CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-490

MEDICAL REVIEW(S)

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of NDA re-submission

NDA	NDA 21-490
Type of Application	Re-submission (Complete response)
Applicant:	Warner Chilcott Inc. 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866
Drug Name:	
Established name:	(norethindrone and ethinyl estradiol tablets, chewable)
Trade:	OVCON® 35
Chemical:	norethindrone and ethinyl estradiol
Pharmacologic category:	combination estrogen and progestin steroid hormone
Indication:	prevention of pregnancy
Route of Administration:	oral
Dosage Form:	chewable tablets supplied in 28-day dispenser
Strength:	0.4 mg norethindrone and 0.035 mg ethinyl estradiol per active tablet
Dosing Regimen:	one active tablet per day for 21 consecutive days followed by one inactive tablet per day for 7 consecutive days
Related Submissions:	NDA 17-576 Ovcon® 50 28-day: approved 8-28-75 NDA 17-716 Ovcon® 35 28-day: approved 3-29-76 NDA 18-127 Ovcon® 35 21-day: approved 7-05-78 NDA 18-128 Ovcon® 50 21-day: approved 7-05-78
Related Documents:	a. Safety Updates P-017 (dated 7-17-03), P-016 (dated 4-26-02) and P-015 (dated 5-14-01) for NDA 17-716 b. Annual Reports Y-031 (dated 6-24-03), Y-030 (dated 6-13-02) and Y-029 (dated 8-09-01) for NDA 17-716 c. Safety Update P-019 (covering 8-01 through 7-03) for NDA 17-576, Ovcon® 50
Submitted:	March 29, 2002 (original NDA) and May 14, 2003
Review Completed:	November 3, 2003
Review Finalized:	November 13, 2003
Medical Reviewer:	Daniel Davis, MD, MPH

EXECUTIVE SUMMARY

1 Recommendations

1.1 Recommendations on Approvability

From a clinical perspective, this reviewer recommends approval of Ovcon® 35 chewable tablets containing norethindrone 0.4 mg and ethinyl estradiol 0.035 mg. —

— — he

new product will be marketed only as a 28-day regimen.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps

No special 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 marketed Ovcon® 35 oral tablets.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

Since the approvable letter of January 31, 2003, there have been no additional clinical studies. The only issues were three CMC related items that have been adequately addressed and resolved.

2.2 Efficacy

No clinical trials were held for contraceptive efficacy, but Ovcon 35 chewable tablets are expected to be equally effective and to have a similar systemic safety profile as the presently approved and marketed product (Ovcon® 35).

2.3 Safety

2.3.1 Submitted clinical trial safety data

Oral Safety: The results in Study 07401, submitted in the original NDA, showed no evidence of any potential for irritation to the oral soft tissues with once daily use of the study product over a 21-day span. No other safety issues were identified during this oral safety study.

2.3.2 Other safety data

The Division of Drug Risk Evaluation (DDRE) was consulted for the original NDA submission to review the FDA's AERS database for all adverse event reports associated with Ovcon® 50 and Ovcon® 35 since their original FDA approvals in 1975 and 1976. A total of 440 reports were identified, which is a very low number. The total of 11 thromboembolic and thrombotic adverse events for this combination hormonal oral contraceptive is extremely low. The Drug Risk reviewer and the medical (clinical) reviewers concluded that there were no outstanding safety issues with Ovcon® 35 regular tablets or the newly formulated Ovcon® 35 chewable tablets.

A follow-up consultation was requested from the DDRE. Their AERS search for AE reports listing either Ovcon 50 or Ovcon® 35 between the previous consult of January 2003 and October 24, 2003 revealed that there were no additional reports entered into AERS. In addition, AERS was searched for reports submitted under the four NDAs for Ovcon products (17-576, 17-716, 18-127, and 18-128) and no reports were found.

The following three periodic reports, submitted since January 31, 2003, were also reviewed and showed no additional SAEs or safety concerns:

1. Ovcon 50, NDA 17-576, periodic report P-019 covering 8-01 through 7-03
2. Ovcon 35, annual report YY-031, stamp date 6-24-03
3. Ovcon 35, periodic report P-017, stamp date 7-17-03, covering to 2-28-03

Based on the two DDRE consultations and review of the three additional periodic reports, it appears that Ovcon® 35 has a very good long-term safety record. Ovcon® 35 has been marketed for over 27 years. Although the AERS reporting system is not complete, in the AERS database since 1976 there are reports for only one death, 4 pulmonary emboli and 3 cerebrovascular accidents for Ovcon® 35 oral tablets.

Drug-Drug Interaction
No special studies were performed for this NDA. The Product Insert (PI) label does contain a revised section for Drug-Drug Interactions.

Overall Benefits and Risk: The benefits of effective contraception and the labeled non-contraceptive benefits of combination hormonal oral contraceptives are well defined. The important risks have also been well characterized, although data continue to emerge which lead to periodic reevaluations of the benefit/risk relationship. Currently, it is generally accepted that for most women low dose combination hormonal oral contraceptives (products containing 0.035 mg or less of ethinyl estradiol) provide effective contraception with minimal risk of serious adverse events.[1] Each Ovcon® 35 chewable tablet contains the progestin norethindrone 0.4 mg and the estrogen ethinyl estradiol 0.035 mg. All other approved oral contraceptive products containing norethindrone have from 0.5 to 1.0 mg norethindrone. In summary, based on the information reviewed, the risk benefit ratio for Ovcon 35 chewable tablets is acceptable.

2.4 Dosing

The tablets are taken in order for 28 consecutive days, preferably at the same time each day. The product will be marketed as a unit 28-pill dispenser (21 white active tablets and 7 green placebo tablets). Each tablet may be simply swallowed, or chewed and swallowed; if chewed, this should be followed by immediately swallowing 8 ounces of a fluid to be sure that the tablet fragments in the oral cavity reach the stomach. Directions for when to take the first pill from the starting pack are clearly stated, as well as what to do if any pills are missed, not taken on time, or if the consumer is switching from another hormonal contraceptive product.

[1] Carr BR, Ory H. Estrogen and progestin components of oral contraceptives: relationship to vascular disease. *Contraception* 1997; 55:267-72.

2.5 Special Populations

This product was not studied in any special populations. The reviewing Division (DRUDP) did not feel that new studies in special populations were required as the doses of the active components in Ovcon 35 chewable tablets (0.035 mg ethinyl estradiol and 0.4 mg norethindrone) are the same as those in the presently marketed Ovcon 35. The contraindications, warnings and precautions for combination hormonal oral contraceptives have been well established over the years. These are adequately described in the agreed-upon labeling for the proposed new product.

APPEARS THIS WAY
ON ORIGINAL

Clinical Review

1 Introduction and Background

1.1 Description of Drug

Ovcon® 35 chewable tablet (norethindrone and ethinyl estradiol) is a spearmint flavored oral contraceptive containing 0.4 mg norethindrone and 0.035 mg ethinyl estradiol per active tablet. It has been developed [redacted]. The chewable form of Ovcon 35, to be marketed only in a 28-day regimen, will provide women with the choice of either chewing the tablet or swallowing the tablet whole. This additional feature (chewing the tablet) is anticipated by the sponsor to enhance compliance. This will be the first oral contraceptive with a chewable formulation.

