

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-490

**ADMINISTRATIVE DOCUMENTS AND
CORRESPONDENCE**

14 PATENT CERTIFICATION

Not applicable for a 505(b)(1) application in accordance with 21 CFR 314.50(i).

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

EXCLUSIVITY SUMMARY for NDA # 21-490 SUPPL # _____

Trade Name Ovcon 35 Generic Name norethindrone / ethinyl estradiol chewable

Applicant Name Warner/ Chilcott HFD- 580

Approval Date November 14, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/ X / NO / ___ /

b) Is it an effectiveness supplement? YES / ___ / NO / X /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES / X / NO / ___ /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / ___ / NO / X /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / ___ / NO / X /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /__X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 17-576 Ovcon 50

NDA # 17-716 Ovcon 35 (28 d)

NDA # 18-127 Ovcon 35 (21 day)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other

than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES // NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO //

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO:

YES /___/ NO /___/

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO //

If yes, explain:

- (c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # PR 07401

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____	Study # _____
NDA # _____	Study # _____
NDA # _____	Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # PR 07401

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES /X_/ ! NO /___/ Explain:
!
!
!
!

Investigation #2 !
IND # YES /___/ ! NO /___/ Explain:
!
!
!
!
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
! _____
!

Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! _____
!

! :
! :
! :

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / /

If yes, explain: _____

Karen Anderson Project Manager, HFD-580

Signature of Preparer
Title:

Date

Signature of Office or Division Director
See signature page

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-490 Supplement Type (e.g. SE5): Supplement Number:

Stamp Date: March 29, 2002 Action Date: January 31, 2003 and 2nd Action date: Novemeber 14, 2003

HFD 580 Trade and generic names/dosage form: Ovcon[®] 35 (norethindrone / ethinyl estradiol , chewable) tablets

Applicant: Warner Chilcott, Inc. Therapeutic Class: 3S

Indication(s) previously approved: prevention of pregnancy in women who elect to use this method of contraception

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: prevention of pregnancy

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Karen Anderson, N.P. - Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337**

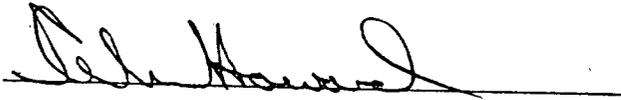
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Karen Anderson
10/27/03 09:53:47 AM

CERTIFICATION ABOUT THE USE OF DEBARRED PERSON

I hereby certify that Warner Chilcott, Inc. did not and will not use in any capacity the services of any person debarred under section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application for OVCON[®] 35 (norethindrone and ethinyl estradiol chewable tablets).



Alvin Howard
Vice President Regulatory Affairs

3/28/02

Date

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM**

NDA	NDA 21-490
Type of Application	Complete Response to Approvable Action
Applicant	Warner Chilcott Inc. 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866
Proprietary Drug Name	Ovcon® 35
Established Drug Name	norethindrone and ethinyl estradiol tablets, chewable
Indication	prevention of pregnancy
Route of Administration	oral
Dosage Form	chewable tablets supplied in 28-day dispenser
Dosage Strength	0.4-mg norethindrone + 35 µg-ethinyl estradiol
Dosing Regimen	one active tablet per day for 21 consecutive days (Days 1-21) followed by one inactive tablet per day for 7 consecutive days (Days 22-28)
Date of Submission	May 13, 2003
CDER Receipt Date	May 14, 2003
Date of Memorandum	November 14, 2003
Reviewer	Scott E. Monroe, MD Clinical Team Leader, DRUDP

RECOMMENDATION

It is recommended that Ovcon® 35 (norethindrone and ethinyl estradiol tablets, chewable) be approved for marketing for the prevention of pregnancy. The Applicant has satisfactorily addressed the three chemistry deficiencies listed in the Approvable Letter of January 31, 2003 and has submitted acceptable final labeling.

Postmarketing (Phase 4) Commitments

- No Phase 4 postmarketing clinical studies or risk management steps are recommended.

INTRODUCTION AND BACKGROUND

Ovcon® 35 (norethindrone and ethinyl estradiol tablets, chewable), hereafter referred to as Ovcon 35 chewable, is a combination oral contraceptive drug product that contains 0.4-mg norethindrone and 35-µg ethinyl estradiol per tablet. It has been developed

Ovcon® 35
28-day tablets was approved under NDA 17-716 by the FDA in 1976 and continues to be marketed in the U.S. Ovcon 35 chewable differs from the currently marketed product in that users of the new product will be able to swallow the tablet whole or chew and then swallow the tablet. The Applicant states that this option may improve compliance with dosing for some women. The dosing regimen for the proposed new drug product, like that of the presently marketed product, consists of one active tablet per day for 21 consecutive days followed by one inactive tablet per day for 7 consecutive days. Ovcon 35 chewable is currently not marketed anywhere in the world.

