CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-871

MEDICAL REVIEW

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS

CLINICAL TEAM LEADER MEMORANDUM

NDA	NDA 21-871
Type of Application	Original NDA
Applicant	Warner Chilcott Company, Inc. 100 Enterprise Drive Rockaway, NJ 07866
Proprietary Drug Name	Loestrin® 24 Fe
Established Drug Name	Norethindrone acetate and ethinyl estradiol tablets, USP, and ferrous fumarate tablets
Indication	Prevention of pregnancy
Route of administration	Oral
Dosage Form	Tablets supplied in 28-day dispenser
Dosage Strength	Active Tablets: 1 mg norethindrone + 20 μg ethinyl estradiol
Dosing Regimen	One active tablet per day for 24 consecutive days (Days 1-24) followed by one ferrous fumarate (inactive) tablet per day for 4 consecutive days (Days 25-28)
Date of Submission	April 15, 2005
PDUFA Goal Date	February 17, 2006
Date of Memorandum	February 17, 2006
Reviewer	Scott E. Monroe, MD Clinical Team Leader/Deputy Director, DRUP

RECOMMENDATIONS

Recommendation regarding Approvability

I recommend that Loestrin® 24 Fe (norethindrone acetate and ethinyl estradiol tablets, USP, and ferrous fumarate tablets) be approved for the indication "prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception." This recommendation is based on the data provided in the original NDA submitted on April 15, 2005, additional data and information submitted during the review process, and final revised product labeling submitted on February 17, 2006. Loestrin 24 Fe was shown to have acceptable efficacy (Pearl Index of 1.82) and an acceptable safety profile in the single Phase 3 clinical trial (Study PR-03903) conducted by the Applicant. There are no preclinical toxicology, chemistry, or clinical pharmacology deficiencies.

Recommendation on Phase 4 Studies and/or Risk Management Steps

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

INTRODUCTION AND BACKGROUND

Loestrin® 24 Fe tablets (hereafter referred to as Loestrin 24) is a combination oral contraceptive drug product that contains 1 mg norethindrone (NETA) and 20 µg ethinyl estradiol (EE) per active tablet. Both NETA and EE have a long history of use in combination oral contraceptive products. Two closely related combination oral contraceptives (Loestrin 1.5/30 [1.5 mg NETA and 30 µg EE] and Loestrin 1/20 [1 mg NETA and 20 µg EE]) have been marketed in the U.S. since the mid 1970s.

Rationale for Proposed Dosing Regimen

Since the introduction of combination oral contraceptives for prevention of pregnancy, there has been an effort to reduce the dosage of both the progestin and estrogen component of the products to improve overall safety without decreasing effectiveness. Although this reduction in dosage has not had a significant impact on the effectiveness of combination oral contraceptives when taken in accordance with labeling, the reduction has been associated with an increase in breakthrough vaginal bleeding or spotting (i.e., bleeding at times other than during the planned withdrawal menses). The Applicant has hypothesized that extending the duration of active treatment from 21 days to 24 days, thereby decreasing the drug-free interval to 4 days, might decrease the frequency of breakthrough spotting/bleeding associated with the use of low estrogen dosage combination oral contraceptives. Such a reduction in breakthrough spotting/bleeding might lead to better long-term compliance with dosing and perhaps fewer unplanned pregnancies.

Regulatory Background

Loestrin 24 contains the same daily doses of NETA and EE as the presently approved product Loestrin 1/20 (1 mg NETA/ 20 µg EE) oral tablets that are taken for 21 consecutive days every 28 days. Loestrin 24, however, is taken for 24 consecutive days (i.e., an additional 3 days during each 28-day treatment cycle). In designing the Phase 3 trial for Loestrin 24, it was presumed that the investigational product would be at least as effective as the approved product Loestrin 1/20 in preventing pregnancy through a combination of mechanisms including ovulation inhibition and qualitative changes in the cervical mucus. It was also assumed that because each tablet of Loestrin 24 (a) contains less active hormones than in the approved product Loestrin 1.5/30 (i.e., 1.5 mg NETA and 30 µg EE) and (b) the total cumulative monthly dose of each steroid will be less than with the use of Loestrin 1.5/30, the proposed new drug product would be at least as safe as the approved product. Based on these considerations and a previously established policy within the Division that has permitted clinical databases for combination oral contraceptive products of less than 10,000 x 28-day treatment cycles in certain circumstances, the Applicant was requested to provide efficacy and safety data from at least 600 subjects, each completing six 28-day treatment cycles.