1.2 Regulatory History

NDA 17-716: Ovcon® 35, 28-day regimen was submitted on March 27, 1975 and approved by the FDA on March 29, 1976. It was submitted by Mead Johnson and Company, a subsidiary of Bristol-Myers Squibb Company (BMS). Warner Chilcott, Inc., a subsidiary of Galen Holdings Plc., acquired ownership of the product from BMS in February 2000. Ovcon® 35 21-day, a similar product that differs from the 28-day product only in that it does not contain 7 inert tablets, was approved under NDA 18-127 on July 5, 1978.

NDA 21-490 with the new chewable formulation was originally submitted on April 2, 2002 (stamp date) with a PDUFA due date of February 2, 2003. Ovcon® 35 chewable tablets are a combination hormonal oral contraceptive product designed to provide a once daily 21-day regimen of active tablets followed by 7 placebo tablets. Each spearmint-flavored, white, active, chewable tablet contains 0.4 mg norethindrone (a progestin) and 0.035 mg ethinyl estradiol (an estrogen). Each spearmint-flavored, green placebo chewable tablet contains only inactive ingredients. The sponsor plans on marketing the new Ovcon® 35 chewable tablets only in a 28-pill dispenser. According to the sponsor [redacted]

Clinically, the original NDA included only two studies. In Study 07401, designed to determine if Ovcon® 35 chewable tablets cause 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 held for contraceptive efficacy, but Ovcon 35 chewable tablets are expected to be equally effective and to have a similar systemic safety profile as the presently approved and marketed product (Ovcon® 35).

On January 31, 2003, the NDA was given an approvable action for marketing the product for the prevention of pregnancy. Before the application may be approved, there are three CMC problems to be addressed and resolved:

1. Deficiencies at the manufacturing facility in Mayaguez, Puerto Rico
2. An unacceptable proposed [redacted] shelf life for the drug product

3. — in the final drug product

Labeling of the product was agreed upon, and there was no recommended Phase 4 postmarketing studies or risk management steps.

2 Re-submission of NDA:

The sponsor submitted additional CMC information to the NDA on May 14, 2003. The PDUFA goal date for this re-submission is November 14, 2003. The material has been reviewed by all the reviewing teams, and the sponsor has addressed and resolved all of the above mentioned CMC deficiencies.

3 Postmarketing Safety:

The Division of Drug Risk Evaluation (DDRE) was consulted for the original NDA submission to review the FDA's AERS database for all adverse event reports associated with Ovcon 50® and Ovcon® 35 since their original approvals. These products were approved for U.S. marketing in 1975 and 1976. A total of 440 reports were identified, which is a very low number. The total of 11 thromboembolic and thrombotic adverse events for this combination hormonal oral contraceptive is extremely low. The Drug Risk reviewer and the medical (clinical) reviewers concluded that there were no outstanding safety issues with Ovcon® 35 regular tablets or the newly formulated Ovcon® 35 chewable tablets.

A follow-up consultation was requested from the DDRE. Their AERS search for AE reports listing either Ovcon 50 or Ovcon® 35 between the previous consult of January 2003 and October 24, 2003 revealed that there were no additional reports entered into AERS. In addition, AERS was searched for reports submitted under the four NDAs for Ovcon products (17-576, 17-716, 18-127, and 18-128) and no reports were found.

Reviewer's comment: The following three periodic reports were also reviewed since January 31, 2003 and showed no additional SAEs or safety concerns:

1. Ovcon 50, NDA 17-576, periodic report P-019 covering 8-01 through 7-03
2. Ovcon 35, annual report YY-031, stamp date 6-24-03
3. Ovcon 35, periodic report P-017, stamp date 7-17-03, covering to 2-28-03

Based on the original evaluation, the DDRE update, and the review of the above three submissions, there remain no outstanding safety issues.

4 Division of Medication Errors and Technical Support (DMETS) consult:

DMETS was again consulted for this product. Their final review is dated October 10, 2003. DMETS has no objection to use of the proprietary name, Ovcon 35 and the use of the dosage form descriptor, chewable, in the established name. They had no concerns about the name with regard to promotional claims. Several very minor labeling changes were recommended and discussed thoroughly at the DRUDP monthly NDA status meeting.

Reviewer's comment: DRUDP felt that the label changes recommended by DMETS were indeed very minor and were not significant enough to adopt. DRUDP's comments about changes recommended by DMETS follow:

1. The name Ovcon® 35 with the letters O and V overlapping has been used for over 25 years and is easily recognized by clinicians, health care providers, and current or former users of Ovcon products.
2. The established name of the product will be consistent throughout the entire product literature (as recommended).
3. The color of the labeling need not be distinctly different between Ovcon chewable and Ovcon regular tablets because —
4. The container label which states — is for an identical product inside that is intended for funded clinics only. It should therefore not be sold at a regular pharmacy or through normal commercial channels. If the sponsor wants to have an outside container label that states — this is acceptable to DRUDP.
5. It is generally clear to both the provider and the consumer (user) what is meant by a "reminder" pill, so there is no reason to define or change this word in the label.

5 Labeling:

The sponsor (Applicant) originally submitted labeling based largely on the currently marketed Ovcon® 35 product. The labeling changes, as revised by the Division to make it compatible with current class labeling for a combination hormonal oral contraceptive, were agreed to by the sponsor on January 31, 2003. The Division has subsequently made some additional changes to the label that do not significantly change the content or instructions. The changes simply make the content clearer or more easily read.

Reviewer's comment: The sponsor agreed to the additional changes in the label and carton. The proprietary drug name will be Ovcon® 35, and the established name will be (norethindrone and ethinyl estradiol tablets, chewable).

6 Conclusions and Recommendations:

It is recommended that Ovcon® 35 chewable tablets receive an approval action for marketing for the prevention of pregnancy. The CMC deficiencies noted in the January 31, 2003 approvable letter have been addressed and resolved, and the final printed label agreed upon.

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

Daniel Davis, MD, MPH

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

/s/

Daniel Davis
11/13/03 02:31:39 PM
MEDICAL OFFICER

Scott Monroe
11/13/03 06:55:28 PM
MEDICAL OFFICER
I concur with the recommendation.

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

Medical Officer's Review of Original NDA

NDA	NDA 21-490
Type of Application	Original NDA
Applicant:	Warner Chilcott Inc. 100 Enterprise Drive, Suite 280 Rockaway, NJ 07866
Drug Name:	
Established name:	(norethindrone and ethinyl estradiol tablets, chewable)
Trade:	OVCON® 35
Chemical:	norethindrone and ethinyl estradiol
Pharmacologic category:	combination estrogen and progestin steroid hormone
Indication:	prevention of pregnancy in women who elect to use this product as a method of contraception
Route of Administration:	oral
Dosage Form:	chewable tablets supplied in 28-day dispenser
Strength:	0.4 mg norethindrone and 0.035 mg ethinyl estradiol per day
Dosing Regimen:	one active tablet per day for 21 consecutive days followed by one inactive tablet per day for 7 consecutive days
Related Submission:	NDA 17-576 Ovcon® 50 28-day: approved 8-28-75 NDA 17-716 Ovcon® 35 28-day: approved 3-29-76 NDA 18-127 Ovcon® 35 21-day: approved 7-05-78 NDA 18-128 Ovcon® 50 21-day: approved 7-05-78
Related Documents that Were Reviewed	a. Safety Updates P-016 (dated 4-26-02) and P-015 (dated 5-14-01) for NDA 17-716 b. Annual Reports Y-030 (dated 6-13-02) and Y-029 (dated 8-09-01) for NDA 17-716 c. Correspondence dated 7-09-01, 8-02-01, and 9-10-01
Submitted:	March 29, 2002
CDER Receipt Date:	April 2, 2002
Review Completed:	January 17, 2003
Review Finalized:	January 30, 2003
Medical Reviewer:	Daniel Davis, MD, MPH

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EXECUTIVE SUMMARY

1 Recommendations

1.1 Recommendations on Approvability

From a clinical perspective, this reviewer recommends approval of Ovcon® 35 chewable tablets containing norethindrone 0.4 mg and ethinyl estradiol 0.035 mg. [redacted]

[redacted] The new product will be marketed only as a 28-day regimen.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps

No special 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 marketed Ovcon® 35 oral tablets.