The original NDA 21-490 for the new chewable formulation was submitted on March 29, 2002 (CDER stamp date of April 2, 2002). The original NDA included two clinical studies. Study 07401 was designed to determine if Ovcon® 35 chewable tablets caused oral irritation; no evidence of oral irritation was seen in 52 women who completed the 21-day trial. In Study 03801, Ovcon® 35 chewable tablets were shown to be bioequivalent to the approved product, Ovcon® 35 oral tablets. No clinical trials were conducted for efficacy or safety (other than oral tolerance). However, since Ovcon 35 chewable tablets are bioequivalent to the presently marketed product, they are expected to be equally effective and to have a similar systemic safety profile.

On January 31, 2003, NDA 21-490 received an "Approval Action" because of the following three chemistry, manufacturing and controls (CMC) deficiencies:

1. Deficiencies at the Bristol-Myers Squibb manufacturing facility in Mayaguez, Puerto Rico.
2. A proposed shelf life of — that was not acceptable based on submitted data.
3. Unacceptable total acceptance criteria for — , because of the — in the drug product.

A summary of the clinical and preclinical information submitted under original NDA 21-490 can be found in the primary Medical Officer's Review (dated January 30, 2003) and the Clinical Team Leader Memorandum (dated January 31, 2003).

OVERVIEW OF INFORMATION SUBMITTED IN THE COMPLETE RESPONSE

Information submitted in the complete response included (1) CMC data to address the three deficiencies listed in the Approvable Letter of January 31, 2003, (2) revised package and physician/patient labeling, and (3) a Safety Update.

CLINICAL DATA AND INFORMATION

Safety Update and New Clinical Data

No new safety or efficacy data were submitted as part of the Complete Response of May 13, 2003 or during the present review cycle. The Applicant submitted a Safety Update (Submission of June 10, 2003) that covered the period through June 1, 2003. The Applicant

stated that “there is no new safety information to report for this product. Please note that neither nonclinical nor clinical studies have been ongoing or completed since the submission of the original NDA; similarly, no new information on Ovcon 35 (norethindrone and ethinyl estradiol chewable tablets) has been obtained from a review of the more current scientific literature. In addition, Ovcon 35 (norethindrone and ethinyl estradiol chewable tablets) is not marketed outside of the US; thus there is no non-US post marketing experience to report.”

Postmarketing Safety Data for Ovcon 35 and Ovcon 50

Because the proposed drug product (norethindrone and ethinyl estradiol tablets, chewable) is bioequivalent to the presently marketed product Ovcon 35, postmarketing safety information for Ovcon 35 (and the slightly higher dose product Ovcon 50) were reviewed by the primary Medical Reviewer. The primary Medical Reviewer states in his review of November 13, 2003 that the most recent Periodic Reports for both Ovcon 35 and Ovcon 50 “showed no additional SAEs or safety concerns.”

The Division of Drug Risk Evaluation (DDRE) was consulted for original NDA 21-490 to review the FDA’s Adverse Event Reporting System (AERS) database for all adverse event reports associated with Ovcon 50 and Ovcon 35 since their approvals. Both of these products were approved for marketing in the U.S. in the late 1970s. Based on this review, a total of 440 reports were identified. Among these were the following serious adverse events of particular concern to users of combination oral contraceptives (and the number of reports for these events): pulmonary embolus (n=4), cerebrovascular accident NOS (n=3), phlebitis NOS (n=1), cerebral infarction (n=1), cerebrovascular disorder NOS (n=1), and thrombophlebitis deep (n=1).

A follow-up consultation was requested from the DDRE. A new search of the AERS database for the period between the previous consult of January 2003 and October 24, 2003 revealed that there were no additional safety reports entered into the database listing either Ovcon 50 or Ovcon 35 as suspect drugs. The AERS database also was searched for reports submitted under the four NDAs for the Ovcon products (NDAs 17-576, 17-716, 18-127, and 18-128). No reports were found.

