Medical Officer's Comments

- *Based on the demonstrated bioequivalence of Ovcon 35 chewable tablets to the presently marketed product, it is anticipated that the contraceptive effectiveness of the new formation also will be comparable to that of the presently marketed product (Ovcon 35 28-day).*
- *The Division Director's Summary of Basis of Approval for NDA 17-716 (Ovcon 35 28-day) stated the following: "Ten investigators studied 1,970 women for 20,230 cycles. Of these patients, 229 completed 24 or more cycles. The use effectiveness pregnancy rate is 1.36."*
- *The most recently approved combination oral contraceptive by the Division (Ortho Tri-Cyclen Lo Tablets) had an overall use-effectiveness pregnancy rate of 2.36 per 100 women-years of use in the pivotal clinical efficacy trial.*
- *Based on (1) the demonstrated bioequivalence of Ovcon 35 chewable tablets and the presently marketed formulation and (2) the efficacy data provided in support of NDA 17-716, a clinical efficacy study for the new formation is not required.*
- *In the bioequivalence study, subjects drank 240 ml of water after chewing and swallowing the test tablet. Labeling will need to state that after chewing and swallowing the tablet, the user should drink a full glass (8 ounces) of liquid.*

SAFETY STUDIES AND SAFETY DATA

Clinical Studies

The Applicant conducted one clinical study to assess the local tolerance and safety of the proposed new formulation. Study PR 07401 ("A Clinical Study to Evaluate the Safety of a Chewable, Oral Contraceptive following Daily Use by Human Female Subjects of Childbearing Potential") enrolled 57 women of whom 52 completed all aspects of the study. Subjects took one chewable tablet daily for 21 days. The intraoral soft tissues were examined for inflammation, irritation, abrasions, infection, and any other abnormalities at screening and Study Days 1, 3, 8, 22, and 29.

A formal consultation to review the findings from this study was requested from the Division of Dermatologic and Dental Drug Products (DDDDP). Dr. John Kelsey, DDS, medical reviewer in DDDDP stated the following in the conclusion of his review:

> "The oral irritation study conducted in support of this NDA filing was of appropriate design and was apparently well conducted. The method and frequency of examination were appropriate to detect oral irritation caused by the study medication. The study report states that the only intraoral lesions that occurred during the study were two small aphthous ulcers that occurred in the same patient at different times and locations in the mouth. The Sponsor incorrectly reported an additional intraoral lesion, a "sore on the tongue," as an adverse event, rather than under the Oral Soft Tissue Examination. The aphthous ulcers and tongue sore that were reported are not clearly related to study drug and don't cause concern. Based on this study, this product does not appear to cause significant oral irritation."

Medical Officer's Comments

- *This medical officer concurs with the conclusion of the DDDDP medical reviewer (Dr. Kelsey) and the primary DRUDP medical reviewer (Dr. Davis) that, based on the reported findings from Study PR 07401, Ovcon 35 chewable does not appear to cause significant oral irritation.*
- *No other safety studies were conducted and no other safety data, other than the very limited data from pharmacokinetic Study PR 03801, were included in the Application.*
- *A total of only 85 women were exposed to the new chewable formulation of Ovcon® 35. In the bioequivalence study, 28 women were exposed to only a single dose; in the 21-day oral irritation study, 57 women were enrolled and 52 completed the exposure to once a day dosing for 21 days. Although the number of women exposed to the new chewable formulation is small, Ovcon® 35 has been marketed in the U.S. since 1976. Since the new formulation has been shown to be bioequivalent to the currently marketed product, the systemic safety profile also should be comparable. Therefore, the subject exposure to the new chewable formulation is adequate under these circumstances.*

Postmarketing Safety Data for Ovcon 35

The Division of Drug Risk Evaluation was consulted to review the FDA's Adverse Event Reporting System (AERS) database for all adverse event reports associated with Ovcon 50 and Ovcon 35. 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 particularly concern in users of combination oral contraceptives (and the number of reports for these events): pulmonary embolus (n=4), cerebrovascular accident NOS (n=3), phlebitis NOS (1), cerebral infarction (n=1), cerebrovascular disorder NOS (n=1), and thrombophlebitis deep (n=1).

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.*

Safety Update

The Applicant stated in Amendment No. 13, submitted on 10 January 2003, that all safety data obtained with the new formulation of Ovcon 35 were submitted in the original NDA.

Medical Officer's Comments Regarding 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 should also be comparable to that of the presently marketed product.*
- *There are no outstanding safety issues.*

NON CLINICAL REVIEW ISSUES

Chemistry (CMC)

The chemistry reviewer (A. K. Mitra, Ph.D.) recommended the following: "The application is approvable pending resolution of all the deficiencies recorded in the Draft Deficiency letter." These deficiencies are summarized as follows.