2 Summary of Clinical Findings

2.1 Brief Overview of Clinical Program

The clinical program for Ovcon® 35 chewable tablets consisted of two clinical pharmacology studies. The first study, Protocol PR 03801, was designed to demonstrate bioequivalence to Ovcon® 35 oral tablets. The second study, Protocol PR 07401, was designed to investigate the potential for oral irritation by the new formulation Ovcon® 35 chewable tablets. These two studies were performed at the request of the Division of Reproductive and Urologic Drug Products (DRUDP). No controlled clinical trials to directly investigate the systemic safety and contraceptive efficacy of the product were performed. The designs of the two studies are summarized in the table below.

Overview of Clinical Studies (Prepared by Medical Officer)

Protocol No.	Study Category	Study design	Enrolled / completed	Age range	Dose / Duration	Reviewer Comment
PR 03801	Phase 1: PK: Bio-equivalence	Single-center, open-label, single dose, 2-period, 2 treatment, crossover study	28 / 27	20 - 34	1 chewable or 1 marketed Ovcon® 35 tablet	PK data was collected for 60 hours post dose
PR 07401	Phase 1: PD; oral safety	Single-center, open-label, multiple dose, single treatment, oral irritation study	57 / 52	18 - 44	1 chewable tablet daily for 21 days	Evaluations on Days 1, 3, 8, 22, 29

Study 03801 investigated the bioavailability of Ovcon® 35 chewable tablets compared to that of the presently marketed Ovcon® 35 oral tablets in 27 healthy women. In Study 07401, the local irritation potential of Ovcon® 35 chewable tablets was investigated in 57 women of reproductive age.

2.2 Efficacy

In Study 03801, the 90% confidence intervals for the differences between the formulation means for Ovcon 35 chewable tablets and Ovcon 35 (presently marketed product) for the parameters AUC 0-t, AUCinf and C_{max} were within the acceptable range of 80-125%. The two tablets were

therefore considered to be bioequivalent. Since Ovcon® 35 chewable tablets are bioequivalent to the previously approved product (Ovcon® 35 oral tablets), they are expected to be equally effective in preventing pregnancy. As noted above, no clinical trials were required by DRUDP to determine the efficacy of the proposed product as part for this NDA application. The March 26, 1976 approval for NDA 17-716, the original Ovcon® 35 28-day oral tablets, was based on the following clinical data:

- N = 1970 women of reproductive age
- Exposure (use) = 20,230 cycles (1,556 woman-years)
- Pregnancies = 21
- Pearl Index = 1.36 (# of pregnancies per 100 women per year)
- 229 women completed 24 or more cycles

This amount of clinical data and the Pearl Index are acceptable with the DRUDP current requirements for approval of combination hormonal contraceptive products.

2.3 Safety

2.3.1 Submitted clinical trial safety data

Oral Safety: The results in Study 07401 showed no evidence of any potential for irritation to the oral soft tissues with once daily use of the study product over a 21-day span.

General Safety: There were no deaths, serious adverse events (SAEs), or discontinuations due to adverse events (AEs) in the two clinical pharmacology studies. There were 6 discontinuations (7%) in the 85 subjects. Five were for protocol non-compliance, and 1 woman was lost to follow-up. Of the very limited laboratory testing, there were no laboratory findings of concern in the two studies.

2.3.2 Other safety data

Additional safety data that were reviewed included:

- past two annual reports for the marketed Ovcon® 35 oral tablets
- AERS database from 1976 through December 2002 for Ovcon® 35 and Ovcon® 50

Based on the review of these additional data, it appears that Ovcon® 35 has a very good long-term safety record. Ovcon® 35 has been marketed for over 25 years. As late as 2001 it had a potential distribution of — woman-years, and in 2000 of — woman-years. The AERS reporting system is certainly not complete; however, since 1976 in the AERS database, there are reports for only one death, 4 pulmonary emboli and 3 cerebrovascular accidents for Ovcon® 35 oral tablets.

Drug-Drug Interaction

No special studies were performed for this NDA. The Product Insert (PI) label does contain a revised section for Drug-Drug Interactions.

Overall Benefits and Risk: The benefits of effective contraception and the many labeled non-contraceptive benefits of combination hormonal oral contraceptives are well defined. The important risks have also been well characterized, although data continue to emerge which lead to periodic reevaluations of the benefit/risk relationship. Currently, it is generally accepted that for most women low dose combination hormonal oral contraceptives (products containing 0.035 mg or less of ethinyl estradiol) provide effective contraception with minimal risk of serious adverse

events.[1] Each Ovcon® 35 tablet contains the progestin norethindrone 0.4 mg and the estrogen ethinyl estradiol 0.035 mg. All other approved oral contraceptive products containing norethindrone have from 0.5 to 1.0 mg norethindrone. In summary, based on the information reviewed, the risk benefit ratio for Ovcon 35 chewable tablets is acceptable.

2.4 Dosing

The tablets are taken in order for 28 consecutive days, preferably at the same time each day. The product will be marketed as a unit 28-pill dispenser (21 white active tablets and 7 green placebo tablets). Each tablet may be simply swallowed, or chewed and swallowed; if chewed, this should be followed by immediately swallowing 8 ounces of a fluid to be sure that the tablet fragments in the oral cavity reach the stomach. Directions for when to take the first pill from the starting pack are clearly stated, as well as what to do if any pills are missed, not taken on time, or if the consumer is switching from another hormonal contraceptive product.

2.5 Special Populations

This product was not studied in any special populations. The reviewing Division (DRUDP) did not feel that new studies in special populations were required as the doses of the active components in Ovcon 35 chewable tablets (0.035 mg ethinyl estradiol and 0.4 mg norethindrone are the same as those in the presently marketed Ovcon 35. The contraindications, warnings and precautions for combination hormonal oral contraceptives have been well established over the years. These are adequately described in the agreed-upon labeling for the proposed new product.

[1] Carr BR, Ory H. Estrogen and progestin components of oral contraceptives: relationship to vascular disease. *Contraception* 1997; 55:267-72.

Clinical Review

1 Introduction and Background

1.1 Description of Drug

Ovcon® 35 chewable tablet (norethindrone and ethinyl estradiol) is a spearmint flavored oral contraceptive containing 0.4 mg norethindrone and 0.035 mg ethinyl estradiol per tablet. It has been developed [redacted]. The chewable form of Ovcon 35, to be marketed in a 28-day regimen, will provide women with the choice of either chewing the tablet or swallowing the tablet whole. The additional convenience is anticipated by the sponsor to enhance compliance.

Reviewer's comment: In this review, the study drug will be called Ovcon® 35 chewable tablets and the currently marketed drug will be called Ovcon® 35 oral tablets.

