

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm.

1061 Rockville, MD 20852

USA

7719 00 JUL 26 Schering

Schering AG
Dr. Wilhelm Kuhnz
Dept. Pharmacokinetics
13342 Berlin
Germany

Your Ref.

Your letter dated

Our Ref. (please indicate when replying)

Telephone: +49-30- 468-12948
+49-30- 4 68-11 11
Telefax: +49-30- 468-11527

Date

2000-07-14

Combined Oral Contraceptives – Labeling for Healthcare Providers and Patients (Draft Guidance, June 2000)

Dear Madam, Sir,

With regard to the above mentioned draft guidance, I would like to make the following comment:

3. Drug Interactions

(page 9) Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol.

Comment: Since ascorbic acid is occasionally used in high doses, and since it, like ethinyl estradiol, is extensively metabolized to sulfate conjugates, it was hypothesized that gram quantity doses of ascorbic acid might interfere with the sulfation of ethinyl estradiol resulting in an increased oral bioavailability of the drug. Two studies carried out in small numbers of women seemed to confirm this interaction: ethinyl estradiol availability appeared to be increased by 50-60 % when 1 g ascorbic acid was given half-hour before estrogen administration [1,2]. However, in a more recent study this finding has been re-investigated in 37 women and there was clear evidence for the absence of a significant interaction of ascorbic acid with the metabolism of ethinyl estradiol [3]. Based on the outcome of this study it was suggested to remove ascorbic acid from the list of drug interactions with oral contraceptive steroids.

I hope that you will find these comments helpful for finalizing the guidance document.

Yours sincerely,

Dr. W. Kuhnz

cc: Dr. G.Rohlf, Dr. B. Müller

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Dr. Wilhelm Kuhnz, Schering AG

2000-07-14

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References

- [1] Back DJ, Bates M, Breckenridge AM et al. Drug metabolism by gastrointestinal mucosa: Clinical aspects. In: Prescott and Nimmo, eds. Drug Absorption. Sydney: Adis Press, 1980:80-87
- [2] Back DJ, Breckenridge AM, McIver M, Orme ML'E, Purba H, Rowe PH. Interaction of ethinylestradiol with ascorbic acid in man. Br Med J 1981;282:1516
- [3] Zamah NM, Hümpel M, Kuhnz W, Louton T, Rafferty J, Back DJ. Absence of an effect of high vitamin C dosage on the systemic availability of ethinyl estradiol in women using a combination oral contraceptive. Contraception 1993, 48:377-391.

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