Team Leader Comment

- *Seven hundred forty three (743) subjects started treatment with Loestrin 24, and 580 completed at least 161 days of treatment. The total number of 28-day treatment cycles was 3,823. Although slightly less than 600 subjects completed 6 cycles of treatment (the number requested by the Division), the overall exposure to study drug is adequate to assess the safety and effectiveness of the proposed drug product. Both*

Loestrin 1/20 and Loestrin 1.5/30 are considered to be safe and effective combination oral contraceptives and the proposed drug product (Loestrin 24) exposes women to daily doses of NETA and EE that are identical to those of Loestrin 1/20 and cumulative monthly doses that are intermediate between those of the 2 approved products.

OVERVIEW OF CLINICAL DATA SUBMITTED IN SUPPORT OF APPLICATION

In NDA 21-871, the Applicant provided data from 2 pharmacokinetic studies (a single-dose food effect study [PR-01904] and a multi-dose [one cycle] pharmacokinetic characterization study [PR-01804]) and a single Phase 3 efficacy and safety trial (PR-03903). Study PR-03903 was an open-label, randomized, active-controlled, multicenter study in sexually active women, age 18 to 45, at risk of becoming pregnant. The treatment phase included six 28-day cycles. Randomization was 4:1 for Loestrin 24 versus the active comparator Loestrin 1/20.

Seven hundred forty three (743) subjects started treatment with Loestrin 24 and 186 subjects started treatment with Loestrin 1/20. An overview of subject enrollment and disposition is provided in Table 1.

Table 1 Subject Enrollment and Disposition

Subject Disposition	Loestrin 24 N (%)	Loestrin 1/20 N (%)	Overall N (%)
Randomized subjects	751	187	938
Treated subjects	**743 (98.9)**	**186 (99.5)**	**929 (99.0)**
MITT subjects (A)	705 (93.9)	181 (96.8)	886 (94.5)
Completed Treatment (B)	**580 (77.2)**	**141 (75.4)**	**721 (76.9)**
Discontinued early	**168 (22.4)**	**45 (24.1)**	**213 (22.7)**
Lost to follow-up	63 (8.4)	16 (8.6)	79 (8.4)
Adverse event	46 (6.1)	13 (7.0)	59 (6.3)
Withdrawal of consent	24 (3.2)	8 (4.3)	32 (3.4)
Lack of efficacy	4 (0.5)	2 (1.1)	6 (0.6)
Protocol violation	1 (0.1)	0 (0.0)	1 (0.1)
Other reasons	30 (4.0)	6 (3.2)	36 (3.8)

A: MITT = modified intent-to-treat population that consisted of all subjects who started treatment and had at least one post-treatment pregnancy assessment.

B: The Completed Treatment population was defined as the subset of MITT subjects who completed at least 161 days of treatment.

Percentages are relative to all randomized subjects.

Source: Table 3, pg. 25, Integrated Summary of Efficacy.

In the Loestrin 24 group, 168 subjects (22.4%) did not complete the clinical trial. In the Loestrin 1/20 group, 45 subjects (24.1%) did not complete the clinical trial. The percentages of subjects terminating prematurely for the reasons listed in Table 1 were similar across the 2 treatment groups. In the Loestrin 24 group, 63 subjects (8.4%) were lost to follow-up, 46 subjects (6.1%) discontinued due to adverse events, 24 subjects (3.2%) withdrew consent, 4 subjects (0.5%) discontinued because of lack of efficacy, and the remaining 31 subjects (4.1%) were withdrawn for protocol violations or other reasons.

EFFICACY ASSESSMENTS AND FINDINGS

Primary Efficacy Assessment

The incidence of pregnancy was the primary efficacy outcome measure in Study PR-03903. Efficacy was assessed in the Modified Intent-to-Treat (MITT) population of all treated subjects, defined as women who started treatment with Study Drug and who were evaluated for pregnancy at least once after beginning study medication. All pregnancies that were found to have an estimated date of conception after the day on which Study Drug was started and within 14 days of the last dose of Study Drug were classified as on-treatment pregnancies (i.e., treatment failures). The primary efficacy analysis was the pregnancy rate expressed in terms of the Pearl Index (PI), which is defined as the number of pregnancies per 100 women on treatment for 1 year. Only treatment cycles in which subjects used no alternative method of contraception were used to calculate the Pearl Index. Pregnancy rates were also calculated by life table methods. Pregnancy rates were calculated separately for subjects ≤ 35 years of age and for subjects of all ages.

