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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fisher Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Warner Chilcott Inc. submits this petition in accordance with 21 C.F.R. § 10.20 and § 10.30 regarding the acceptance for filing, review, and approval by the Commissioner of the Food and Drug Administration (the "Commissioner") of abbreviated new drug applications ("ANDAs") for 0.4 mg Norethindrone (NE) and 35 µg Ethinyl Estradiol (EE) oral chewable tablet products that list OVCON-35[®] Fe (now called Femcon[®] Fe) 28-day 0.4 mg NE and 35 µg EE chewable tablets (NDA 21-490, referred to herein as the "Chewable Tablets") as the reference listed drug. The petition requests that the Commissioner refrain from taking administrative action regarding the approval of all such ANDAs in which bioequivalence has not been established to the Ovcon-35 28-day oral tablet formulation (NDA 17-716, hereby referred to as Ovcon-35 Oral Tablets) and to the Chewable Tablets, and that does not include an oral irritation study showing equivalence to the Chewable Tablets.

As described in detail below, this action is requested to ensure that there is sufficient data within the ANDA application to demonstrate that the generic formulation of 0.4 mg NE and 35 µg EE chewable tablets is therapeutically equivalent to a marketed formulation, i.e., Ovcon-35 Oral Tablets, for which safety and efficacy have been previously determined through clinical testing, as well as to the product for which it will be designated as being substitutable, the Chewable Tablets.

A. Action Requested

By this petition the undersigned requests that the Commissioner stay final approval and/or effective date of final approval of any 0.4 mg NE and 35 µg EE chewable tablet ANDAs unless there is pharmaceutical equivalence and compliance with the applicable bioequivalence regulations, specifically, 21 C.F.R. § 320, and, as amended Section 505(j)(8) of the Federal Food, Drug, and Cosmetic Act ("FDCA"). Complete bioequivalence testing ensures the generic version has the same clinical effect and is as safe as the innovator product. The new drug application ("NDA") for the Chewable Tablets was approved based on data from a bioequivalence study comparing the Chewable Tablets to Ovcon-35 Oral Tablets and an oral

irritation study. The petition requests that only ANDA applications seeking approval for a therapeutically equivalent (i.e. pharmaceutically equivalent and bioequivalent) generic version of the Chewable Tablets that include pharmacokinetic comparison to Ovcon-35 Oral Tablets, as well as to the Chewable Tablets, with independent evidence for both swallowed administration and chewed administration followed by 8-oz liquid immediately after swallowing, should be considered.

The requested actions for demonstration of bioequivalence for ANDAs of 0.4 mg NE and 35 µg EE tablets, either oral or chewable, is based on the following:

- The Chewable Tablets were approved on the basis of a bioequivalence study comparing the chewable tablets (chewed) to Ovcon-35 Oral Tablets (swallowed), both followed by 240 ml of water and a clinical study assessing the potential for irritation of the oral mucosa by the chewable tablets;
- The Chewable Tablets were approved as a new drug on the basis of information filed in an NDA. However, no clinical efficacy and safety trials have been conducted for this formulation; and
- The Chewable Tablets were approved on the basis of bioequivalence data for both chewed and swallowed methods of administration.

B. Statement of Grounds

1. Regulatory History

Ovcon-35 Oral Tablets (NDA 17-716) were approved based on a new drug development package of data including evidence of safety and efficacy. The Chewable Tablets, developed as an alternative for potentially improved compliance, was approved on the basis of a bioequivalence study comparing the Chewable Tablets to Ovcon-35 Oral Tablets, as well as a targeted study assessing the potential for irritation of the oral mucosa by the chewable tablets. As there had been no major safety or efficacy issues with Ovcon-35 Oral Tablets, FDA reviewers agreed that it was reasonable to assume the same efficacy and safety profile for the new, chewable formulation. FDA reviewers concluded that “a large clinical trial was not needed since the Chewable Tablets is only a new formulation of norethindrone and ethinyl estradiol that was shown to be bioequivalent to an approved combination hormonal contraceptive product (Ovcon® 35)”¹ that had a long history of safe and effective use.

Because no Phase 3 clinical studies were done in support of the Chewable Tablets, this formulation does not have an independently characterized efficacy and safety profile. Rather, its safety and efficacy has been cross-referenced to the original formulation of Ovcon-35 Oral Tablets through the demonstration of bioequivalence.

¹ See Medical Review (s), Application Number: 21-490, Center for Drug Evaluation and Research, pg. 12, available at http://www.fda.gov/cder/foi/nda/2003/21-490_Norethindrone%20and%20Ethinyl%20Estradiol_Medr.pdf

2. Demonstration of Bioequivalence

The Chewable Tablets can either be chewed and swallowed or swallowed whole. In the case when the tablets are chewed, it is necessary to drink water or other fluids after chewing. This ensures that chewed fragments of the Chewable Tablets reliably reach the stomach and are absorbed. Accordingly, dosing for bioequivalence testing included immediately consuming 8 ounces of fluid after the tablets were chewed. Because bioequivalence testing was conducted under these conditions, such instructions also are explicit in the Dosage and Administration directions of the package insert.

The direct demonstration of bioequivalence of the Chewable Tablets (chewed) and Ovcon-35 Oral Tablets (swallowed) did not include a pharmacokinetic comparison of the two formulations where both were swallowed, i.e., the Chewable Tablets swallowed intact was not directly compared to Ovcon-35 Oral Tablets swallowed. Rather, formulation comparison and in vitro dissolution data supported the proposed labeling for the Chewable Tablets, which may be swallowed whole without chewing.