1. The most critical of the deficiencies was a "withhold" recommendation by the Office of Compliance based on their inspection of one of the manufacturing facilities. This recommendation was based on one of the manufacturing facilities (Bristol-Myers Squibb facility, Mayaguez, Puerto Rico) not being in compliance with cGMP.
2. The proposed — shelf life for the drug product was not acceptable, based on stability data submitted by the Applicant.
3. — it was recommended by the chemistry reviewer 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:

Toxicology and Preclinical Pharmacology

The toxicology team leader (Dr. Alex Jordan) stated in his review that "Ovcon 35 is approvable from the standpoint of Pharmacology." He also states "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 ..."

Medical Officer's Comment

- *Because of the CMC-related deficiencies, it is recommended that this Application receive an approvable action.*

DRUG NAME

The Applicant initially proposed the following proprietary and established names

- Proprietary name: Ovcon® 35
- Established name: (norethindrone and ethinyl estradiol chewable tablets)

A formal consultation was requested from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, to review these names. In their initial response to the consultation, DMETS stated "...DMETS has conducted a review of the proposed proprietary name — ...DMETS has no objection to —." However, an email from Alina Mahmud, Team Leader, DMETS on January 29, 2003, stated that " —

Most chewable tablets include the word 'chewable' in juxtaposition to the official compendial name."

DMETS also recommended a change that they felt would reduce the potential for error. The current and proposed layout of the proprietary name of "Ovcon" 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 Comment

- *The review Division (DRUDP) does not believe that the word Ovcon, with a partially transposed letter "v" poses a safety risk. It has been used for this product for many years.*
- *Based on further discussion with DMETS and the Sponsor, it was agreed that the proprietary name for the new formulation would be Ovcon® 35 and the established name would be (norethindrone and ethinyl estradiol tablets, chewable).*
- *DRUDP believes the proprietary name "Ovcon® 35" is acceptable for the new chewable formulation since the Applicant intends to discontinue marketing Ovcon® 35 (non-chewable formulation) as soon as the present product is approved.*

LABELING

The Applicant submitted labeling based largely on the presently marketed Ovcon 35 drug product. The label was revised by the Division to make it compatible with current class labeling for a combination oral contraceptive and submitted to the Applicant for review and comment.

Medical Officer's Comment

- *An important addition to the label was to instruct the patient that if the tablet is chewed and swallowed, she "should drink a full glass (8 ounces) of liquid immediately after swallowing."*
- *The Applicant's final proposed labeling submitted on January 30, 2003 is acceptable.*

RECOMMENDED PHASE IV STUDIES AND RISK-MANAGEMENT STEPS

No Phase 4 postmarketing 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 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. — , 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.

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

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/s/

Scott Monroe
1/31/03 04:05:12 PM
MEDICAL OFFICER

Donna Griebel
1/31/03 04:35:31 PM
MEDICAL OFFICER

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

PID#: D030024

DATE: January 10, 2003

FROM: Evelyn R. Farinas, R.Ph., M.G.A.
Post Marketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

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

SUBJECT: Consult
Drug: Ovcon-35 and Ovcon-50 (norethindrone and ethinyl estradiol tablets)
Reaction: AERS update (1993-2002)

EXECUTIVE SUMMARY

An AERS search for adverse event reports listing Ovcon-50 and Ovcon-35 revealed that there were a total of 440 reports, which may include duplicates. Most were of domestic origin. The three most frequently reported adverse events were in decreasing frequency: unintended pregnancy (127), menometrorrhagia (66) and drug ineffective (43). The frequency of reporting of other additional adverse events of interest (i.e., thromboembolic and thrombotic events) was five counts of chest pain, four of pulmonary embolus (PE), three of cerebrovascular accident NOS, and one count each of cerebral infarction, cerebrovascular disorder NOS, phlebitis NOS, and thrombophlebitis deep. Most reports (80%) listed Ovcon-35 as the suspect drug. Over the last 10 years (1993 through 2002) the number of reports sent to the Agency averaged 17 reports per year, and decreased from a high of 60 reports in 1997 to a low of two in 2002. Where listed (in less than half of the reports), most events occurred in women in the 21-30 age group. There were 35 reports with a serious outcome, including one fatality. This fatal outcome case listed PE as the adverse event in a 20-year old female. Line listing from AERS indicate that overall, during the 26 years of marketing, there has been a small number of reports submitted for Ovcon-35 and Ovcon-50, although a true assessment of reporting rate is not possible without use data. Line listings and a hands-on review of the serious outcome cases also suggest that use of Ovcon tablets does not lead to serious thromboembolic events. However, the higher than expected failure rate in the AE reports is a concern.

BACKGROUND

The Division of Reproductive and Urologic Drug Products (DRUDP) requested a search in AERS for reports between 1993 and 2002 listing Ovcon-50 and Ovcon-35 as the suspect drug. Approval dates for Ovcon-50 and Ovcon-35 are August 1975 and March 1976, respectively. At this time, Warner Chilcott, Inc., Ovcon's manufacturer, has a pending application for a new chewable tablet formulation (NDA 21-490).