On-Treatment Pregnancies

The Applicant reported a total of 16 pregnancies among subjects randomized to treatment with Study Drug (13 in the Loestrin 24 group and 3 in the Loestrin 1/20 group). Of the 13 pregnancies in the Loestrin 24 group, the Applicant determined that 5 had an estimated date of conception that occurred on-treatment, and these cases were classified as treatment failures. The remaining 8 pregnancies were not classified as treatment failures by the Applicant because 5 occurred in subjects who never took Study Drug, 2 occurred in subjects with an estimated date of conception that preceded the start of treatment by approximately 2 weeks, and one occurred more than 14 days after the last dose of Study Drug. Of the 3 pregnancies in the Loestrin 1/20 group, the Applicant determined that 2 had an estimated date of conception that occurred on-treatment, and these cases were classified as treatment failures. The remaining single pregnancy occurred in a subject who never started Study Drug.

Team Leader Comment

- *The primary FDA Medical Reviewer (Dr. Davis) reviewed copies of the source data (e.g., sonograms) that the Applicant used to determine the estimated date of conception for all reported pregnancies. Dr. Davis concurred with the Applicant's estimated dates of conception and concluded, as did the Applicant, that 5 subjects in the Loestrin 24 group and 2 subjects in the Loestrin 1/20 group had become pregnant while using Study Drug.*

Pregnancy Rates

Based on the 5 on-treatment pregnancies in the Loestrin 24 group and 3,565 x 28-day treatment cycles during which no backup contraception was used, the Applicant calculated the Pearl Index in subjects of all ages to be 1.823 (see Table 2). In subjects ≤ 35 years of age, there were 4 reported pregnancies in 2,909 x 28-day treatment cycles, resulting in a Pearl Index of 1.788.

Table 2 Pearl Index Values for Loestrin 24 and Loestrin 1/20 Treatment Groups

	Loestrin 24 All Ages N = 705	Loestrin 24 Age 18-35 N = 579	Loestrin 1/20 All Ages N = 181	Loestrin 1/20 Age 18-35 N = 151
Number of pregnancies	5	4	2	2
Number of 28-day treatment cycles *	3,565	2,909	873	709
Pearl Index	**1.823**	**1.788**	**2.978**	**3.667**
95% Confidence Interval**	0.592 - 4.251	0.487 – 4.572	0.36 - 10.73	0.44 - 13.20

* Only cycles for which no alternative method of contraception was used are included.

** Confidence intervals are calculated using exact confidence intervals for binomial estimation of p, where p = (Number of pregnancies/Number of cycles).

Source: Table 5, pg. 20, Primary FDA Medical Review.

The Applicant also estimated the effectiveness of Loestrin 24 and Loestrin 1/20 using a Life Table analysis. Based on this analysis, the 6-cycle cumulative pregnancy rate for subjects of all ages was 0.90% in the Loestrin 24 group and 1.20% in the Loestrin 1/20 comparator group.

Team Leader Comments

- *The Division has approved combination oral contraceptives with Pearl Index values that have approached 2.40 for subjects of all ages. The Pearl Index values of 1.823 (subjects of all ages) and 1.788 (subjects ≤ 35 yrs of age) in the Loestrin 24 treatment group are acceptable for a combination oral contraceptive.*
- *There was an unconfirmed pregnancy in a 24 year old subject in the Loestrin 24 treatment group. The Applicant did not include this subject in their calculation of the Pearl Index. If this subject is included in the calculation of the Pearl Index (a worst case analysis), the Pearl Index values increase to 2.188 (95% CI: 0.803, 4.758) for subjects of all ages and to 2.234 (95% CI: 0.726, 5.208) for subjects ≤ 35 years of age. These values are still acceptable for a combination oral contraceptive and are numerically lower (but not statistically different) than those for the approved active comparator Loestrin 1/20.*

Conclusion of the FDA Primary Medical Reviewer

The following is the conclusion of the FDA primary Medical Reviewer regarding the effectiveness of Loestrin 24 for prevention of pregnancy:

> *In the 579 women who were 18 to 35 years of age, there were 4 confirmed pregnancies in 2,909 evaluable cycles of treatment. The Pearl Index was estimated at 1.79 per 100 women-years of use for this subset of women. If the one unconfirmed pregnancy in a 24 year old woman is counted as an on-treatment pregnancy, then the Pearl Index is increased from 1.79 to 2.23, which is still an acceptable index. These results are comparable to the pregnancy rates reported with combination oral contraceptives in many previous clinical studies submitted to the FDA for presently approved combination oral contraceptives.*