1.2 Regulatory History

NDA 17-716: Ovcon® 35, 28-day regimen was submitted on March 27, 1975 and approved by the FDA on March 29, 1976. It was submitted by Mead Johnson and Company, a subsidiary of Bristol-Myers Squibb Company (BMS). Warner Chilcott, Inc., a subsidiary of Galen Holdings Plc., acquired ownership of the product from BMS in February 2000. A similar product that differs from the 28-day product only in that it does not contain 7 inert tablets (Ovcon® 35 21-day) was approved under NDA 18-127 on July 5, 1978.

Pre-NDA submissions included the following:

1. New Correspondence, stamp date 7-09-01: request for review of 36-page Bioavailablity Study Protocol. Teleconference held 7-26-01.

2. New Correspondence, stamp date 8-02-01: sponsor's reply to 3 questions posed by the Division of Reproductive and Urologic Drug Products (DRUDP) during the teleconference on 7-26-01 [what are 1) the intent in developing a chewable tablet, 2) the exact formulation of the tablet, and 3) will the new chewable tablet replace the current product].

3. N-000 (C), stamp date 9-10-01: request for a teleconference with a medical reviewer to discuss the proposed oral irritation study with the chewable tablet. No record is found of the actual teleconference.

The NDA was submitted on April 2, 2002 with a due date of February 2, 2003.

1.3 Clinical Background and Milestones

Ovcon® 35 (0.4 mg norethindrone and 0.035 mg ethinyl estradiol tablets, USP) 28-day was approved under NDA 17-716 by the FDA on March 29, 1976. Ovcon® 50 28-day, containing 0.050 mg ethinyl estradiol (EE) instead of 0.035 mg EE, was approved under NDA 17-576 on August 28, 1975. These two products have been marketed in the USA for over 27 years as a monophasic combination hormonal contraceptive available in either a 21-pill or 28-pill dispenser containing 21 active and 7 inert tablets.

There have been no major safety or efficacy issues with either Ovcon product. Warner Chilcott, Inc., a subsidiary of Galen Holdings Plc., acquired ownership of the Ovcon® 35 products from BMS in February 2000. The new formulation for the Ovcon® 35 tablet is expected to have the

same safety and efficacy profile as the original Ovcon® 35 oral tablet because the 2 formulations are bioequivalent.

One problem with oral contraceptives (OCs) in general is relatively poor compliance, with users sometimes missing one or more pills or taking the pills at irregular times, resulting in an unplanned or unwanted pregnancy. According to the sponsor, the chewable tablet formulation is expected to allow women to take the oral contraceptive pill more conveniently [can be either chewed and swallowed or simply swallowed whole], thus possibly having a favorable effect on compliance and contraceptive effectiveness.

Reviewer's comment: The sponsor's assumption has not been proved, but it is reasonable. Currently on the USA market, women have the additional choice of a 21-day vaginal ring and a 7-day transdermal patch as delivery systems for combination hormonal contraception, thus avoiding the need to remember a daily pill. The chewable oral contraceptive pill will offer another option.

1.4 Foreign Marketing Status

Ovcon® 35 chewable tablets are not currently marketed anywhere in the world.

1.5 Pharmacologically Related Agents

There are several combination hormonal oral contraceptives currently marketed in the USA that are similar to Ovcon® 35 [norethindrone 0.40 mg and ethinyl estradiol 0.035 mg]. A partial list of products containing ethinyl estradiol (EE) 0.035 mg includes: Brevicon, Demulen 1/35, Modicon, Jenest, Norinyl 1/35 and Tri-Norinyl, Ortho-Novum 1/35, Ortho-Cyclen and Tri-Cyclen. A partial list of contraceptive products containing both norethindrone (NE) and EE 0.035 mg includes: Brevicon, Modicon, Jenest, Norinyl, Ortho 1/35, 7/7/7, and 10/11. The range of NE in these products is 0.5-1.0 mg; no other approved oral contraceptives contain as low a dose of NE as the 0.4 mg found in Ovcon® 35 and Ovcon® 50.

2 Clinically Relevant Findings from Chemistry, Toxicology, Microbiology, and Other Disciplines

2.1 Chemistry, Manufacturing, and Controls

Ovcon® 35 chewable tablets are a mint-flavored combination hormonal oral contraceptive product designed to provide a continuous 21-day regimen of active tablets followed by 7 placebo tablets. Each spearmint-flavored, white, active, chewable tablet contains 0.4 mg norethindrone (a progestin) and 0.035 mg ethinyl estradiol (an estrogen). Each spearmint-flavored, green placebo chewable tablet contains only inactive pharmaceutical ingredients.

According to the sponsor, the formulation, batch size, and manufacturing equipment used for Ovcon® 35 chewable tablets are the same as those for the currently approved Ovcon® 35 oral tablets with the following exceptions: 1) — was deleted, b) flavor components were added, and c) a — was added to incorporate the flavor components. (See the complete chemistry review for further information, details and comments.)

Reviewer's comment: Late in the review cycle there were still several chemistry issues that needed clarification. The sponsor was asked to provide further information on:

- The container closure system for drug substances storage
- Specifications for 3 coloring agents and the spearmint flavor
- In-process control limits for — of drug substances

- The — of ethinyl estradiol used during the manufacturing process
- Justified specification for —
- Specifications for — of the active and placebo tablets
- Stability of the drug product
  - The assay failure of EE at — for samples stored under 25° C/ambient humidity
- Methods validation

2.1.1 Compliance Issues

In addition to the chemistry issues, the CDER Compliance Office determined that one of the manufacturing facilities was deficient with respect to cGMP. According to the reviewing chemist, it is doubtful that the deficiency will be corrected by the January 31, 2003 action date for this NDA.

2.2 Animal Pharmacology and Toxicology

There was no new non-clinical pharmacology and toxicology information submitted for Ovcon® 35 chewable tablets. The sponsor made a cross-reference to NDA 17-716, the original NDA for Ovcon® 35 oral tablets, 28-day regimen, approved on March 29, 1976.

A sweetener (sucralose, NF), a flavoring (spearmint flavor), and a — flavoring (maltodextrin, NF) have been added as inactive ingredients in the manufacturing of Ovcon® 35 chewable tablets.

Reviewer's comment: The sponsor believes that the three new inactive ingredients are not likely to affect the pharmacology and toxicology profiles of Ovcon® 35 as reported in NDA 17-716. Each of the new components is used in foods and is generally recognized as safe (GRAS). Consequently, the sponsor's statement concerning no change in the pharmacology and toxicology profile of Ovcon® 35 is reasonable and acceptable.

3 Human Pharmacokinetics and Pharmacodynamics

3.1 Clinical Pharmacology Study PR 03801

The Ovcon® 35 chewable tablet formulation is based on the currently approved Ovcon® 35 (norethindrone and ethinyl estradiol tablets, USP) oral tablet formulation. The sponsor carried out Study PR 03801 to establish the bioequivalence of the Ovcon® 35 chewable tablet exhibit batch to the Ovcon® 35 oral tablet reference batch. The study dates for PR 03801 were 8-24-01 to 9-24-01; the study site was —, the bioanalytical laboratory was —

Study Design:
This was a single-center, open label, single-dose, randomized, two-period two-treatment crossover study performed in 26 healthy, non-smoking female volunteers and two alternative subjects. There was a 28-day washout interval between the two dose administrations. Serial blood samples were taken for 60 hours post each of the doses for determination of plasma NE and EE concentrations. Each volunteer received a single dose of study drug or reference drug tablet containing 0.4 mg NE + 0.035 mg EE on two occasions, 28 days apart.