DRUG INFORMATION AND LABELING

Currently Ovcon-50 and Ovcon-35 are marketed as tablets to be used in 21- (Ovcon-35only) 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

A search in AERS was conducted on January 7, 2003, for cases listing Ovcon-35 or Ovcon-50 submitted to the Agency between 1993 and 2002. There were no limitations regarding the selection of adverse events.

SUMMARY OF CASE SERIES

Line listings from AERS indicated that from 1976 through 2002 the Agency received 440 reports, almost all of domestic origin (98%). The majority of reports indicated that AE occurred in women aged 21 to 30 years, although age was listed in less than half of the reports. The frequency of reporting for the top five AE and for the AE of interest was:

Unintended pregnancy	127
Menometrorrhagia	66
Drug ineffective	43
Cyst NOS	23
Amenorrhea NOS	20
Chest pain	5
Pulmonary embolus	4
Cerebrovascular accident NOS	3
Hepatic function abnormal	2
Phlebitis NOS	1
Cerebral infarction	1
Cerebrovascular disorder NOS	1
Thrombophlebitis deep	1

Over the last 10 years (1993 through 2002) the number of reports sent to the Agency averaged 17 reports per year, and decreased from a high of 60 reports in 1997 to a low of two in 2002. The frequency of reporting in the most recent ten years is:

1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
37	29	12	20	60	2	2	3	5	2

There were 35 reports listing a serious outcome, the majority of which were in women 30 years of age or younger (mean 27.8, median 26). There were three counts of PE in this group, including a fatality in a 20-year old woman. No other details, such as duration of therapy, time to onset or medical history were provided in this 1990 fatal outcome report. Two additional reports listed phlebitis. The most frequently reported AE among the serious outcome reports was unintended pregnancy (n=8). Ovcon-35 was listed as the suspect drug in 80% of the reports (n=28).

DISCUSSION

Line listing data from the AERS search revealed that most of the 440 reports received by the Agency were periodic reports, listing a non-serious outcome. Most of the adverse events reported with a frequency of five or more are listed in the labeling (e.g., changes in menstrual flow, alopecia, headache, vomiting, etc.). Unintended pregnancy was listed in 28% of the reports. The typical failure rate during the first year of continuous use of combined oral contraceptives is 3% (Table 1, Ovcon-35 and Ovcon-50 labeling). Very few reports were associated with thromboembolic AE and stroke. Where listed (in less than half of the reports), most events occurred in women in the 21-30 age group. The majority of reports listed Ovcon-35 as the suspect drug (n=386).

A hands-on review of the 35 serious-outcome reports indicated that most were associated with the 35-mcg ethinyl estradiol strength (28 of the 32 listing strength). There were few thromboembolic events reported. As with the total number of reports, unintended pregnancy was cited most often in the serious outcome reports. Some reports (6) indicated use for an unapproved indication (e.g., regulation of menses, estrogen replacement, polycystic ovary disease and cardiac regulation).

Over the last 10 years (1993 through 2002) the number of reports sent to the Agency averaged 17 reports per year, and decreased from a high of 60 reports in 1997 to a low of two in 2002. This sudden peak and subsequent decrease in reporting may be associated with the January 1997, voluntary recall of one lot of Ovcon-35 28-day regimen compact. At that time, the manufacturer (Bristol-Myers Squibb Company) issued a recall due to mis-packaging, in which color-coded tablets were packaged in reverse order. The colors were transposed between the active ingredient tablet (peach) and the inert tablet (green). The manufacturer indicated this error did not pose a health threat. A formulation change or new indication might be a possible explanation for the fluctuations in reporting; however, a search in the Division File System indicated that there were no supplements for new indications nor formulation changes approved for any of the Ovcon tablets in 1997, nor in subsequent years.

CONCLUSION

Line listing from AERS indicate that overall during the 26 years of marketing there has been a small number of reports submitted for Ovcon-35 and Ovcon-50, although a true assessment of reporting rate is not possible without use data. Line listings and a hands-on review of the serious outcome cases also suggest that use of Ovcon tablets does not lead to serious thromboembolic events. The higher than expected failure rate in the AE reports is a concern.

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/s/

Evelyn Farinas
1/17/03 02:26:59 PM
CSO

Julie Beitz
1/24/03 07:47:16 AM
DIRECTOR

Teleconference Meeting Minutes

Date: January 6, 2003 **Time**: 4:00 PM **Location**: PKLN; 17B43

NDA 20-544 **Drug:** Ovcon 35 (norethindrone and ethinyl estradiol chewable tablets)

Indication: Contraception

Sponsor: Warner Chilcott, Inc.