Medical Officer’s Comments

- *The total number of adverse event reports in the AERS database for Ovcon 50 and Ovcon 35 is very low.*
- *The number of reports of thromboembolic and thrombotic adverse events for a combination oral contraceptive is remarkably low.*

Medical Officer’s Assessment of Overall Safety

- *Although the number of women exposed to the new chewable formulation is small, Ovcon 35 tablets has been marketed in the U.S. since the late 1970s. Based upon the review of the AERS database described above, no postmarketing safety issues or safety concerns were identified with the presently marketed product. Since the new formulation has been shown to be bioequivalent to the currently marketed product, the systemic safety profile of Ovcon 35 chewable tablets should be comparable to that of the presently marketed product.*
- *There are no outstanding safety issues.*

NON CLINICAL REVIEW ISSUES

Chemistry (CMC)

Approvability. The Chemistry Reviewer (A. K. Mitra, Ph.D.) states in his review that "The sponsor has adequately addressed all the Chemistry deficiencies. Therefore, the application may be approved."

Toxicology and Preclinical Pharmacology

No new toxicology data were submitted as part of the Complete Response. The toxicology team leader (Dr. Alex Jordan) stated in his review of original NDA 21-490 that "Ovcon 35 is approvable from the standpoint of Pharmacology." He also stated "There are no new toxicology data and none are needed. There are three new inactive ingredients. Sucralose, NF a food additive ... spearmint flavor and maltodextrin are substances generally recognized as safe ..."

DRUG NAME

The Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, was again consulted for this drug product. In their Consultation Response of September 15, 2003, they state "DMETS has no objections to the use of the proprietary name, Ovcon 35 and the use of dosage form descriptor, chewable, in the established name. DMETS considers this a final review." They also stated that "DDMAC has no objections to use of the proprietary name, Ovcon 35 from a promotional perspective."

DMETS also recommended some labeling revisions to minimize potential errors with the use of the product. These are listed and fully addressed in the primary Medical Officer's Review. The most significant of the recommendations concerned the current and proposed layout of the proprietary name of Ovcon, which partially transposes the letter "v" over the first letter "O" (see below).



At quick glance, DMETS felt that the name read Ocon rather than Ovcon. They recommended that the name be clearly identified without obscuring any letters to avoid the potential for confusion.

Medical Officer's Comments

- *The review Division (Division of Reproductive and Urologic Drug Products, DRUDP) does not believe that the word Ovcon, with a partially transposed letter "v" poses a safety risk. The proprietary name has been used for this product for many years without posing a safety concern. DRUDP does not believe that, based on presently available information, a change in the presentation of the name "Ovcon" is required.*
- *Although the primary Medical Reviewer did not believe that further clarification of the term "reminder pill" in the Patient Information Inserts was needed, the term will be changed to "green reminder pill" to enhance clarity as recommended by DMETS.*

LABELING

The Applicant originally submitted labeling identical to that agreed upon during the review of original NDA 21-490. During the present review cycle, minor editorial changes were recommended by DRUDP to make the label fully compatible with current class labeling for a combination oral contraceptive.

Medical Officer's Comment

- *The Applicant's final proposed labeling submitted on November 14, 2003 incorporated DRUDP's recommendations and is acceptable.*

RECOMMENDED PHASE IV CLINICAL STUDIES AND RISK-MANAGEMENT STEPS

No Phase 4 postmarketing clinical studies or risk management steps are recommended. The long-term safety of Ovcon® 35 has been well established over the past 27 years. There is no reason to expect a different safety profile for this new chewable formulation that was shown to be bioequivalent to the currently marketed Ovcon® 35 oral tablets.

CONCLUSIONS AND RECOMMENDATIONS

It is recommended that Ovcon® 35 (norethindrone and ethinyl estradiol tablets, chewable) be approved for marketing for the prevention of pregnancy. The Applicant has satisfactorily addressed the three chemistry deficiencies listed in the Approvable Letter of January 31, 2003 and has submitted acceptable final labeling.

Postmarketing (Phase 4) Commitments

- No Phase 4 postmarketing clinical studies or risk management steps are recommended.

Scott E. Monroe, MD
Clinical Team Leader, DRUDP

Donna Griebel, MD
Deputy Director, DRUDP

Cc: HFD-580/D. Griebel/D. Shames/S. Monroe/D. Davis

This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.

/s/

Scott Monroe
11/14/03 01:46:13 PM
MEDICAL OFFICER

Donna Griebel
11/14/03 02:08:05 PM
MEDICAL OFFICER

T03-74
November 14, 2003

Media Inquiries: 301-827-6242
Consumer Inquiries: 888-INFO-FDA

**FDA Approves Ovcon 35 as the First Chewable
Oral Contraceptive Tablet for Women**

The FDA today approved Ovcon 35, an oral, spearmint-flavored contraceptive tablet that can be chewed and swallowed. This new version of Ovcon 35, indicated for the prevention of pregnancy, provides one more alternative to the many types of oral contraceptives currently on the market. Ovcon 35 contains a progestin (norethindrone) and an estrogen (ethinyl estradiol) found in products that are already marketed.