3. Potential Importance of Bioequivalence Drift

Pharmacokinetic bioequivalence between an innovator drug and a generic formulation is a necessary criterion for making a conclusion of therapeutic equivalence without proving such equivalence with clinical determinations of efficacy and safety². Bioequivalence between drug formulation B (generic) and drug formulation A (innovator) supports the assumption that the therapeutic properties (efficacy and safety) of formulation B, though untested, are equivalent to those previously demonstrated for formulation A. However, the assumed therapeutic link between products demonstrated by bioequivalence testing is recognized to suffer from the potential limitation of bioequivalence drift³. According to the concept of bioequivalence drift, sequential alterations in formulation, manufacturing process or other variables may create a situation whereby consecutive formulations remain bioequivalent but the latest vs. initial formulations may not prove bioequivalent. In such a situation, the presumption of therapeutic equivalence between the latest and initial formulations, i.e., the product that demonstrated safety and efficacy in well-controlled clinical trials in the patient population may not be valid.

The Chewable Tablets represents a formulation change from Ovcon-35 Oral Tablets for which the conclusion of therapeutic equivalence has been established through demonstration of bioequivalence. However, a subsequent formulation change to a new version of chewable tablets could potentially introduce sufficient bioequivalence drift to invalidate the implied assumption of therapeutic equivalence with the initial swallowed drug formulation. Since therapeutic efficacy of this product is all or none (pregnancy prevention or failure), it would be imprudent to assume the link between pharmacokinetic and therapeutic equivalence to any

² Food and Drug Administration. 2003. Guidance for Industry: Bioavailability and bioequivalence studies for orally administered drug products – general considerations.

³ Anderson, S., and Hauck, W.W. 1996. The transitivity of bioequivalence testing: potential for drift. *Int. J. Clin. Pharmacol. Ther.* 34:369-374.

other reference product than Ovcon-35 Oral Tablets for which clinical properties have been objectively determined.

4. Manufacturing Issues

The Chewable Tablets is an immediate-release formulation. In the approval documents, FDA's chemistry reviewer stressed the importance of "in process control or regulatory specifications" to ensure lot uniformity, and further noted "important parameters" to characterize the chewable formulation. Generic formulations of the Chewable Tablets could potentially have unexpected properties of efficacy and/or safety if process control is not sufficient to ensure lot uniformity.

5. Safety Considerations

The Chewable Tablets were investigated in an oral safety study to characterize the risk of irritation to the oral soft tissues. Mimicking the daily oral dosing regimen for this drug, the oral safety trial was a single cycle, 21-day multiple dose study. A detailed protocol, involving scoring of irritation, inflammation, abrasions and infection at multiple oral sites, was necessary to demonstrate the absence of product-related oral adverse reactions. Given the chronic exposures necessary for successful oral contraception, equivalent tolerability of a generic formulation of the Chewable Tablets could only be established by similar clinical testing of irritation potential.

As with all safety studies, it can be difficult to assess causality of observed adverse effects. In the case of the oral irritation study conducted for the Chewable Tablets, two aphthous ulcers were concluded to be unlikely related to use of the tablets⁴. Since the clinical investigator was not able to discount the remote possibility that the tablets may have contributed to the ulcers, it would be prudent for a generic formulation of the Chewable Tablets to evaluate this potential risk, as well as others, with a cross-over comparative trial. In this way it would be possible to conclude that oral irritation and other oral risks from the generic formulation were not worse than with the original formulation.

6. Overall Conclusions

The Chewable Tablets was approved as a new drug, yet clinical efficacy and safety trials were not conducted for this formulation. Rather, its therapeutic characteristics were assumed by reference to the non-chewable formulation, Ovcon-35 Oral Tablets. Any similar assumptions of therapeutic properties of a generic formulation of the Chewable Tablets would only be scientifically supportable if bioequivalence has been established with the reference listed drug for which efficacy and safety are known, i.e. Ovcon-35 Oral Tablets, as well as with the Chewable Tablets. Without such direct evidence of similarity, bioequivalence drift could

⁴ See Medical Review (s), Application Number: 21-490, Center for Drug Evaluation and Research, pg. 16, available at http://www.fda.gov/cder/foi/nda/2003/21-490_Norethindrone%20and%20Ethinyl%20Estradiol_Medr.pdf

create the situation in which the generic chewable formulation was no longer therapeutically equivalent to a reference listed drug of known clinical characteristics.

In bioequivalence testing of a generic formulation of the Chewable Tablets, which, by regulation requires identical labeling (i.e., may be administered by chewing or swallowing without chewing), it is scientifically justified to require swallowing with liquids after chewing to ensure reliable dosing. It is also scientifically justified to require that evidence be presented of bioequivalence of a generic of the Chewable Tablets when taken by swallowing without chewing.

In oral safety testing of a generic formulation of the Chewable Tablets, irritation scores and specific risks such as aphthous ulcers should be evaluated via cross-over oral irritation studies, with the requirement that the generic formulation prove no worse than the innovator product.

To further support the assumption of substitutability of a generic of the Chewable Tablets, it is furthermore justified to require that manufacturing process control and release specifications match those of the Chewable Tablets.

C. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR §25.31.

D. Economic Impact

Pursuant to 21 CFR §10.30(b), a statement of the effect of requested action on various economic indicators will be submitted only if requested by the Commissioner.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

A handwritten signature in black ink, consisting of a series of loops and a long horizontal stroke extending to the right.