Team Leader's Overall Assessment of Contraceptive Efficacy of Loestrin 24

- *I concur with the assessment of the primary Medical Reviewer that the efficacy of Loestrin 24, based on the data provide in NDA 21-871 regarding the prevention of pregnancy, is acceptable for a combination oral contraceptive.*

Secondary Efficacy Objective

It was anticipated by the Applicant that the overall bleeding profile (several parameters of bleeding/spotting) for Loestrin 24 would be better than that for Loestrin 1/20. Comparisons were performed by the Applicant between the Loestrin 24 and Loestrin 1/20 treatment groups with regard to incidence of withdrawal bleeding, incidence of intracyclic bleeding (IB), number of IB episodes, number of IB days, and number of bleeding/spotting episodes. These comparisons and their outcomes are reviewed in detail in the primary Medical Review.

Team Leader Comments

- *For the most part, there were no statistically significant or clinically meaningful differences across the 2 treatment groups in terms of any of the parameters of bleeding that were examined. In particular, there was no significant difference either in the incidence of intracyclic bleeding or in the number of intracyclic bleeding/spotting days across the 2 treatment groups. However, there was a trend toward a greater percentage of subjects in the Loestrin 24 group not having monthly withdrawal bleeding.*
- *The findings of Study PR-03903 do not support the Applicant's hypothesis that 3 additional days of active treatment (i.e., extending the active treatment period from 21 to 24 days during each 28-day cycle) would reduce the incidence of intracyclic bleeding. This goal, however, was a secondary objective. Failure to successfully achieve this objective should not preclude approval of Loestrin 24 for marketing if the data submitted in this NDA indicate that the drug product is both safe and effective for the prevention of pregnancy.*

SAFETY FINDINGS

Clinical Trial Data

Serious Adverse Events

In clinical trial PR-03903, there were no deaths in either treatment group. Three serious adverse events were reported (one event in each of 3 subjects) in the Loestrin 24 treatment group. These events were a partial thyroidectomy, thyroid cancer, and a back injury. None of the adverse events was considered to be related to study drug and none led to discontinuation from the study. There were no serious adverse events in the smaller Loestrin 1/20 treatment group.

Adverse Events Associated with Discontinuation of Treatment.

A total of 46 subjects (6.1%) in the Loestrin 24 group and 13 subjects (7.0%) in the Loestrin 1/20 group discontinued treatment due to an adverse event. All but 3 of these events were reported as mild or moderate in intensity. The 3 events reported as severe were all related to menstrual cramping or dysmenorrhea. None of the 46 adverse events was considered to be serious. The most commonly reported adverse events leading to discontinuation of treatment in Loestrin 24 subjects are listed below:

- Abnormal bleeding: 10 subjects (includes metrorrhagia, spotting, irregular bleeding)
- Nausea: 6 subjects
- Mood changes: 6 subjects (includes mood change, depression, irritability, and nervousness)
- Dysmenorrhea: 4 subjects
- Edema/weight gain: 3 subjects
- Increased blood pressure: 3 subjects

The 14 other adverse events that led to discontinuation in either 1 or 2 of the Loestrin 24 subjects were fatigue, contact lens problems, premenstrual syndrome, amenorrhea, breast discharge, rash, syncope, acne, abdominal pain, irritable bowel symptoms, yeast infection, and headache.

Team Leader Comment

- *The number of subjects and the specific adverse events associated with discontinuation of treatment in the Loestrin 24 treatment group is expected and similar to those reported in other clinical trials with presently approved combination oral contraceptives. These findings do not raise any safety concerns.*

Common Adverse Events

Adverse events reported as occurring in 1% or more of subjects are listed by body system and preferred term in Table 3. In the Loestrin 24 group, the 5 most commonly reported adverse events were headache (6.3% of subjects), vaginal candidiasis (6.1%), upper respiratory tract infection (5.1%), nausea (4.6%), and dysmenorrhea (4.4%). The percentages of subjects reporting these events in the Loestrin 1/20 group were similar.