There were two study periods of 3 days each; each period included 1½ days of confinement, 2 overnight stays, and 3 return visits at 36, 48, and 60 hours after dosing for drawing blood

samples. All subjects fasted for 10-hours overnight in the study facility prior to dosing; they were further confined to the site for 24 hours after the single dose.

All subjects enrolled in the study satisfied the inclusion/exclusion criteria [essentially normal healthy females on no medications and off all steroids and other protocol-excluded drugs for standard washout periods]. The principal investigator (PI) reviewed medical histories, clinical lab evaluations, and performed physical exams prior to subjects being enrolled in the study. The subjects were not to consume any food or beverages containing alcohol or xanthines for 48 hours prior to study drug administration and throughout the 60-hour postdose period. Grapefruit-containing foods and beverages were prohibited for 10 days before dosing and for 60 hours postdose. Subjects were to be free of nicotine and tobacco for at least 3 months prior to study enrollment. In addition, prescription and OTC medications were prohibited beginning 7 days prior to dosing and during the study.

Demographic Information:
All the subjects were female. There were 15 Caucasians (54%), 10 Hispanics (36%), 2 African Americans (7%), and 1 American Indian. The mean age was 28 with a range of 20 to 34 years. The mean weight (kg) was 61.7, median weight (kg) 70.2, with a range of 50.4 to 79.0. The mean height (cm) was 163, median height 168, with a range of 150 to 173.

Reviewer's comment: There are no demographic data that are of concern. The study group is reasonably representative of the target population for this drug.

Subject Disposition:
Of the 28 enrolled subjects, 27 completed the study. One subject was discontinued from the study because she had a positive pregnancy test at the Period 2 check-in. Protocol deviations were minor and mainly included hemolyzed blood samples, minimally late blood draws or storage times, or aliquot allocation errors. There were no significant protocol deviations except for the one pregnant subject who was withdrawn from the study after completing the first of the two study periods.

Informed Consent and IRB Approval:
These were reviewed by this reviewer and felt to be adequate.

Study Methods:
Plasma norethindrone and ethinyl estradiol were analyzed by GC/MS methods validated over the range — and —, respectively. The limit of quantification (LOQ) for NE was — and for EE was —. Noncompartmental PK parameters were calculated for plasma norethindrone and ethinyl estradiol. Analyses of variance (ANOVA) were performed on the 3 ln-transformed PK parameters, AUC_{0-t}, AUC_{inf} and C_{max}. The ANOVA model included sequence, period and formulation as fixed effects, and subject nested within sequence as a random effect. Consistent with the 2 one-sided test for bioequivalence, the 90% confidence interval (CI) for the difference between drug formulation least-square means (LSM) of the 3 ln-transformed parameters was calculated. The 90% CIs for the differences between the formulations were within 80 to 125%.

Sponsor's Conclusions:
Ovcon® 35 chewable tablets and Ovcon® 35 oral tablets were bioequivalent based on the PK parameters of AUC_{0-t}, AUC_{inf} and C_{max}. (See Table 1 below). The mean t_{max} values for norethindrone in the chewable tablet and the original tablet were 1.2 and 1.5 hours, respectively. The mean t_{max} values for ethinyl estradiol in the chewable tablet and the original tablet were 1.4 and 1.7 hours, respectively.

Table 1 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 %)*
$AUC_{0-\infty}$ (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 %)*

* n = 26, including Subject No. 13 in all PK analyses of EE
**n = 25 since $AUC_{0-\infty}$ could not be calculated for Subject No. 10 in Periods 1 and 2.
Source: Division biopharmaceutical reviewer M-J Kim

Reviewer's comment: The FDA biopharmaceutical scientist reached the same conclusion as the Sponsor regarding the bioequivalence of the 2 products [see the complete Biopharm Review of the study data]. This clinical reviewer also reviewed the individual subject profiles (semi-log plots) of the plasma NE and EE concentrations for each subject. There appeared to be only small differences in the plasma concentration for EE and NE in the plots for the Ovcon® 35 chewable tablet versus the original tablet.

The study protocol required that after chewing and swallowing the tablet, subjects were to drink 240 mL (8 ounces) of water. Because bioequivalence was assessed under these specific conditions, the label will state that after chewing the tablet, the woman should drink 8 ounces of liquid immediately after swallowing.

Adverse Events:
There were no SAEs reported for this study. A total of 18 subjects reported 50 mild AEs with some duplication of the same AE in the same subject within the same study period. Six of these 18 subjects accounted for 34 of the 50 AEs. No AEs were judged to be of moderate or serious intensity. The reported AEs (and number of reports for each) are listed below in order of frequency:

- Nausea- (12)
- Headache- (11)
- Dizzy- (6)
- Tired- (6)
- Feels weak- (2); warm- (2); peripheral tingling- (2); ear pressure- (2); URI symptoms- (2)
- Vomited- (1); cramps- (1); vaginal spotting- (1); bitter taste in mouth- (1); pregnancy- (1)

Reviewer's comment: The safety profile from this very limited two single-dose study is acceptable. The above numbers are from this reviewer's analysis of the sponsor's AE data in appendix 5.4, Volume 14, page 407-09 of the NDA. Subjects #7, 16 and 27 alone reported 24 AEs with viral and vasovagal type symptoms. The subject with the cramping and vaginal spotting was found to be pregnant subsequent to her receiving her first (and only) dose of study drug. The two most common symptoms (nausea and headache) are commonly associated with

oral contraceptives. There were 17 blood samples taken per 60-hour study period, which could certainly have contributed to the reports of tiredness and dizziness.

3.2 Dose Selection

This NDA is for a new dosage form (chewable tablet) of the sponsor's existing marketed product Ovcon® 35 28-day (norethindrone and ethinyl estradiol tablets, USP). The doses of ethinyl estradiol (0.035 mg) and norethindrone (0.4 mg) are the same as those in the Sponsor's currently marketed product. The main chemical difference in the new dosage formulation from the currently marketed product is the addition of a flavor and sweetener, — of two excipients, and the — yellow #6 dye —

Reviewer's comment: The doses of norethindrone and ethinyl estradiol are acceptable.

4 Description of Clinical Data and Sources

4.1 Overall data.

There are only two studies included in this NDA. The PK bioequivalence study is discussed in Section 3.1 of this review. Although it can be considered a pharmacodynamic study, the oral irritation study (Study PR 07401) is discussed in Section 7.3 (Safety Studies). A large clinical trial was not needed since Ovcon 35 chewable tablets is only a new formulation of norethindrone and ethinyl estradiol that was shown to be bioequivalent to an approved combination hormonal oral contraceptive product (Ovcon® 35).

4.2 Listing of Clinical Trials

Data from 2 clinical trials were submitted in support of the NDA. The designs of the two studies are summarized in the table below.

Overview of Clinical Studies (Prepared by Medical Officer)

Protocol No.	Study type	Study design	Enrolled / completed	Age range	Dose / Duration	Reviewer Comment
PR 03801	Phase 1 PK: Bio-equivalence	Single-center, open-label, single dose, 2-period, 2 treatment, crossover study	28 / 27	20 - 34	1 chewable or 1 marketed Ovcon® 35 tablet for 1 day	PK data was collected for 60 hours post dose
PR 07401	Phase 1 PD; oral safety	Single-center, open-label, multiple dose, single treatment, oral irritation study	57 / 52	18 - 44	1 chewable tablet daily for 21 days	Evaluations on Days 1, 3, 8, 22, 29

Reviewer's comment: As noted previously, no additional clinical trials were indicated or required by DRUDP.