The directions for use tell women that the pill may be swallowed whole or chewed and swallowed. If the pill is chewed and then swallowed, the woman should drink a full glass (8 ounces) of liquid immediately afterwards so that the full dose of medication reaches the stomach and no residue is left in the mouth.

Ovcon 35 is available only in a 28-day regimen. Each package contains 21 round, white tablets, with

-More-

Page 2, T03-74, Ovcon 35

11/17/2003

norethindrone and ethinyl estradiol followed by seven reminder green (inactive) tablets to complete a 4-week-cycle.

Like other birth control pills, Ovcon 35 is effective for prevention of pregnancy when used as directed. The risks of using this product are similar to those of all birth control pills and include an increased risk of blood clots, heart attack, and stroke. The labeling also carries the warning that cigarette smoking by women, especially over age 35 increases the risk of serious cardiovascular side effects from use of combination hormonal contraceptives.

The product is manufactured by Bristol Myers Squibb Company, Princeton, N.J., and will be marketed by Warner Chilcott, Inc., Rockaway, N.J.

####

Teleconference Meeting Minutes

Date: September 26, 2003 **Time:** 11:00 AM **Location:** PKLN; 17B30

NDA 21-490 **Drug:** Ovcon 35 (norethindrone and ethinyl estradiol chewable tablets)

Indication: Contraception

Sponsor: Warner Chilcott, Inc.

Type of Meeting: Guidance

Meeting Chair: Amit K. Mitra, Ph.D. – Chemistry Reviewer, for the Division of Reproductive and Urologic Drug Products, DNDC II, Office of New Drug Chemistry

Meeting Recorder: Karen Anderson, NP - Project Manager, DRUDP (HFD-580)

FDA Attendees:

Amit Mitra, Ph.D. - Chemistry Reviewer, DRUDP (HFD-580)

Karen Anderson – Project Manager, DRUDP (HFD-580)

External Attendees:

Ileana Brown Manager, Regulatory

Alvin Howard Vice President Regulatory

Meeting Objective: Extension of Shelf life for the drug product.

Background: Discussion of recent amendment to the NDA from the sponsor requesting to increase the shelf life from _____ to 18 months.

Discussion/Decisions Made:

- The acceptance criteria for ethinyl estradiol assay on batch release is to be within _____ to obtain a shelf life of 18 months.

Action Items:

- To send in amendment reflecting this change

Chair Concurrence: A. Mitra

Prepared by: K. Anderson

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Amit K. Mitra
11/4/03 08:37:16 AM



Warner Chilcott, Inc.

RECEIVED

OCT 22 2003

FDR / CDER

RECEIVED

OCT 21 2003

CDR/CDER

October 17, 2003

ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

ORIGINAL

N-000-BL

**Re: NDA 21-490, OVCON[®] 35 (norethindrone/ethinyl estradiol tablet, chewable) – Amendment 26
Draft Container Labeling**

Dear Sir or Madam:

Provided herein is the draft container labeling for OVCON[®] 35 (norethindrone and ethinyl estradiol tablets, chewable) consisting of carton and foil labeling provided as hard copy and electronically. Carton and foil labeling is provided for trade, physician's sample and clinic sale presentations; note that the physician's sample consists of a box and a carton tray. Electronic labeling is provided as pdf files according to the guidance document titled "Providing Regulatory Submissions in Electronic Format - General Considerations", January 1999. Files were scanned with McAfee VirusScan v4.5.1 SP1.

Please contact the undersigned at 973.442.3229 if there are any questions stemming from this submission.

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosure

Desk Copy (cover letter): Ms. Karen Anderson via facsimile

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Warner Chilcott, Inc.	DATE OF SUBMISSION October 17, 2003
TELEPHONE NO. (Include Area Code) (973) 442-3200	FACSIMILE (FAX) Number (Include Area Code) (973) 442-3280
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): Warner Chilcott Rockaway 80 Corporate Center 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 21-490

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) norethindrone and ethinyl estradiol tablets, chewable	PROPRIETARY NAME (trade name) IF ANY OVCON® 35	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (If any)	CODE NAME (If any)	
DOSAGE FORM: Chewable Tablet	STRENGTHS: 0.4 mg norethindrone and 0.035 mg ethinyl estradiol/day	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE: Prevention of pregnancy in women who elect to use this product as a method of contraception		

APPLICATION INFORMATION

APPLICATION TYPE (check one) NEW DRUG APPLICATION (21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE 505 (b)(1) 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: _____ Holder of Approved Application: _____