Type of Meeting: Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, 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:
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemistry Reviewer, DRUDP (HFD-580)
Vendateswa Jarugula, Ph.D. – Acting Team Leader for Pharmacokinetics, OCPB @ DRUDP (HFD-580)
Myong-Jin Kim, Pharm. D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Karen Anderson – Project Manager, DRUDP (HFD-580)

External Attendees:

Olu Aloba, Ph.D.	Director, Pharmaceutics
Ileana Brown	Manager, Regulatory
Tina DeVries, Ph.D.	Vice President, Pharmaceutics
Alvin Howard	Vice President Regulatory

Meeting Objective: To inform the sponsor of pending chemistry as well as clinical pharmacology issues.

Background: The proposed dissolution specification is too broad and therefore resolution of the issues on setting the specification of dissolution is warranted.

Discussion/Decisions Made:
- Dissolution – The proposed dissolution acceptance criteria are deemed too broad. Based on the dissolution profile of the bio-batch Q of ~ at 30 minutes is considered to be more reasonable acceptance criteria.
- No stability data are available to demonstrate whether the new acceptance criteria are applicable to the drug product during the shelf-life.
- If the drug product has difficulty to meet the acceptance criteria during the shelf-life, the expiration date should be adjusted accordingly.

Action Items:
- Implement the dissolution specifications: Q= → at 30 minutes.
- Test the stability samples with the new dissolution acceptance criteria.

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/s/

Moo-Jhong Rhee

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I concur

Warner Chilcott, Inc.

January 10, 2003

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Fishers Document Room
Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-490, OVCON® 35 (norethindrone/ethinyl estradiol chewable tablet) - Amendment No. 13 Safety Update Report

Dear Sir or Madam:

Reference is made to the New Drug Application for OVCON® 35 (norethindrone and ethinyl estradiol chewable tablet) submitted on March 29, 2002. In accordance with 21 CFR 314.50 (d)(5)(vi)(b) Warner Chilcott would like to state 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 the US; thus, there is no non-US post-marketing experience to report.

In conclusion, there is no new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions and adverse reactions in the proposed labeling submitted in the original NDA.

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

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-490

INFORMATION REQUEST LETTER

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:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ovcon® 35 (norethindrone/ethinyl estradiol chewable tablet).

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

Please provide information on the container closure system for storage of the drug substances.

Excipients

Please provide your specifications for FD&C yellow #6 aluminum lake, FD&C blue#1 aluminum lake, D&C yellow #10 aluminum lake, and spearmint flavor.

Drug Product

1. Please adopt in-process control limits for [redacted] of the drug substances. This control is necessary to assure uniformity of the drug substances throughout the batch.

2. Please justify the [redacted] of ethinyl estradiol used during manufacturing of Ovcon 35 chewable tablets [redacted]

3. Please adopt a justified specification for [redacted]

4. Please adopt specifications for [redacted] of the active and placebo tablets, unless justified.

5. Provide CFR reference for the [redacted] used in the manufacture of the [redacted] oags for bulk storage of tablets prior to packaging.

6. The specification for ethinyl estradiol and norethindrone related substances should be adjusted based on safety and manufacturing capability as recommended in ICHQ6A. Please provide safety information of individual related substances.

Stability of the drug product

1. Please provide an explanation for the assay failure of ethinyl estradiol (potency [redacted] at [redacted] time points for samples stored under 25° C/ambient humidity.

2. According to the stability data provided, the proposed shelf life of [redacted] is not acceptable.

3. [redacted] you should modify the stability commitment to state "Warner Chilcott would place the first three commercial production lots on accelerated and long term stability according to the attached protocol". The stability protocol should include frequency of testing and specific tests including the [redacted] assay, [redacted]

Methods Validation

1. Provide a list of reference standards for related substances of ethinyl estradiol and norethindrone that you have kept in retain for methods validation to be performed by the FDA laboratory.

2. For dissolution sample assay testing using HPLC, the acceptance criteria resolution between ethinyl estradiol and norethindrone should be greater than [redacted] unless justified.

3. For potency and content uniformity assay testing using HPLC, the acceptance criteria for resolution between ethinyl estradiol and norethindrone should be not less than [redacted], unless justified.

Labeling

Rx only and storage conditions should be included on the blister card label.

If you have any questions, call Karen Anderson, NP, Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug
Products, HFD-580
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
1/7/03 03:49:04 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-490

Warner Chilcott, Inc.
Attention: Alvin Howard
Vice President, Regulatory Affairs
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OVCON Chewable (norethindrone/ethinyl estradiol) Tablets.

We have received your submission dated March 29, 2002, received April 2, 2002.

We have completed the Microbiology review of your submission and have the following recommendations and comments:

You should explain why microbial limits testing will not be conducted on the finished product.