4.3 Postmarketing Experience

This specific product with the chewable formulation is not currently marketed in the USA or elsewhere in the world.

4.4 Literature Review

No special review of the medical literature was needed or indicated. The Sponsor's development plan for this product was carried out with input from the Division (DRUDP), and the almost identical product, Ovcon® 35 oral tablets was approved by the FDA in March 1976. The risks and benefits of hormonal oral contraceptives are well established and FDA-approved products have been in use since the 1960s.

5 Clinical Review Methods

5.1 How Review was Conducted

The review was conducted by first reading the materials listed in Volumes 1, 14, 15, and 16 (the clinical sections of the NDA). Attention was paid to the proposed label. No special analyses were performed by this reviewer because there were no major clinical issues in the approval of this new formulation (chewable tablet) of an already marketed oral contraceptive product. The two major approval issues are 1) the stability (approved shelf life) of the ethinyl estradiol in the new formulation and 2) the fact that one of the manufacturing facilities (located in Puerto Rico) had significant cGMP deficiencies that were not corrected by the action date.

5.2 Overview of Reports and Materials Consulted in Review

The essential elements reviewed were the following:

- data in the 4 clinical volumes listed above
- NDA 21-490 safety update report
- past two annual reports for the marketed Ovcon® 35 oral tablets
- proposed label
- DRUDP files for NDA 17-716 dating back to 1975
- AERS database from 1976 through December 2002
- DRUDP bio-pharmaceutical review
- formal consultation from the Dental & Dermatology Division providing a 6-page report regarding the oral tolerance and safety of the proposed product
- brief consultation from the Division of Medication Errors and Technical Support, Office of Drug Safety, to review the proposed proprietary name "Ovcon® 35 [redacted]

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

Some of the calculations (e.g. percentages, totals, and confidence intervals) were checked for accuracy. No Division of Scientific Investigations (DSI) inspection of the two clinical sites was held (see reviewer's comment). There were no CRFs for review because there were no deaths or SAEs. The informed consents and IRB letters were reviewed.

Reviewer's comment: The quality and integrity of the studies, safety monitoring, and data collection was adequate. The decision to not have any clinical site inspections was a result of the new draft policy from DSI that states that new NDAs do not automatically require clinical site inspections. Ovcon® 35 chewable tablet is not an NME, not first in its class, not intended for a novel population, not used for a new diagnostic category, and not delivered via a new route of administration. Under these circumstances, site inspections were not indicated.

5.4 Informed consent and standard of patient care

The subjects' informed consents and the IRB letters were reviewed and felt to be adequate. Acceptable safety monitoring was in place for the two Phase 1 studies. The PK bioequivalence

study was primarily performed in-house [~36 hours per dosing period] followed by three outpatient blood drawings.

5.5 Financial Disclosure Evaluation

The financial disclosure statement was reviewed by the medical officer and found acceptable.

6 Integrated Review of Efficacy

6.1 Efficacy Conclusion

Ethinyl estradiol and norethindrone, a synthetic estrogen and a progestin, are widely used as components of combination oral contraceptives. Norethindrone 0.4 mg and ethinyl estradiol 0.035 mg (35 micrograms) daily for 21 days, the two synthetic hormones in Ovcon® 35 chewable tablets, are already used in the approved product Ovcon® 35 oral tablets. The chewable tablet formulation is expected by the sponsor "to allow women to take the pill more conveniently and therefore more reliably, thus having a favorable effect on compliance and efficacy."

No actual use study was performed comparing the efficacy of the new chewable formulation with that of the previously approved formulation. The sponsor believes that the efficacy of Ovcon 35 chewable tablets will be the same, or better than, the previously approved formulation because Study PR 03801 (see Section 3.1) showed bioequivalence of the new product (Ovcon 35 chewable tablets) to that of the presently marketed product (Ovcon 35 oral tablets). The sponsor claims there is no reason to believe that the contraceptive effectiveness will be significantly different. The 3-29-76 approval for NDA 17-716, the original Ovcon® 35 28-day oral tablets, was based on the following clinical data:

- N = 1970 women of reproductive age
- Exposure (use) = 20,230 cycles (1,556 woman-years)
- Pregnancies = 21
- Pearl Index = 1.36 (# of pregnancies per 100 women per year)
- 229 women completed 24 or more cycles

Reviewer's comment: This reviewer agrees with the sponsor's conclusion. This amount of clinical data and the Pearl Index are acceptable with the DRUDP current requirements for approval of combination hormonal contraceptive products. Whether the compliance will be better remains to be shown, but the contraceptive effectiveness should be at least as good as the approved Ovcon® 35 oral tablet, assuming that the new formulation Ovcon® 35 product is taken as directed.

6.2 Efficacy Studies

There was no controlled clinical study for efficacy. Therefore, there is no detailed review of a study by indication. Ovcon® 35 chewable tablets are bioequivalent to Ovcon® 35 oral tablets (see Section 3.1 and the separate biopharmaceutical review). Ovcon® 35 oral tablets, 28-day regimen, is the subject of NDA 17-716 that was approved on March 29, 1976. The product has been marketed in the USA since shortly thereafter.

7 Integrated Review of Safety

7.1 Safety Conclusions

In a study to determine if Ovcon® 35 chewable tablets cause oral irritation (Protocol PR 07401), no evidence of clinically significant oral irritation was seen (Report RR 00802). Ovcon® 35 chewable tablets are expected to have a similar systemic safety profile as Ovcon® 35 oral tablets because the two products are bioequivalent.

Reviewer's comment: The reviewer concurs with the sponsor's safety conclusion.

7.2 Safety Studies and Subject Exposure to Drug

There were only two studies submitted with the NDA. A total of 85 women were exposed to the new formulation of Ovcon® 35 chewable tablets. 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.

Reviewer's comment: Although the number of women exposed to the new chewable formulation for this product was small, Ovcon® 35 oral tablets have been marketed since 1976. Extensive systemic safety data is available for the specific combination of NE 0.4 mg and EE 0.035 mg and for several products with higher amounts of NE (0.5 to 1.0 mg) and the same or higher amounts of EE (0.035 to 0.050 mg). **The subject exposure to the new chewable formulation is adequate under these circumstances.**

7.3 Safety Studies

7.3.1 Review of Oral Safety Study PR 07401 (Report 00802)

This clinical study's primary objective was to determine the local oral irritation potential of the chewable oral formulation of Ovcon® 35 during daily use over a 21-day cycle in women of childbearing potential (the target population of the drug). It was agreed with DRUDP that a single cycle 21-day study would provide sufficient data to determine the oral safety of the new chewable formulation.

Reviewer's comment: A formal consultation was requested from the Division of Dermatologic and Dental Drug Products. The complete review by Dr. John Kelsey, DDS, of Study PR 07401 is found in the CDER Division Filing System. This reviewer agrees with Dr. Kelsey's conclusions that the oral irritation study was well designed and conducted, and that the new chewable formulation does not appear to cause significant oral irritation.

