Body Mass Index (BMI)/Body Weight

[If studies limited eligibility on the basis of BMI/body weight:] The safety and efficacy of [NAME] in females with a BMI or body weight > **[exclusion criteria should be stated]** have not been evaluated *[see Clinical Studies (14)]*.

If data indicate an adverse effect on efficacy, that should be summarized here, and included under *Limitations of Use* in INDICATIONS AND USAGE and described in CLINICAL STUDIES. This section should be omitted if there are no relevant data and BMI/body weight were not exclusionary in the clinical trials.]

10 OVERDOSAGE

There have been no reports of serious adverse outcomes from overdose of CHCs, including ingestion by children. Overdose may cause uterine bleeding in females and nausea.

[If data are available, any pharmacokinetic or clinical statements that are relevant to this heading should be added; also, what should be monitored in case of overdose of the product should be stated.]

11 DESCRIPTION

[This section should include the proprietary name and established name, if any, of the CHC product, as well as key descriptors of the CHC product (e.g., the type of dosage form(s) and routes of administration).]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CHCs prevent pregnancy primarily by suppressing ovulation.

[If studies establish additional mechanisms by which the drug prevents conception, the additional mechanisms should be described here. Speculative claims of untested mechanisms of action should not be included.

Receptor-binding studies should not be added for the purpose of claims unless the claims were previously agreed upon with the division and are adequately supported with data from clinical studies.]

12.2 Pharmacodynamics

[If there are no relevant pharmacodynamic data, this subsection must contain a statement indicating this lack of information (21 CFR 201.57(c)(13)(i)(B)).]

12.3 Pharmacokinetics

[Available information should be provided to include the following subsections:

- **Absorption (including food effect)**
- **Distribution**
- **Elimination**
  - **Metabolism**
  - **Excretion**
- **Specific populations (e.g., geriatric patients, pediatric patients, racial or ethnic groups, patients with renal impairment, patients with hepatic impairment)**
- **Drug interaction studies]**

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[If applicable, nonclinical data should be summarized if human data are not available.]

13.2 Animal Toxicology and/or Pharmacology

[If applicable, nonclinical data should be summarized if human data are not available. Embryo/fetal (Segment II and III) studies should be summarized in subsection 8.1]

14 CLINICAL STUDIES

[Contraceptive efficacy should be reported in terms of the 1-year Pearl Index and 95 percent confidence interval around the point estimate. If studies were conducted in different geographic regions, the U.S. Pearl Index should be the focus of this section.

This information should be preceded by a description of the clinical trial efficacy database, including the overall exposure, demographics, trial design, and any exclusions from the clinical trial database beyond the contraindications to use of hormonal contraceptives. If indications in addition to contraception are sought, presentation of those results should be discussed with FDA.

If available, information about return to fertility following discontinuation of the product should be provided here.]

15 REFERENCES

[References should be minimized, but can include recommendations by an authoritative scientific body or a standardized methodology, scale, or technique if the labeling has to summarize or rely on this information for the safe and effective use of the CHC. Also citations of studies (e.g., epidemiologic studies) that inform labeling about the specific product should be referenced.]

16 HOW SUPPLIED/STORAGE AND HANDLING

[The United States Pharmacopeia storage temperature range, not a single storage temperature value, should be included. Contraceptive products use different dispensers; more complicated dispensers should be described here.]

17 PATIENT COUNSELING INFORMATION

[Although this provides general class counseling statements, these statements should be consistent with information provided in the preceding prescribing information. Some statements, particularly regarding instructions for missed pills or when to rule out pregnancy, should be customized for the particular product.]

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Cigarette Smoking

Cigarette smoking increases the risk of serious cardiovascular events from CHC use. Women who are over 35 years old and smoke should not use [NAME] *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Venous Thromboembolism

The increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater interruption in intake) the same or a different CHC *[see Warnings and Precautions (5.1)]*.

Use during Pregnancy

[NAME] is not to be used during pregnancy. Instruct the patient to stop further intake of [NAME] if pregnancy is confirmed during treatment *[see Contraindications (4)]*.

Sexually Transmitted Infections

[NAME] does not protect against HIV infection and other sexually transmitted infections.

Dosing and Missed Pill Instructions

Patients should take one tablet daily by mouth at the same time every day. Advise patients about what to do in the event pills are missed. See **"What to Do if You Miss Pills"** section in FDA-approved patient labeling *[see Dosage and Administration (2.1)]*. **[Should be modified as warranted for non-oral formulations.]**

Need for Additional Contraception

- Postpartum females who have not yet had a period when they start [NAME] need to use an additional method of contraception until **[product-specific information about starting CHCs in postpartum females should be provided]** *[see Dosage and Administration (2.2)]*.
- There is a need for a back-up or alternative method of contraception when enzyme inducers are used with [NAME] *[see Drug Interactions (7.1)]*.

Lactation

[NAME] may reduce breast milk production. This is less likely to occur if breast-feeding is well established. When possible, nursing women should use other methods of contraception until they have discontinued breast-feeding *[see Use in Specific Populations (8.2)]*.

Amenorrhea and Possible Symptoms of Pregnancy

Amenorrhea may occur. Advise the patient to contact a health care provider in the event of amenorrhea in two or more consecutive cycles or in case of symptoms of pregnancy such as morning sickness or unusual breast tenderness. **[Should be modified as warranted for extended-cycle products.]** *[See Warnings and Precautions (5.8).]*

Fertility following Discontinuation of [NAME]

Resumption of fertility after discontinuing [NAME] is expected. **[Product-specific information about the likely interval before fertility is restored should be provided, if available.]** *[See Clinical Studies (14).]*

[Other relevant information for prescribers to convey to patients to use the drug safely and effectively should be included.

Required manufacturer information (21 CFR 201.1 and 201.100(e) for drugs and 21 CFR part 610, subpart G, for biological products) should be provided at the end of the prescribing information, as well as in the patient labeling (21 CFR 310.501(c)(13)(i)), unless the patient labeling is attached to the prescribing information.]