If you have any questions, call Jennifer Mercier, Regulatory Health Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

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

DATE: July 11, 2002

FROM: John V. Kelsey, D.D.S., M.B.A.
Dental Team Leader, Division of Dermatologic and Dental Drug Products (HFD-540)

THROUGH: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and Dental Drug Products (HFD-540)

SUBJECT: Consult Request for NDA 21-490 OVOCON® 35 —
(Norethindrone and Ethinyl Estradiol Tablets, USP)

TO: Jennifer Mercier
Division or Reproductive and Urologic Drug Products, (HFD-580)

Dental Officer's Review of Consult
NDA 21-490

Drug: OVCON© 35 —
(Norethindrone and Ethinyl Estradiol Tablets, USP)

Sponsor: Warner Chilcott Laboratories

Pharmacologic Category:
Contraceptive

Consult Date: June 21, 2002
Received Date: July 1, 2002
Review Date: July 8, 2002
Due Date: September 1, 2002

Consult: #349

Background:

This consult requests, "review the attached information and forward any comments..." Attached is the final study report of, "A Clinical Study t Evaluate the Safety of a Chewable Oral Contraceptive Following Daily Use by Human Female Subjects of Childbearing Potential." This material was submitted as part of the NDA package for NDA 21-490.

Study Design:

The Sponsor conducted a single center, open label study in 57 healthy female adults of child bearing potential age 18 and above. Subjects took one chewable oral contraceptive daily for 21 days. Subjects were assessed using the Oral Soft Tissue Examination (OSTE) and assessed for intraoral abrasions at Screening and Days 1, 3, 8, 22 and 29. Adverse event data was also collected.

Inclusion Criteria:

1. Female, 18 years of age or older of child bearing potential
2. Good general health and a negative urine pregnancy test on Day 1
3. If they were using oral contraceptives, were willing to switch to the study medication during the course of the study
4. Understood that the experimental medication does not have established efficacy, and were willing to use a non-hormonal (e.g., Barrier) method of contraception during the course of the clinical study
5. Able to read, understand and sign an informed consent

Exclusion Criteria:

1. Were currently using other hormonal contraceptives, aside from oral contraceptives (i.e., Norplant, Mirena IUD, Progestasert IUD), or had a Depo-Provera injection within 3 months prior to enrollment
2. Had any visible disease of the oral mucosa (i.e., a score of greater than "1" on the oral soft tissue examination), which n the opinion of the investigative personnel, would have interfered with the evaluation
3. Had a known sensitivity to oral contraceptives
4. Were 35 or older and smoked
5. Had a contraindication for the use of oral contraceptives (e.g., history of thrombophlebitis or thromboembolic disorders, known or suspected clotting disorders, cerebral vascular or coronary artery disease, known or suspected carcinoma of the breast, known or suspected estrogen-dependent neoplasia, genital bleeding of unknown cause, or a history of benign or malignant liver tumor or liver disorders)
6. Had dentures, which in the opinion of the investigative personnel would have interfered with the study results
7. Were receiving systemic or topical drugs or medications, which in the opinion of the investigative personnel would have interfered with the study results
8. Were females who planned to become pregnant during the study or were breast-feeding

Conduct of the Study:

At the Screening/Baseline visit, medical history and informed consent were obtained and it was established that the subject met the inclusion and exclusion criteria. In addition, a pelvic exam was conducted to identify any condition that would contraindicate oral

contraceptive therapy. A soft tissue exam was conducted and subjects were questioned about their use of concomitant medications. Subjects who met all of the criteria for enrollment in the study were instructed to schedule their Day 1 visit on the first day of their next menstrual cycle (± 2 days). Subjects were instructed to use a barrier method of birth control during the study.

At the Day visit a urine pregnancy test was administered, and concomitant medication and adverse event information were collected. The study medication was dispensed and instructions for use were given. The first dose of the study medication was taken and an oral exam was conducted 30 minutes later. Subjects were given a medication log to record the date and time of medication usage.

On Days 3, 8 and 22 information on concomitant medication and adverse events was collected and an oral soft tissue exam was conducted. Compliance was checked and on Day 22 product usage logs and any unused study drug was collected.

Reviewer's comment: The frequency of examination was appropriate to detect oral irritation caused by the study medication and is consistent with recommendations given to the Sponsor by the Agency.

Subjects returned to the study site on Day 29, at which time concomitant medication and adverse event information were collected, a final soft tissue exam was conducted and a urine pregnancy test was administered.

Visit Schedule:

	Screening/ Baseline	Treatment Period				Final Visit
		Day 1	Day 3	Day 8	Day 22	Day 29
Informed Consent	X					
Medical History	X					
Inclusion/Exclusion	X					
Urine Pregnancy test		X				X
Pelvic Examination	X					
Oral Soft Tissue Exam	X	X*	X	X	X	X*
Product Dispensed		X				
Concomitant Meds.	X	X	X	X	X	X
Adverse Events		X	X	X	X	X
Compliance			X	X	X	
Return Study Prod.					X	

* Day 1 soft tissue exam took place 30 min. following the first dose of study medication.