Study Design:
This was a single-center, open label study carried out at the —
— The study consisted of a single 21-day treatment period. A pelvic exam was performed at the screening/baseline visit to evaluate any conditions that would render the subject ineligible for oral contraceptive use and enrollment in the study. Enrolled subjects received the chewable oral contraceptive starting at the Day 1 visit, scheduled on the first day (± 2 days) of their next menstrual cycle after the baseline visit. Oral soft tissue examinations were performed at baseline, and on Days 1, 3, 8, and 22 of the treatment period. An additional follow-up examination was performed at the Day 29 final visit.

Target enrollment was 50 completed subjects evaluable for analysis. Actual enrollment was 57 subjects; 52 women completed all aspects of the study. The dates of the study were 10-29-01 to 12-19-01. The principal investigators were John Frascella, DMD, FAGD, and Marc Clachko, MD.

Study Population:
Healthy female subjects, aged 18 years or older, of childbearing potential, and fulfilling the inclusion/exclusion criteria were eligible for enrollment in the study. Subject-age ranged from

18 to 44 years, with a mean age of 32.8. All subjects were female: 74% were Caucasian, 14% were African-American, 9% Hispanic, with 1 Asian and 1 multiracial.

Reviewer's comment: Standard criteria for enrollment in an oral hormonal contraceptive study were used. For example, smokers age 35 and over were excluded. Women with any visible disease of the oral mucosa were also excluded.

Subject Disposition:
Ninety-three women were screened and 57 were enrolled and received treatment with the study product. Five subjects (9%) 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. No subject discontinued because of an AE.

Informed Consent and IRB Approval:
These were reviewed by this reviewer and felt to be adequate.

Study Methods:
The Oral Soft Tissue Examination (OSTE) for inflammation, irritation, abrasions, infection, and any other abnormalities was performed at baseline and on Days 1, 3, 8, 22, and 29. Safety was evaluated by the assessment of any AE reported during the study. Additionally, a pelvic exam was performed at the screening/baseline visit. A urine pregnancy test was performed at the Day 1 visit, which was on the first day (± 2 days) of the subject's menstrual cycle. No other clinical laboratory tests were done during the study.

Determination of irritation potential was based the OSTE and the review of scores of irritation, inflammation and abrasions assigned to 9 oral sites (lips, buccal, labial and sublingual mucosa, attached gingivae, tongue, hard/soft palate, uvula, and oropharynx). The OSTE used a scale of 0 to 3 (0= normal to 3= severe), and the severity of abrasions was separately scored using a scale of 0 to 3 (none, mild, moderate, severe).

Sponsor's Conclusions:
The oral examinations revealed no evidence of product-related irritation associated with use of the new chewable formulation in any subject. Of the oral sites that were specifically graded for evidence of irritation, inflammation, or abrasions, all were assigned scores of zero (normal) for every subject at every study visit, with the exception of 1 subject. This subject showed two mild aphthous ulcers, 1 each on Days 8 and 22, which were judged by the investigator as unlikely to be related to the study product. There were no product-related AEs of the oral cavity. The only reported AEs possibly or probably related to the study drug were the four subjects (7%) who had mild or moderate nausea. In 3 of these 4 cases, the subject specifically reported that the nausea was temporally related to the study dose. In all 4 cases, the subject continued the study treatment regimen to completion without interruption. Thus, the product was well tolerated.

Adverse Events:
The overall experience of AEs in the study showed that 15 women (26%) reported a total of 22 AEs. Two of the AEs were rated severe (menstrual cramps and a toe fracture) and 4 (nausea) were considered related to study drug. Non drug-related AEs, judged to be mild or moderate (and the number of reports for each included the following:

- Pharyngitis- (2)
- Vaginal bleeding/spotting- (2)
- Headache-(2)

- Menstrual cramps- (2, including the severe AE noted above)
- Sore on tongue- (1)
- Muscle tightness- (1)
- Bronchitis- (1)

Safety Labs:
No general clinical laboratory tests were performed for this short study. A urine pregnancy test was performed for each subject on Day 1 (start of active treatment) and Day 29 (final study visit). In all cases, the pregnancy tests were negative.

Reviewer's comment: This reviewer and the formal consultation from the Dermatologic and Dental Division (Dr. John Kelsey, DDS, dental reviewer) agree with the sponsor's conclusion that no product-related irritation or safety issues in the oral cavity were seen with this new chewable formulation for Ovcon® 35 (norethindrone 0.4 mg and ethinyl estradiol 0.035 mg). The AE profile is acceptable; the label for this product and all oral contraceptives lists nausea (and vomiting) as common side effects.

7.4 Integrated Overview of Safety in Studies PR 07401 and PR 03801

7.4.1 Deaths

There were no deaths in the two clinical pharmacology studies.

7.4.2 Serious Adverse Events (SAEs)

There were no reported SAEs in the two studies.

7.4.3 Premature Discontinuations

In the two studies combined, there were 6 discontinuations (7%) in 85 subjects. Five were for protocol non-compliance, and 1 woman was lost to follow-up. There were no discontinuations due to AEs.

7.4.4 Laboratory Parameters

Pregnancy testing was done in both trials. There were no chemistry, hematological, or other special tests performed in the 21-day oral irritation trial. Baseline chemistry, hematology, urinalysis, HIV, hepatitis B and C screening were performed for the bioequivalence study. In addition, at the completion of the study, a clinical laboratory evaluation (chemistries, hematology, and urinalysis) was performed.

Reviewer's comment: There were no laboratory findings of concern in the two studies, with the exception of the one woman in the bioequivalence study who was discontinued because of a positive pregnancy test before the second single-dosing period. Her pregnancy test was negative prior to the first single-dosing period, so it was appropriate to enroll her in the study and then discontinue her before the second study period.

7.5 Safety Update and Postmarketing Safety Data for Ovcon 35

Sources of Information:
The two most recent annual reports for NDA 17-716 (Ovcon® 35) and the AERS DataMart for NDA 17-716 and NDA 18-128 (Ovcon® 50) were reviewed. Also reviewed was the sponsor's Safety Update submitted as Amendment No. 13 on 1-10-03 during the NDA review cycle. There was no integrated summary of safety (ISS) submitted with the NDA. The sponsor reasoned that because the Ovcon® 35 chewable tablets are bioequivalent to the approved Ovcon® 35 oral

tablets, the two products "are expected to be equally effective and to have similar systemic safety profiles." Furthermore, a consultation with the agency's Division of Drug Safety was requested on 1-07-03.

Reviewer's comment: For this NDA that consists of a new formulation of an established oral contraceptive product, it is acceptable that an ISS, per se, was not submitted. Because Ovcon® 35 has been marketed in the US for over 25 years, adequate data was available and reviewed for the overall safety of this product.

The NDA Safety Update Report states that there is no new safety information to report. Neither non-clinical nor clinical studies have been ongoing or completed since the submission of the original NDA. No new information on Ovcon® 35 oral tablets was obtained from a review of current scientific literature. In addition, Ovcon® 35 chewable tablets are not marketed outside the US; thus, there is no non-US postmarketing experience to report. The sponsor concludes that there is no new safety information that "may reasonably affect the statements in the proposed labeling submitted in the original NDA."