TYPE OF SUBMISSION (check one) ORIGINAL APPLICATION AMENDMENT TO A PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION Submission of requested container labeling

PROPOSED MARKETING STATUS (check one) PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (List related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA 17-716 OVCON 35 (norethindrone and ethinyl estradiol tablets, USP), 28 day regimen;
NDA 17-576 OVCON 50 (norethindrone and ethinyl estradiol tablets, USP), 28 day regimen;
DMF — DMF — DMF — DMF — DMF —

RECEIVED
OCT 21 2003
CDR/CDER

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one) Draft Labeling Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
 - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
 - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
 - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(l)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify)

CERTIFICATION

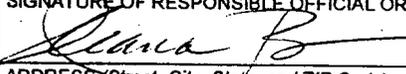
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Ileana Brown Manager, Regulatory Affairs	DATE October 17, 2003
ADDRESS (Street, City, State, and ZIP Code) Rockaway 80 Corporate Center, 100 Enterprise Drive, Suite 280, Rockaway, NJ 07866		TELEPHONE NUMBER (973) 442-3200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
REG-09
401 Rockville Pike
Rockville, MD 20852-1448
FORM FDA 356h (4/00)

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

13 Draft Labeling Page(s) Withheld

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE Received:
July 3, 2003

Desired Completion Date:
September 1, 2003
PDUFA Date: November 14, 2003

ODS CONSULT #: 02-0183-1

TO: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Karen Anderson
Project Manager
HFD-580

PRODUCT NAME:
Ovcon 35
(Norethindrone and Ethinyl Estradiol Tablets,
Chewable)
0.4 mg/35 mcg – 28 day regimen

NDA SPONSOR: Warner Chilcott

NDA #: 21-490

SAFETY EVALUATOR: Linda Y. Kim-Jung, R.Ph.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) has conducted a final review of the proposed proprietary name Ovcon 35 with the use of the dosage form descriptor, chewable, to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Ovcon 35 and the use of dosage form descriptor, chewable, in the established name. DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days then the name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document. In addition, DMETS recommends implementation of the labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
2. DDMAC has no objections to use of the proprietary name, Ovcon 35 from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Phone: (301) 827-3242
Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 15, 2003

NDA NUMBER: 21-490

NAME OF DRUG: **Ovcon 35**
(Norethindrone and Ethinyl Estradiol Tablets, Chewable)
0.4 mg/35 mcg – 28 day regimen

NDA SPONSOR: Warner Chilcott

I. INTRODUCTION

This review is in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for a final review of the proprietary name, *Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable)*. The container label, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors. The proposed proprietary name, Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable) was found acceptable by DMETS on November 15, 2002 (ODS Consult 02-0183). Since that review, DMETS has not identified any new proprietary or established names with the potential to look-alike and or sound-alike confusion with Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable).

PRODUCT INFORMATION

The proprietary name "Ovcon" has been utilized in the U.S. marketplace since January 1982. Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable) is an extension of Warner Chilcott's combination oral contraceptive Ovcon product line. Ovcon is currently marketed as Ovcon 35 (21 and 28 day regimen) and Ovcon 50. Ovcon 35 (28 tablets) provides a regimen for oral contraception derived from 21 white tablets composed of a combination of 0.4 mg of norethindrone and 0.035 mg of ethinyl estradiol followed by 7 green tablets of inert ingredients. Ovcon 35 (21 tablets) contains the same 21 white tablets without the green tablets. Differing only in the dosage form, Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable) contains equal amounts of norethindrone and ethinyl estradiol as the currently marketed Ovcon 35 Tablets. The recommended dosage is one chewable tablet once daily. Ovcon 35 Chewable Tablets will only be available in a 28 day pack.

II. RISK ASSESSMENT

The DMETS medication error staff conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable) to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted.⁴ The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An Expert Panel discussion was conducted to review all findings from the searches. In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name "Ovcon."

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable). Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns about the name, Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable), with regard to promotional claims.
2. The expert panel did not have any concerns with the proposed proprietary name, Ovcon 35 (Norethindrone and Ethinyl Estradiol Tablets, Chewable).
3. DMETS' Phonetic Orthographic Computer Analysis (POCA) was unavailable to search at the time of this review.

B. ADVERSE EVENT REPORTING SYSTEMS (AERS) DATABASE SEARCH

DMETS searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Ovcon-35. The MEDRRA Preferred Term (PT), "Medication Error" and the drug name, Ovcon% were used to perform the search. The search uncovered one report that was not related to name confusion with Ovcon.

¹MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

²Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

4. We recommend that the labeling (e.g., color) be distinctly different between Ovcon 35 chewable and Ovcon 35 regular tablets.