Oral Soft Tissue Assessment:

The Oral Soft Tissue Examination (OSTE) looked at inflammation, irritation and/or infection. The examiner assessed 11 areas of the mouth (buccal, labial and sublingual

mucosa, tongue, hard and soft palate, uvula and oropharynx), which were rated as normal or abnormal using a scale as follows:

0 Normal
1 Erythema plus slight edema
2 Moderate erythema and/or edema (beginning of tissue breakdown or slough)
3 Severe inflammation/irritation (definite blistering, ulceration or epithelial slough)

Reviewer comment: The scale for assessing the oral soft tissue is similar to scales used to measure oral mucositis. It has the advantage that the mouth is divided into multiple areas, thereby encouraging discipline in the examination process. It is an acceptable way of assessing oral irritation.

Any abrasions reported by the subject or observed by the oral health investigator were noted, and the location of each abrasion was specified. The severity of each abrasion was scored using the following scale:

0 None
1 Mild
2 Moderate
3 Severe

Reviewer's comment: Because there was no description of the various levels of abrasion given, this scale would not be useful in a quantitative sense. However, since no subjects in the study experienced abrasion, the specific merits of the scale are irrelevant.

Results:

Ninety-three women were screened and 57 were enrolled and received treatment with the study product. Five subjects discontinued the study prematurely – 4 were non-compliant to the protocol and one was lost to follow-up. All treated subjects (57) are included in the safety analysis for this study.

Subject Enrollment and Disposition

Total no. of Subjects, n(%)	
Screened	93
Enrolled	57
Treated	57 (100%)
Completed	52 (91.2%)
Discontinuations, n(%)	
Total	5 (8.8%)
Due to:	
AE	0
Protocol noncompliance	4 (7.0%)
Lost to follow-up	1 (1.8%)

Reviewer's comments:

1. *There were 18 protocol deviations involving 16 subjects. All appear to be minor, including missed doses of study product, examinations outside of the prescribed visit window and the like.*

2. *Compliance was good. Of the 52 completers, only 3 were not in complete compliance with the treatment regimen and those violations were minor. Similarly, the concomitant medications taken by the subjects would not be expected to have had an impact on the safety profile of the product.*

Subjects were examined on Days 1, 3, 8, 22 and 29 for irritation, inflammation and/or abrasion. Only one subject experienced any soft tissue abnormalities. That patient presented with a 2 mm aphthous ulcer on each of two separate occasions at different locations in the mouth. It was the opinion of the investigator that these ulcers were unrelated to study treatment.

Reviewer's comment: Because aphthous ulcers are attributable to multiple, poorly defined etiologies, it is possible that the ulcers reported in this patient may have been due to the study medication. However, aphthous ulcers are common and benign and the fact that a single subject experienced aphthous ulcers does not raise concern.

Adverse events were experienced by 15 subjects who experienced 22 AE's overall.

Reviewer's comments:

1. *One of the adverse events that was reported was a "sore on the tongue" experienced by subject #58. This sore was reported by the subject and lasted for 16 days during the treatment period and was deemed as not likely to be related to study medication. This lesion should have been observed by the examiner and should have been reported under the results for the Oral Soft Tissue Examination.*

2. *This reviewer won't comment on the overall AE profile for this study. Presumably the AE's for this study will be captured in the overall safety database.*

Conclusions and Recommendation:

The oral irritation study conducted in support of this NDA filing was of appropriate design and was apparently well conducted. The method and frequency of examination were appropriate to detect oral irritation caused by the study medication. The study report states that the only intraoral lesions that occurred during the study were two small aphthous ulcers that occurred in the same patient at different times and locations in the mouth. The Sponsor incorrectly reported an additional intraoral lesion, a "sore on the tongue," as an adverse event, rather than under the Oral Soft Tissue Examination.

The aphthous ulcers and tongue sore that were reported are not clearly related to study drug and don't cause concern. Based on this study, this product does not appear to cause significant oral irritation. The overall safety database should be reviewed to assess whether other intraoral lesions were reported in subjects taking the study medication.

