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9/8/00 H.K.H.

Organon Inc.

September 13, 2000

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

**Docket No. 00D-1350**  
**Comments on Draft Guidance for Industry**  
**Combined Oral Contraceptives – Labeling for**  
**Healthcare Providers and Patients (June 2000)**

Dear Sir/Madam:

Reference is made to the *Federal Register*/ Vol. 65, No. 132 / Monday, July 10, 2000/ Notice of Availability of the Draft Guidance for Industry entitled, "Combined Oral Contraceptives – Labeling for Healthcare Providers and Patients" (June 2000). Reference is also made to Organon's NDA 20-713 for Mircette® (desogestrel/ethinyl estradiol and ethinyl estradiol) Tablets and the FDA correspondence dated May 22 and August 11, 2000; and NDA 20-071 for Desogen® (desogestrel and ethinyl estradiol) Tablets and the FDA correspondence dated June 5, 2000 for FDA-mandated changes to product labeling. Organon herewith provides questions/comments on this draft guidance.

1. Organon requests the names of all persons involved in the preparation of the draft guidance.
2. Under **CLINICAL PHARMACOLOGY**, the text regarding minimal androgenicity should be retained for certain products that contain this information.
3. Under **CONTRAINDICATIONS**, "Deep vein thrombosis (current or history)" is not consistent with information found in the **WARNINGS** section as it does not specify "for those who have a history of these conditions in association with estrogen use."
4. Under **CONTRAINDICATIONS**, please provide references in support of the contraindication, "Valvular heart disease with complications." Please refer to **WARNINGS**, 1. Cardiovascular disease, c. Valvular heart disease. 
5. Under **CONTRAINDICATIONS**, "Severe hypertension" should be clarified as "Uncontrolled severe hypertension."
6. Under **CONTRAINDICATIONS**, what is the rationale for eliminating endometrial carcinoma?

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7. Under **WARNINGS**, 1. Cardiovascular disease, the statement, "For COCs containing 50 µg EE, there is an increased risk of DVT compared to COCs containing less than 50 µg EE," should be included in the first paragraph. (Gerstman 1991)
8. Under **WARNINGS**, 1. Cardiovascular disease, a. Deep vein thrombosis, pulmonary embolism, the following sentences should replace the proposed paragraph for products containing desogestrel to be consistent with the FDA-mandated changes for Mircette® and Desogen® labeling:

"Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1-2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk." (FDA correspondence to Organon dated May 22, June 5, and August 11, 2000)

Additionally, the position of this paragraph is not logical. This third generation specific text should be moved to the end of this section after the general COC statements or be included in the first paragraph immediately following the sentence, "Smoking does not appear..." as it pertains to the risk of venous thromboembolic events.

9. Under **WARNINGS**, 1. Cardiovascular disease, a. Deep vein thrombosis, pulmonary embolism, as with the other COC statements in this section, the sentence, "The presence of factor V Leiden mutation and other hereditary coagulation disorders increases the risk of thromboembolic disease" should be clarified with the addition of "in COC users" at the end.
10. Under **WARNINGS**, 1. Cardiovascular disease, a. Deep vein thrombosis, pulmonary embolism, the sentence, "COC use is contraindicated for women who have active deep vein thrombosis or pulmonary embolism and for those who have a history of these conditions in association with estrogen use" is not consistent with the statement under **CONTRAINDICATIONS**, which does not specify the association with estrogen use.
11. Under **WARNINGS**, 1. Cardiovascular disease, to follow the preceding comment, valvular heart disease should then be changed to section d.
12. Under **WARNINGS**, 2. Elevated blood pressure, the statement, "For women whose current blood pressure is greater than 160+/100+ mm/Hg..." is clearer for the reader.
13. Under **WARNINGS**, 4. Lipid metabolism, the text, "High-density lipoprotein cholesterol (HDL-C) and triglycerides may..." that previously appeared under **PRECAUTIONS**, Interactions with Laboratory Tests, should be retained.
14. Under **WARNINGS**, 5. Headaches, the second sentence starting with "These symptoms..." is vague. Please repeat the phrase "Focal neurologic symptoms."
15. Under **WARNINGS**, 7. Breast cancer, the second paragraph is actually a benefit and should be moved to the **NONCONTRACEPTIVE HEALTH BENEFITS** section.

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16. Under **PRECAUTIONS**, 3. Drug Interactions, why were concerns about antibiotics removed?
17. Under **PRECAUTIONS**, 3. Drug Interactions, St. John's Wort should be included as it may interfere with metabolism.
18. Under **PRECAUTIONS**, 4. Drugs that affect laboratory tests, b. "Glucose tolerance may be impaired and insulin levels increased" is not consistent with the Carbohydrate metabolism section under **WARNINGS**.
19. Under **PRECAUTIONS**, 8. Fertility following discontinuation, please provide references that support the delay of conception. We suggest the sentence, "If affected, ovulation may be unpredictable in the first month or two following cessation of COCs."
20. Under **NONCONTRACEPTIVE HEALTH BENEFITS**, as discussed above, the sentence, "Breast cancers diagnosed in current or previous OC users tend to be less invasive than in nonusers" from the Breast cancer section under **WARNINGS** should be included in this section.
21. Organon requests confirmation that it is the intent to provide the patient with only the **PATIENT LABELING (INSTRUCTIONS FOR USE)**.
22. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, the statement "*Manufacturer to provide product specific information*" should be added to the description for 21-or 28-day pill packs for products which are neither monophasic regimens nor have a 7 day placebo interval.
23. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **Be sure you have two things ready at all times**, second bullet should be clarified for the patient to have an extra pill pack for when it is needed or in case a pill is lost (e.g., falls down the drain).
24. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **If you miss 2 or more pills in a row**, please provide support for these instructions which are different from the previous guidance.
25. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **If you miss 2 or more pills in a row**, should be consistent with the **MISSED PILLS** section (page 16). Please include the 3 bullets from the **MISSED PILLS** section or refer to the **MISSED PILLS** section.
26. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **IF YOU ARE TAKING OTHER MEDICINES**, second bullet re antibiotics, the patient should be instructed to use a backup method of birth control and not merely suggested.
27. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **IF YOU HAVE SEVERE VOMITING...**, again the patient should be instructed to use a backup method of birth control and not merely suggested.

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28. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **A FINAL REMINDER**, the patient is directed to call the healthcare professional or a phone number. Is the latter necessary?
29. Under **PATIENT LABELING (INSTRUCTIONS FOR USE)**, **A FINAL REMINDER**, the patient is directed to the professional product labeling for references. The **LABELING FOR HEALTHCARE PROVIDERS** does not include a listing of references.

Should have any questions regarding these comments, kindly contact the undersigned at (973) 325-4833.

Sincerely,



Albert P. Mayo  
Executive Director, Regulatory Affairs

GR/

via Facsimile (301) 827-6870

**1 From** 9/7/00

Date 9/7/00

Sender's Name Albert P. Mayo Phone (973) 325-4833

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**2 Your Internal Billing Reference Information** X1 10500-86506

**3 To**

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**Questions?**  
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