B. CONTAINER LABEL

Please define the container label which states “_____” versus other container label without such statement. There is no explanation in the HOW SUPPLIED section of the insert labeling. Is for “_____” any different from the other 28-day packs?

C. PATIENT PACKAGE INSERT LABELING

WHAT TO DO DURING THE MONTH subsection, statement #2 states “Start the next pack on the day after your last “reminder” pill. Define what a “reminder” pill is.

IV. RECOMMENDATIONS

1. DMETS has no objections to the use of the proprietary name, Ovcon 35 and the use of dosage form descriptor, chewable, in the established name.
2. DMETS recommends the labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC has no objections to use of the proprietary name, Ovcon 35 from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, Project Manager, at 301-827-3242.

Linda Y. Kim-Jung, R.Ph.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)

Concur:

Denise P. Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety (ODS)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Linda Kim-Jung
10/9/03 02:37:41 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/9/03 02:49:27 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/10/03 10:41:55 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 27, 2003

FROM: Evelyn R. Farinas, R.Ph., M.G.A., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430
(DDRE)

THROUGH: Mark Avigan, M.D., C.M., Acting Director
Division of Drug Risk Evaluation, HFD-430
(DDRE)

TO: Daniel Davis, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580
(DRUDP)

SUBJECT: Consult: Update of AERS adverse event reports from January 8, 2003
through October 24, 2003
Drugs: Ovcon-50 and Ovcon-35 (norethindrone and ethinyl estradiol)
NDA#'s 17576, 17716, 18127, 18128

PID # D030631

EXECUTIVE SUMMARY

An AERS search for adverse event reports listing Ovcon-50 and Ovcon-35 between the previous consult of January 2003 and October 24, 2003, revealed that there were no additional reports entered into AERS for this product in this 9-month interval or in 2003. It is unknown if the sponsor has any periodic type reports included in the annual periodic summary to be submitted at later time. As stated in the previous consult, during the 26 years of marketing, there have been a total of 440 reports received for Ovcon-35 and Ovcon-50 since the first approval in 1975.

Background

Ovcon-50 and Ovcon-35 products manufactured by Warner Chilcott were approved between 1975 and 1978. A new formulation filed under NDA 21-490 is pending on review. Warner Chilcott provided a complete response on May 14, 2003, to the January 31, 2003 approvable letter for NDA 21-490 that addressed a chemistry GMP deficiency at one of their facilities. ODS provided a review of a total of 440 AERS reports associated with these products on January 10, 2003. Because these drugs have been on the market for 26 years, our overall summary indicated that reporting rate of any adverse event was not feasible without complete use data. DRUDP requested that DDRE review

the AERS data for 2003 in order to update their review for the second action, which has a goal date of November 14, 2003.

DRUG INFORMATION AND LABELING

Currently Ovcon-50 and Ovcon-35 are marketed as tablets to be used in 21- (Ovcon-35 only) or 28-day regimens for oral contraception. The active OVCON 35 peach-colored tablets contain 0.4 mg norethindrone and 0.035 mg ethinyl estradiol. The active OVCON 50 yellow-colored tablets contain 1 mg norethindrone and 0.05 mg ethinyl estradiol. In the **CONTRAINDICATIONS** and **WARNINGS** sections, the labeling addresses the population who should not use oral contraceptives, and the risk of cardiovascular side effects associated with oral contraceptive use. The **WARNINGS** section also includes a boxed warning listing the increased risk of cigarette smoking and cardiovascular side effects from oral contraceptive use. The **ADVERSE REACTIONS** section lists serious adverse reactions that have been associated with the use of oral contraceptives (e.g., arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease, etc.)

Methods

AERS was searched for adverse event reports listing Ovcon-35 or Ovcon-50 as suspect drug that were submitted to the FDA between January 11, 2003 and October 24, 2003. In addition, AERS was searched for reports submitted under the four NDA's for Ovcon products (17-576, 17-716, 18-127 and 18-128).

Results

AERS searches revealed that in the 9-month interval between January 11, 2003, and October 24, 2003, there were no reports entered into AERS listing Ovcon-35 or Ovcon-50 as suspect drug.