John V. Kelsey, DDS, MBA

cc: NDA 21-490
HFD-540/Div File
HFD-540/TL/Kelsey
HFD-540/DO/Gilkes/Hyman
HFD-540/PM/Kozma-Fornaro
HFD-540/PTTL/Jacobs
HFD-540/PT/See
HFD-580/PM/Mercier

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/s/

John Kelsey
7/11/02 03:58:32 PM
MEDICAL OFFICER

Jonathan Wilkin
7/14/02 04:18:16 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Jonathan Wilkin**
Director, Division of Dermatologic and Dental Drug Products; HFD-540

FROM: Jennifer Mercier, HFD-580, 7-4260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 21, 2002		21-490	Original NDA submission	March 29, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ovcon 35 (norethindrone/ethinyl estradiol chewable tablets)	**Standard**		September 1, 2002

NAME OF FIRM: Warner Chilcott, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Microbiology Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:
Please review the attached information and forward any comments to Jennifer Mercier at 7-4260. This study was requested in the IND stage of the development of this drug.
HFD-580/Division File
HFD-580/Mercier

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jennifer L. Mercier
6/21/02 11:31:36 AM

Filing Meeting Minutes

Date: May 20, 2002 **Time**: 10:30-11:00 AM **Location**: PKLN; 17B43

NDA 21-490 **Drug:** Ovcon® 35 (norethindrone/ethinyl estradiol) Chewable Tablet

Indication: pregnancy prevention

Sponsor: Warner Chilcott, Inc.

Type of Meeting: Filing

Meeting Chair: Dena Hixon, MD - Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Jennifer Mercier - Project Manager, DRUDP (HFD-580)

FDA Attendees:
Dena Hixon, M.D. – Acting Deputy Director, DRUDP (HFD-580)
Ridgely Bennett, M.D. – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. – Chemist, DNDCII @ DRUDP (HFD-580)
Kate Meaker, M.S. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Myong Jin Kim, Pharm.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Jennifer Mercier – Project Manager, DRUDP (HFD-580)

Meeting Objective: To establish if the submission is fileable.

Background: Warner Chilcott, Inc. submitted a NDA on April 2, 2002 for a chewable oral contraceptive. OVCON 35 (norethindrone/ethinyl estradiol) Tablets is currently approved as oral tablets and the sponsor has submitted this NDA for a new chewable tablet. This submission is based on bioequivalence to the approved oral formulation and clinical studies for evaluation of oral irritation only. There are no controlled clinical trials in this application.

Discussion/Decisions Made:
Clinical comments:

- This application is fileable.
- There are no clinical issues for this application because it is a NDA with bioequivalence study only.
- The medical officer will review the labeling for this product pending final review.
- The NDA should be consulted to the Dermatologic Division for review of the local irritation study.

Clinical Pharmacology and Biopharmaceutics comments:

- This application is fileable.

- This NDA is based on one bioequivalence study.
- The Ovcon 35 chewable tablet formulation studied in Study PR 03801 (Report CR 01002) is the same as the to-be-marketed formulation.
- The sponsor should be asked if they have any food effects studies on this product or the previously approved product. The sponsor should submit any information on food effect if there are any studies performed.
- All subjects in bioequivalence studies were instructed to chew the tablets, but the proposed labeling allows for either chewing or swallowing them whole. The sponsor will need to limit the labeling instructions to chewing or present data to demonstrate bioequivalence with swallowing the tablet whole.

Statistical comments:

- No statistical review is needed for this application.

Toxicology comments:

- This application is fileable.

Chemistry:

- SThis application is fileable.
- There will be some issues regarding the shelf-life of this product because of the limited amount of stability data that was submitted in the NDA, and failure of one lot under accelerated conditions.
- A microbiology consult is need for this application.

Action Items:

- Submit a consult to the Division of Microbiology. (done: 5.17.02)
- Submit a consult to the Dermatologic Division regarding the local irritation study.
- Contact the sponsor to request that they provide evidence of bioequivalence with swallowing the tablets whole or change the proposed labeling for dosage and administration to indicate that the tablets must be chewed. (Done: June 7, 2002)

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/s/

Dena Hixon

6/11/02 02:46:19 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Peter Cooney**
Director, Division of Microbiology, HFD-160

FROM: Jennifer Mercier, HFD-580, 7-4260

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 17, 2002		21-490	Original NDA submission	March 29, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Ovcon 35 — (norethindrone/ethinyl estradiol chewable tablets)	**Standard**		September 1, 2002

NAME OF FIRM: Warner Chilcott, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE—NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Microbiology Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS:

Please review the attached information and forward any comments to Jennifer Mercier at 7-4260. The chemist is interested in the review of the composition and specification. The sponsor did not conduct microbial limit test on the drug product.

HFD-580/Division File
HFD-580/Mercier

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jennifer L. Mercier
5/17/02 09:23:40 AM

Screening of New NDA
Division of Biometrics II

Date: May 14, 2002

NDA #: 21-490

Priority Classification: 3S

Trade Name: OVCON 35

Applicant: Warner Chilcott, Inc.

Generic Name: Ethinyl estradiol / Nonethindrone

Date of Submission: April 2, 2002

Indication: Prevention of pregnancy

No. of Controlled Studies: none

User Fee Goal Date: 1/31/03

Date of 45-Day Meeting: 5/20/02

Medical Officer: Ridgely Bennett, M.D.

Project Manager: Jen Mercier

Screened by: Kate Meaker, M.S.

