

**Wyeth**

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5600 Fishers Lane, rm. 1061  
Rockville, MD 20852

**Re: Docket No. 2000D – 1350: Draft Guidance for Industry: Labeling for Combined Oral Contraceptives (Revision 1)**

To whom it may concern:

Reference is made to the 05 March 2004 Federal Register Notice (69 FR 10457) which announced the availability of the Draft Guidance for Industry entitled “Labeling for Combined Oral Contraceptives.”

The purpose of this correspondence is to provide the Agency with comments from Wyeth on the Draft Guidance. These comments, which are attached to this letter, pertain only to the labeling that would be implemented for all combined oral contraceptives (i.e., class labeling) and does not concern labeling information Wyeth considers to be specific for its products subject to the Guidance.

Please call me at 484-865-8424 if there are any questions regarding the information contained in this submission.

Sincerely,



Lester S. Gibbs, Ph.D.  
Associate Director  
Worldwide Regulatory Affairs

**00D-1350**

**C18**

**Guidance for Industry - Labeling for Combined Oral Contraceptives**  
**Revised Draft Guidance –March 2004**

Wyeth Pharmaceuticals Comments

- Wyeth recommends that throughout the 2004 Draft Guidance document the term “OCs” should be changed to “COCs”, because this document does concern combined oral contraceptives.
  
- **Boxed Warning in the Prescribing Information entitled **Warning: Cigarette Smoking**:** Wyeth recommends that the wording in this section from the 2000 Draft Guidance be retained. That earlier wording provides for an appropriate warning of the risks of smoking and COC use and allows the clinician to make the final determination about the individual woman’s medical history and current status regarding smoking rather than designating smoking as a contraindication. The wording “not recommended” in the 2004 Draft Guidance implies that women who are over 35 years of age who smoke are contraindicated from using COCs. (See also comments below under **CONTRAINDICATIONS**).
  
- **INDICATIONS AND USAGE**
  - Within the **INDICATIONS AND USAGE** section, Wyeth prefers the proposed wording from the 2000 Draft Guidance, “Combined oral contraceptives (COCs) are indicated for the prevention of pregnancy”, as opposed to the proposed wording from the 2004 draft, “(Name of OC) is indicated for use by women to lower the risk of becoming pregnant.” The 2004 proposed language may imply that the efficacy of the COC is questionable.
  
- **CONTRAINDICATIONS**
  - Within the **Contraindications** section, “Smoking and over 35” should be deleted as a contraindication. Wyeth believes that the decision whether to prescribe a COC should take into consideration the medical history, smoking status and contraceptive needs of individual patients. Wyeth agrees with the wording in the Boxed Warning that describes smoking and OC use. The concepts relayed in the 2000 Draft Guidance give health care providers the essential information needed to weigh the risks of pregnancy against those risks associated with COC use in their patients who are over 35 years of age and smoke.

- The words “endometrial cancers” should be added to the first bullet so that the phrase would read as follows: “Breast cancer, endometrial cancer, or other hormone-sensitive cancer, now or in the past.”
- “Thrombophlebitis or pulmonary embolism, now or in the past” should be removed and replaced with “history of deep-vein thrombophlebitis or thromboembolic disorders”, as appears in the current label for Wyeth COC products, e.g. Alesse® and Triphasil®.
- “Migraines with focal neurologic symptoms” should be changed to “Headaches with focal neurologic symptoms”, because migraine is a specific diagnosis.
- “Allergy to any components of this drug product” should be changed to “Hypersensitivity to any components of this drug product”

- **WARNINGS**

- **Myocardial infarction:** In line 183, “two to six” should be changed to “2.0 to 6.0”. Also, line 189 should be changed from “39” to “39.0”, for consistency with other numeric representations.
- **Cerebrovascular diseases:** Wyeth recommends adding the following statement: “Women with migraine (particularly headaches with focal neurological symptoms, see **CONTRAINDICATIONS**) who take combination oral contraceptives may be at an increased risk of stroke.”
- **Carcinoma of the Breast and Cervix:** Wyeth proposes deletion of the following statement: “There is substantial evidence that OCs do not increase the incidence of breast cancer.” and further recommends that the words “and thorough” be deleted from the subsequent sentence in that section.
- **Gallbladder Disease:** Wyeth recommends the following addition as the first sentence to this section: “COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.”
- **Liver Disease:** The team recommends retention of the wording that appears in the 2000 Draft Guidance.
- **High Blood Pressure:** The team recommends deletion of the phrase “progestational activity” from line 264, as this phrase is not meaningful.

- Wyeth recommends changing the heading “**Vaginal Bleeding Problems**” to “**Vaginal Bleeding Irregularities**”.

- **PRECAUTIONS**

- **Interactions with Laboratory Tests:** In subsection 5b, Wyeth recommends that the following statement: “Patients dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy.” be moved to the section entitled **Drug Interactions; Changes in plasma levels of co-administered drugs**. Wyeth also recommends a cross-reference to section 5.5 be added.
- **Geriatric Use:** Wyeth recommends that the statement be changed to read as follows: “COCs are not indicated for use in women over 65 years of age.”

- **PATIENT LABELING**

- **BOXED WARNING:** Consistent with comments above regarding the Boxed Warning in the Prescribing Information, Wyeth prefers to maintain the following language as the Boxed Warning: “Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.”
- Wyeth recommends that the statement immediately under Boxed Warning (lines 482-483) be changed to read as follows “Birth control pills are used to prevent pregnancy.” The proposed 2004 Draft Guidance language may imply that the efficacy of the COC is questionable.
- **WHO SHOULD NOT TAKE (OC NAME):** Consistent with the comment to the Prescribing Information regarding the Contraindications, Wyeth recommends removing “Smoke and are over 35 years old” from this section of the Patient Labeling.
- **WHAT ARE COMMON SIDE EFFECTS OF BIRTH CONTROL PILLS:** There appear to be inconsistencies between the Patient Labeling and the Prescribing Information. This should be rectified. For example, there are some adverse experiences in the Prescribing Information that Wyeth believes should be included in the Patient Labeling (i.e., Acne;

Decreased libido; Fluid retention; Ocular effects, including decreased tolerability to contact lenses).

- **Call your health care provider right away if you have:** Wyeth recommends that “Breast lumps” be added to the list of events.