Evelyn R. Farinas, R.Ph., M.G.A.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Evelyn Farinas
10/27/03 03:20:00 PM
DRUG SAFETY OFFICE REVIEWER

Min Chen
10/27/03 03:39:36 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
PKLN Rm. 6-34**

FROM: **Daniel Shames, M.D.**

**Director, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)**

DATE June 30, 2003	IND NO.	NDA NO. 21-490	TYPE OF DOCUMENT Complete Response to AE	DATE OF DOCUMENT May 14, 2003
NAME OF DRUG Ovcon 35 (norethindrone/ ethinyl estradiol tablets, chewable)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 3S (Oral Contraceptive)	DESIRED COMPLETION DATE September 1, 2003
NAME OF FIRM: Warner Chilcott, Inc.				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

This request is for a re-review of the last label as it was reviewed greater than 6 months ago. The sponsor and DRUDP agree with the label as submitted to the EDR during the first review cycle. The sponsor received an AE January 31, 2003 related to a cGMP issue. They came back with a complete response May 14, 2003. The new goal date is November 14, 2003, however, DRUDP may be ready to approve much earlier.

PDUFA DATE:
ATTACHMENTS:

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Karen Anderson
6/30/03 01:39:27 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-490

Warner Chilcott, Inc.
Attention: Ms. Ileana Brown
Manager, Regulatory Affairs
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Ms. Brown:

We acknowledge receipt on May 14, 2003 of your May 13, 2003 resubmission to your new drug application for Ovcon[®] 35 (norethindrone and ethinyl estradiol tablets, chewable).

We consider this a complete, class 2 response to our January 31, 2003 action letter. Therefore, the user fee goal date is November 14, 2003.

If you have any question, call Karen Anderson, N.P., Regulatory Project Manager, at (301) 827-4259.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Margaret Kober
5/28/03 03:53:22 PM
Chief, Project Management Staff

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 5, 2003

TO: Margaret Kober, R.Ph. - CPMS / DRUDP (HFD-580)

FROM: Karen Anderson, N.P. - Project Manager / DRUDP (HFD-580)

SUBJECT: **Close out AE Action January 31, 2003**
NDA 21-490,
Ovcon[®] 35 (norethindrone/ethinyl estradiol, Chewable) Tablets

The following amendments to NDA 21-490 must be closed out in DFS to complete the AE Action January 31, 2003:

April 29, 2002	C
May 16, 2002	PW
June 5, 2002	BZ
June 12, 2002	XR
August 16, 2002	BC
September 10, 2002	BC
October 17, 2002	BC
December 3, 2002	BC
December 9, 2002	BZ
December 12, 2002	C
December 19, 2002	BC
December 23, 2002	BC
January 22, 2003	BC
January 27, 2003	BB
January 29, 2003	BL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Karen Anderson
2/6/03 12:50:57 PM
CSO

Margaret Kober
2/6/03 01:46:47 PM
CSO

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS
CLINICAL TEAM LEADER MEMORANDUM**

NDA	NDA 21-490
Type of Application	Original NDA
Applicant	Warner Chilcott Inc. 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866
Proprietary Drug Name	Ovcon® 35
Established Drug Name	(norethindrone and ethinyl estradiol tablets, chewable)
Indication	Prevention of pregnancy
Route of administration	Oral
Dosage Form	Chewable tablets supplied in 28-day dispenser
Dosage Strength	0.4-mg norethindrone + 35 µg-ethinyl estradiol
Dosing Regimen	One active tablet per day for 21 consecutive days (Days 1-21) followed by one inactive tablet per day for 7 consecutive days (Days 22-28)
Date of Submission	March 29, 2002
CDER Receipt Date	April 2, 2002
Date of Memorandum	January 31, 2003
Reviewer	Scott E. Monroe, MD Clinical Team Leader, DRUDP

RECOMMENDATION

It is recommended that Ovcon® 35 receive an approvable action for marketing for the prevention of pregnancy. Before the application may be approved, the following deficiencies will need to be addressed and resolved:

1. During a recent inspection of the manufacturing facility for the final drug product (Bristol-Myers Squibb facility, Mayaguez, Puerto Rico), an Agency field investigator conveyed deficiencies to the facility's representative. Satisfactory resolution of these deficiencies is required.
2. Based on available stability data, the proposed — shelf life for the drug product is not acceptable.

3. Because _____, it is recommended that the Applicant:
- a. Tighten the acceptance criterion for _____ substances to not exceed _____ during the shelf life.
 - b. Adopt the following _____ assay specification for ethinyl estradiol:

No Phase 4 postmarketing studies or risk management steps are recommended.

INTRODUCTION AND BACKGROUND

Ovcon® 35 chewable formulation (hereafter referred to as Ovcon 35 chewable) is a combination oral contraceptive drug product that contains 0.4-mg norethindrone and 35-µg ethinyl estradiol per tablet. It has been developed

_____ Ovcon® 35 28-day tablets was approved under NDA 17-716 by the FDA in 1976 and continues to be marketed in the U.S. Ovcon 35 chewable differs from the currently marketed product in that users of the new product will be able to swallow the tablet whole or chew and then swallow the tablet. The Applicant states that this option may improve compliance with dosing for some women. The dosing regimen for the proposed new drug product, like that of the presently marketed product, consists of one active tablet per day for 21 consecutive days followed by one inactive tablet per day for 7 consecutive days. Ovcon 35 chewable is currently not marketed anywhere in the world.