Annual report Y-030 (NDA 17-716) and submission P-016 (stamp date 4-26-02) covered March 1, 2001 through February 28, 2002 were reviewed and contained the following information:

- SAEs included 1 pulmonary embolus and 1 DVT; non-serious labeled (NS/L) AEs included 1 rash and 3 reports of menorrhagia
- Stability data for up to [redacted] is available
- Medline database was searched by the sponsor: no new safety information was found for non-clinical or clinical studies
- Post-marketing studies of Ovcon® 35 oral tablets have not been conducted during the reporting period
- Unit distribution report for Ovcon® 35-28: [redacted] boxes of 6 Dispensers, 4,044 (Clinic pack) boxes of 6 Dispensers, and [redacted] sample packs. Total = [redacted] units (41.3% of the previous year's total)

Annual report Y-029 (stamp date 8-09-01) and submission P-015 covered March 1, 2000 to February 28, 2001 was reviewed and contained the following information:

- No SAEs were reported; 6 AEs were reported
- Unit distribution report for Ovcon® 35-28: [redacted] boxes of 6 Dispensers, [redacted] (Clinic pack) boxes of 6 Dispensers, and [redacted] (sample packs) boxes of 6 Dispensers. Total = [redacted] units x 6 packs/unit = [redacted] packs.

Reviewer's comment: In one year, a woman will use 13 packs for contraception, so the above unit distribution of over [redacted] packs represents a maximum of [redacted] women-years of the product distributed. The exact figure of actual usage is unknown.

7.6 Other Safety Consultations

7.6.1 Office of Drug Safety, Division of Drug Risk Evaluation

The risk evaluation reviewer (E. Farinas, R.Ph., M.G.A.) searched AERS for both Ovcon® 35 and Ovcon® 50 since they were approved. The total number of safety reports for both products combined was 440, almost all coming from the US. In the past 10 years, there have been a combined total of 152 safety reports with 138 (91%) from 1993-97 and only 14 (9%) from 1998-

2002. From the combined 440 safety reports, there was 1 death, 13 hospitalizations, 4 pulmonary emboli, and 3 cerebrovascular accidents (CVA).

Because the sponsor intends to market only Ovcon® 35 chewable tablets, the DRUDP medical reviewer focused on only the Ovcon® 35 reports in the AERS DataMart database since the approval of Ovcon® 35 in 1976. This search revealed 366 reports including the following SAEs:

- 1 death (due to a pulmonary embolus)
- 4 pulmonary emboli (1 death included here)
- 2 CVA and 1 cerebrovascular infarction
- 1 DVT

Reviewer's comment: After reviewing all the above sources and data, it appears that Ovcon® 35 has a very good safety record. It has been marketed for over 25 years and in 2001 had a potential distribution of — woman-years and in 2000 had a potential distribution of — woman-years. The reporting system is certainly not complete, but only one death, 4 pulmonary emboli and 3 CVAs have been reported for Ovcon® 35 since its approval in 1976.

7.6.2 Proprietary Name

A formal consultation was requested from the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, to review the proposed proprietary name "**Ovcon 35** —." The consult was to help determine the potential for confusion with approved proprietary and established names as well as pending names. Originally, DMETS had no objections to the use of — An email from the Team Leader Alina Mahmud on January 29, 2003, however, stated that "DMETS discourages the use of — Most chewable tablets include the word 'chewable' in juxtaposition to the official compendial name." This means that "

Reviewer's comment: After discussions with the DRUDP chemistry team leader and the sponsor, it was agreed that the proprietary name (trade name) will be OVCON® 35, and the established name will be (norethindrone and ethinyl estradiol tablets, chewable).

In their review of the draft container label, draft carton and package insert labeling for Ovcon 35 chewable tablets, DMETS focused on safety issues relating to possible medication errors. They identified one area of possible improvement, in the interest of minimizing potential user error. The current and proposed layout of the proprietary name transposes the letter "v" over the first letter "o" (see below). At quick glance, the name reads Ocon rather than Ovcon. DMETS recommended that the name be clearly identified without obscuring any letters in the name to avoid potential for confusion.

Reviewer's comment: —

— Ovcon® 35 has used the overlapping "o" and "v" for many years on their marketed product (container, carton, dispenser, package insert, etc.). The reviewing teams in DRUDP do

not feel that the labeling revision suggested above is needed for this new formulation of an oral contraceptive that has been marketed since 1976.

8 Dosing, Regimen and Administration Issues

The tablets are taken in order for 28 consecutive days, preferably at the same time each day. With the 28-pill dispenser (21 white active tablets and 7 green placebo tablets), one pill is taken each day with no interruption between pill packs. Each tablet may be simply swallowed whole or chewed and swallowed.

Reviewer's Comment. If the tablet is chewed, the person should drink a full glass (8 ounces) of liquid immediately after swallowing to be sure that the tablet fragments in the oral cavity reach the stomach. Directions for when to take the first pill from the beginning pack are clearly stated in labeling as well as what to do if any pills are missed, not taken on time, or the individual is switching from another hormonal contraceptive method to Ovcon® 35.

9 Use in Special Populations

9.1 Gender Studies

No special gender studies were conducted. This product is intended for use only in reproductive-aged females.

9.2 Age and Race Studies

No studies were conducted to investigate possible effects of age and race on the safety or efficacy of this product. The contraindications, warnings and precautions for combination hormonal oral contraceptives have been well established over the years. The active ingredients and doses of these ingredients in this product (0.4 mg norethindrone and 0.035 mg ethinyl estradiol) are the same as those in the presently approved product. The sponsor and DRUDP did not feel that studies to investigate possible effects of age and race on the safety or efficacy of this product were required or indicated.

9.3 Pediatric Waiver

Safety and efficacy of Ovcon® 35 was previously established in women of reproductive-age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users of this product age 16 and older. Therefore, no studies were indicated in the pediatric age population and none were required.

9.4 Studies in Other Special Populations

This product was not studied in any special populations. The contraindications, warnings and precautions for combination hormonal oral contraceptives have been well established over the years. The sponsor and DRUDP did not feel that studies in special populations were indicated.

10 Conclusions and Recommendations

10.1 Safety and Efficacy Conclusions

In Study 07401 to determine if Ovcon® 35 chewable tablets cause 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. Ovcon 35 chewable tablets are expected to be equally effective and to have a similar systemic safety profile as the presently approved and marketed product (Ovcon® 35).

The benefits of effective contraception and many labeled non-contraceptive benefits of combination hormonal oral contraceptives are well defined. The important risks have also been well characterized, although data continue to emerge which lead to periodic reevaluations of the benefit/risk relationship. Currently, it is generally accepted that for most women low dose combination hormonal oral contraceptives (products containing 0.035 mg or less of ethinyl estradiol) provide effective contraception with minimal risk of serious adverse events.

10.2 Recommendations on Approvability (Regulatory Action)

From a clinical perspective, this reviewer recommends approval of Ovcon® 35 chewable tablets containing the new formulation of norethindrone 0.4 mg and ethinyl estradiol 0.035 mg.

10.3 Labeling Issues and Revisions

Changes were made in the sponsor's proposed label to make it compatible with the current class labeling for combination hormonal oral contraceptive products. The Clinical Pharmacology section was extensively revised; other revisions were less extensive. There was considerable discussion by teleconference with the sponsor concerning the proprietary product name and the established name. The primary issue was the use of the word ' — see Section 7.6.2). The final revised version of the proposed PI and PPI label sent by the sponsor on January 30, 2003 is acceptable.

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

/s/

Daniel Davis
1/31/03 01:12:47 PM
MEDICAL OFFICER

Scott Monroe
1/31/03 03:17:15 PM
MEDICAL OFFICER
I concur.