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BUC & BEARDSLEY
919 EIGHTEENTH STREET, N.W.
SUITE 600
WASHINGTON, D.C. 20006-5503

WRITER'S TELEPHONE

(202) 736-3610

TELEPHONE
202-736-3600
FACSIMILE
202-736-3608

February 19, 1999

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
1451 Rockville Pike, Suite 6027-41
Rockville, MD 20852

Dear Dr. Woodcock:

Having recently seen Mr. Charles Cooper's February 1, 1999 letter, a copy of which was sent to you, I wanted to note certain central errors in his letter.

As you know, Wyeth-Ayerst has argued in its Citizen Petition and in correspondence and discussions with you and your colleagues that it is scientifically and therefore legally inappropriate for FDA, in reviewing the NDA for Duramed's five estrogen product, to rely for evidence of safety on data on Premarin and other drugs which do not have the same active ingredient. In his letter, Mr. Cooper again virtually acknowledges that Duramed has done no animal or long-term clinical safety studies of its own, but has instead apparently relied on studies of other products which contain combinations of estrogens different from those in Cenestin. He attempts to justify this reliance with the statement that FDA "commonly relies upon studies done on other estrogen class drugs in approving new drugs, even where the new drug does not contain precisely the same combination of active ingredients." He goes on to cite FDA's recent approvals of Activelle and Levlite as examples of situations in which FDA relied upon safety studies done on "a broad range of estrogen class drugs." Mr. Cooper is squarely wrong on his two examples. In fact, as discussed below, if FDA follows the same policies with respect to Cenestin as it has with Activelle and Levlite, it will disapprove the Cenestin NDA and advise Duramed that it will not approve it until the company has done the kinds of studies in animals and humans that the sponsor of Activelle conducted.

Activelle contains two active ingredients, 17 beta estradiol and norethindrone acetate. Although these individual steroids have long been marketed as single ingredient products in the United States, the two steroids have not been marketed together in the United States. Accordingly, the sponsor did not rely for its safety data solely on the information available on

Janet Woodcock, M.D.
February 19, 1999
Page 2

the individual active ingredients or on other combinations of active ingredients (nor did it rely solely on data derived from marketing of the combination in other countries). Instead, it conducted preclinical toxicology studies in rats and monkeys, and extensive clinical studies as well. Specifically, Activelle was studied in a dose ranging study in 333 women for 12 weeks, and in a phase III study of nearly 1200 women over the course of one year. The total number of subjects included in the final safety update was 3600.¹

As is the case with Cenestin, the combination of steroids in Activelle had not previously been approved through an NDA. Yet although Cenestin has apparently not been the subject of pre-clinical safety work and has been reported to have been studied in only 120 women for just 12 weeks, Activelle was the subject of animal safety studies and has been studied in 333 women for 12 weeks and nearly 1200 women for one year with significant additional clinical safety data submitted before approval. Not only did the Activelle sponsor carry its burden of demonstrating safety by conducting both animal and clinical studies, the clinical studies of Activelle were of far more women for a far greater duration than appear to have been conducted with Cenestin. The Activelle situation, therefore, flatly contradicts Mr. Cooper's assumption of reliance on studies of the individual steroids, and, instead, supports Wyeth-Ayerst's argument that safety studies of the actual combination of estrogens for which approval is sought are necessary.

The Levlite situation also supports Wyeth-Ayerst's position on this issue, not Duramed's. Levlite contains 0.1 mg levonorgestrel and 0.02 mg of ethinyl estradiol. Combinations of those two ingredients at higher doses were approved in the U.S. in 1992, and Wyeth-Ayerst's Alesse, containing the same ingredients as Levlite at the same doses, was approved in 1997. Thus, Levlite is an example of a product which contains the same active ingredients at the same dose, and the same active ingredients at lower doses, not, as Mr. Cooper supposes, an example of a situation where "the new drug does not contain precisely the same combination of active ingredients" as previously approved drugs.

Even so, the fact is that Levlite, a drug which has the same active ingredients in the same or lower doses as previously approved drugs, was studied in more women for a longer period of time than Cenestin, a drug which does not have the same active ingredient as any previously approved drug. In fact, the sponsor of Levlite conducted two Phase III trials in which 1590 women took the drug for six cycles each with no notable safety findings, and the NDA also contained published reports of studies in which a total of more than 500 women

1. Wyeth-Ayerst obtained the November 10, 1998 Medical Officer's Review for NDA 20-907 and other materials on Activelle and also Levlite from FOI Services, which had previously obtained them from FDA under the Freedom of Information Act.

Janet Woodcock, M.D.
February 19, 1999
Page 3

took a drug containing the same active ingredients at the same dose for 12 cycles, again with no notable safety findings.

Again, the comparison to Cenestin is stark: the Levlite sponsor assessed safety in studies conducted for at least twice as long in 15 times more women than Duramed did. Far from relying on reports of studies of the same or different estrogens, the Levlite sponsor conducted the kinds of studies which Wyeth-Ayerst has insisted must be conducted of Cenestin.

In short, if FDA applies the law and science as Wyeth-Ayerst has urged in its Citizen Petition and consistent with the principles manifest in the approvals of ActiVelle and Levlite, it will refuse to approve the Cenestin NDA.

Sincerely,



Nancy L. Buc

cc: Lisa D. Rarick, M.D.
Jane A. Axelrad, Esq.
Yuan-Yuan Chiu, Ph.D.
David J. Horowitz, Esq.