OVERVIEW OF CLINICAL DATA SUBMITTED IN SUPPORT OF APPLICATION

Clinical data from 2 studies were submitted in support of this application. Table 1 provides an overview of these studies. Study PR 03801 was a single dose, 2-treatment, 2-period, crossover pharmacokinetic study designed to show that Ovcon 35 chewable tablets (the proposed new formulation) are bioequivalent to Ovcon 35 28-day tablets (presently marketed formulation). Study PR 07401 was designed to assess the oral tolerance and safety of Ovcon 35 chewable tablets taken once daily for 21 consecutive days.

Table 1 Overview of Clinical Studies Submitted in Support of NDA 21-490

Protocol No.	Study Objective	Study design	No. subjects enrolled / completed	Age range	Dose / duration of dosing	Comment
PR 03801	To show bio-equivalence between the 2 formulations	Single-center, open-label, single dose, 2 period, 2 treatment, crossover study	28 / 27	20-34	1 chewable or 1 marketed Ovcon® 35 tablet	Blood samples for PK analyses collected for 60 hours post dose
PR 07401	To assess oral tolerance and safety of new formulation	Single-center, open-label, multiple dose, single treatment, oral irritation study	57 / 52	18-44	1 chewable tablet daily for 21 days	Oral evaluations on Days 1, 3, 8, 22, and 29

Medical Officer's Comment

- *The limited new clinical data submitted by the Applicant are adequate to support approval of Ovcon 35 chewable tablets from a clinical perspective if (1) the new drug product is shown to be bioequivalent to the currently marketed product and (2) there are no oral tolerance or oral safety issues. Both of these criteria were satisfied as described below.*

Human Pharmacokinetic and Efficacy Studies

Data from a single pharmacokinetic study designed to show bioequivalence between Ovcon 35 chewable tablets and the currently marketed product were submitted in the NDA. No efficacy studies, per se, were conducted with Ovcon 35 chewable tablets.

Study PR 03801 (“A Study to Determine the Bioavailability of WC 2045 Tablets Relative to that for Norethindrone 0.4 mg and Ethinyl Estradiol 35 µg Tablets, USP”) was an open-label, single-dose, randomized, 2-period, 2-treatment, pharmacokinetic crossover study. A total of 27 female subjects completed the clinical phase of the study. Based on the outcome of this study both the Applicant and the FDA biopharmaceutical reviewer concluded that Ovcon 35 chewable tablets are bioequivalent to the currently marketed product (Ovcon 35 tablets). The pharmacokinetics findings from this trial are summarized in Table 2.

Table 2 Pharmacokinetic Parameters for New and Original Formulations

Parameter	NE * (Ovcon Chewable vs. Ovcon Oral) 90 % CI (ratio of LSM)	EE * (Ovcon Chewable vs. Ovcon Oral) 90 % CI (ratio of LSM)
AUC _{0-t} (pg•h/mL)	92.5 – 108.8 % (100.3%)	104.1 – 114.7 % (109.3 %)
AUC _{0-∞} (pg•h/mL)	94.4 – 111.1 % (102.4 %)	103.0 – 112.7 % (107.7 %)
C _{max} (pg/mL)	83.1 – 99.1 % (90.7 %)	111.2 – 121.0 % (116.0 %)

NE = norethindrone; EE = ethinyl estradiol.

Source: NDA 21-490, Volume 14, pg 35.

The biopharmaceutical reviewer (Myong-Jin Kim, Pharm.D.) stated the following in her review:

“The BE [bioequivalence] study supports that Ovcon Chewable chewed and Ovcon Oral swallowed whole are bioequivalent under fasting conditions. The proposed labeling of this NDA indicates that Ovcon Chewable may be chewed or swallowed whole. Although a BE study comparing Ovcon Chewable swallowed versus Ovcon Oral swallowed was not performed, the in-vitro dissolution data support the proposed labeling since the formulation changes are minor. Comparative in-vitro dissolution results of Ovcon Chewable and Ovcon Oral show that the dissolution profiles are similar for both EE and NE.

Since the BE study was conducted by administering Ovcon Chewable and Ovcon Oral with 240 mL of water, the dosage and administration section of the label should indicate that Ovcon Chewable is to be taken with water if it were to be chewed and swallowed.”