Volume numbers in statistical section: 1.17-20

Anticipated Review Completion Date: none

Comments:

1. OVCON 35 is currently approved as an oral tablet. This application requests approval for a chewable tablet form.

2. This submission is based on bioequivalence to the approved oral form. There are no controlled clinical studies in this application.

3. A statistics review is not needed for this application.

Statistical Reviewer

Concur: Dr. Welch

cc:
Archival NDA #21-490
HFD-580
HFD-580/RBennett, JMercier, DShames
HFD-715/ENevius, MWelch, KMeaker

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/s/

Katherine Meaker
5/15/02 03:50:42 PM
BIOMETRICS

Mike Welch
5/16/02 11:14:14 AM
BIOMETRICS
Concur

GALEN
HOLDINGS PLC

ORIGINAL

RECEIVED
MAY 0 1 2002
HFD-580/CDER

April 29, 2002

NEW CORRESP

NC

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-490, OVCON® 35 (norethindrone/ethinyl estradiol chewable tablet) - Amendment No. 1 Correction to User Fee Cover Sheet

Dear Sir or Madam:

Reference is made to the New Drug Application for OVCON 35 (norethindrone/ethinyl estradiol chewable tablet) submitted on March 29, 2002 and specifically to the copy of the User Fee Cover Sheet therein enclosed. Ms. Beverly Friedman, User Fee Staff, has contacted Warner Chilcott and has confirmed that a full NDA user fee has been assessed for NDA 21-490 because the data contained in Report RR 00802.0, "A Clinical Study to Evaluate the Safety of a Chewable, Oral Contraceptive Following Daily Use by Human Female Subjects of Childbearing Potential" (Protocol PR 07401) have been deemed to be clinical data required for approval.

Warner Chilcott has now forwarded the payment for the balance of the user fee due and has revised the User Fee Cover Sheet to indicate that the Application requires clinical data for approval and that the required clinical data are contained in the Application. A copy of the revised User Fee Cover Sheet is herein enclosed for archival.

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

Sincerely,

Ileana Brown
Manager
Regulatory Affairs

Enclosure

Desk Copy: Ms. Jennifer Mercier (HFD-580)

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
DATE
CSO INITIALS

Rockaway 80 Corporate Center ■ 100 Enterprise Drive, Suite 280 ■ Rockaway, New Jersey 07866
Phone: (973) 442-3200 Fax: (973) 442-3283 800-521-8813

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	DATE OF SUBMISSION
Warner Chilcott, Inc.	April 29, 2002
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(973) 442-3200	(973) 442-3280
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Warner Chilcott Rockaway 80 Corporate Center 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866	

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)*	PROPRIETARY NAME *(trade name)* IF ANY
norethindrone and ethinyl estradiol chewable tablets	OVCON® 35

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Chewable Tablets	0.4 mg norethindrone and 0.035 mg ethinyl estradiol/day	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 Correction of User Fee Cover Sheet

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 —

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, 211or 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	DATE
Ileana Brown	Ileana Brown Manager, Regulatory Affairs	April 29, 2002

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
Rockaway 80 Corporate Center, 100 Enterprise Drive, Suite 280, Rockaway, NJ 07866	(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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Warner Chilcott, Inc.
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, New Jersey 07866

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 442-3200

3. PRODUCT NAME

OVCON 35 (norethindrone and ethinyl estradiol chewable tablets)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 21-490

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4300

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes 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
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice-President, Regulatory Affairs	4/29/02

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-490

Warner Chilcott, Inc.
Attention: Alvin Howard
Vice President, Regulatory Affairs
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Ovcon® (norethindrone/ethinyl estradiol) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	March 29, 2002
Date of Receipt:	April 2, 2002
Our Reference Number:	NDA 21-490

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 2, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 2, 2003.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier, B.S.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
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/

Jennifer L. Mercier
4/10/02 04:18:52 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-490	Efficacy Supplement Type	Supplement Number	
Drug: Ovcon® 35 (norethindrone / ethinyl estradiol chewable tablets)		Applicant: Warner Chilcott, Inc.	
RPM: Karen Anderson, N.P.		HFD- 580	Phone # (301) 827-4260
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	January 31,2003 & November 14, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee #3981	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes (x) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	N/A
• Information: Verify that patent information was submitted	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity Summary (approvals only)	X
Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	11.07.03
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	10.17.03
• Reviews	
❖ Post-marketing commitments	N/A
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	Filing
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
❖ Clinical review(s) *(indicate date for each review)*	
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	X
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Statistical review(s) *(indicate date for each review)*	5.16.02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	1.03.03
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	3.29.02., 1.30.03, 11.5.03
❖ Environmental Assessment	N/A
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	10.18.02
❖ Facilities inspection (provide EER report) Withhold 1st. cycle	Date completed: 11.04.03 ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Jan. 23, 2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

46 Draft Labeling Page(s) Withheld