Table 3 Adverse Events Reported in > 1% of Subjects by Treatment Group

Body System and Preferred Term	Loestrin 24 N = 743 n (%)	Loestrin 1/20 N = 186 n (%)	Overall N= 929 n (%)
Nervous System Disorders			
Headache	47 (6.3)	13 (7.0)	60 (6.5)
Infections and Infestations			
Vaginal candidiasis	45 (6.1)	10 (5.4)	55 (5.9)
Upper respiratory tract infection NOS	38 (5.1)	9 (4.8)	47 (5.1)
Sinusitis NOS	23 (3.1)	4 (2.2)	27 (2.9)
Vaginitis bacterial NOS	23 (3.1)	3 (1.6)	26 (2.8)
Urinary tract infection NOS	18 (2.4)	5 (2.7)	23 (2.5)
Pharyngitis streptococcal	11 (1.5)	2 (1.1)	13 (1.4)
Gastroenteritis viral NOS	8 (1.1)	4 (2.2)	12 (1.3)
Gastrointestinal Disorders			
Nausea	34 (4.6)	6 (3.2)	40 (4.3)
Vomiting NOS	14 (1.9)	1 (0.5)	15 (1.6)
Diarrhea NOS	9 (1.2)	1 (0.5)	10 (1.1)
Dyspepsia	8 (1.1)	2 (1.1)	10 (1.1)
Reproductive System and Breast Disorders			
Dysmenorrhea	33 (4.4)	5 (2.7)	38 (4.1)
Breast tenderness	25 (3.4)	2 (1.1)	27 (2.9)
Metrorrhagia	14 (1.9)	2 (1.1)	16 (1.7)
Pelvic pain	10 (1.3)	2 (1.1)	12 (1.3)
Investigational Findings			
Smear cervix abnormal	23 (3.1)	6 (3.2)	29 (3.1)
Weight increased	15 (2.0)	3 (1.6)	18 (1.9)
Skin and Subcutaneous Tissue Disorders			
Acne NOS	20 (2.7)	5 (2.7)	25 (2.7)
Psychiatric Disorders			
Mood swings	16 (2.2)	5 (2.7)	21 (2.3)
Depression	8 (1.1)	4 (2.2)	12 (1.3)
Musculoskeletal and Connective Tissue			
Back pain	7 (0.9)	3 (1.6)	10 (1.1)
General Disorders			
Fatigue	8 (1.1)	2 (1.1)	10 (1.1)

NOS = Not otherwise specified
Source: Table 15, pg. 31, primary Medical Review.

Team Leader Comment

- *None of these adverse events are unexpected in women using combination oral contraceptives. The number of women reporting these events is similar to findings from clinical trials with other presently approved combination oral contraceptives and do not raise any safety concern.*

Postmarketing Safety Data

There is no postmarketing experience with this drug product because Loestrin 24 is not approved for marketing in any country. There is extensive postmarketing experience, however, with the 21-day product Loestrin 1/20 and the higher dose product Loestrin 1.5/30, as both these products were approved by the FDA for marketing in the mid 1970s. Because of the similarity between Loestrin 24 and Loestrin 1/20 and Loestrin 1.5/30, the Division of Drug Risk Evaluation was consulted to review the FDA's Adverse Event Reporting System (AERS) database for deaths and serious thrombotic adverse event reports associated with Loestrin 1/20 and Loestrin 1.5/30.

Twenty-four "fatalities" have been reported since May 1980. Eleven cases (2 cases of melanoma and 9 cases of unintended pregnancies ["fetal deaths"]) were not considered either as possibly drug-related or of relevance, thereby resulting in 13 reported deaths in users of Loestrin 1/20 or Loestrin 1.5/30 over the past 25 years. The primary cause of death in these 13 cases was listed as follows: pulmonary embolism (7), cerebral vascular accident (2), acute myocardial infarct (2), arterial thrombosis (1), and cardiac surgery (1). The product reported for these 13 cases was: Loestrin 1/20 (n = 6), Loestrin 1.5/30 (n = 2), and not specified (n = 5).

Team Leader Comment

- *Thirteen reported deaths over 25 years of product use raises no concern about the safety of either Loestrin 1/20 or Loestrin 1.5/30 and is within the expected range of deaths associated with the use of a combination hormonal contraceptive.*

For serious thrombotic and thromboembolic adverse events, the search of the AERS database revealed 33 cases of pulmonary embolus, 29 cases of cerebral vascular accident, 27 cases of deep vein thrombosis, and 3 cases of myocardial infarction.

Team Leader Comment

- *The number of reports for serious thrombotic and thromboembolic adverse events for users of Loestrin 1/20 and Loestrin 1.5/30, accumulated over more than 25 years of use, is less than one might expect based on the known rates of these adverse events in users of combination oral contraceptives. Although it cannot be concluded that these 2 products are safer than other combination oral contraceptives, there is no signal that they are less safe.*

Safety Update

A brief safety update was submitted in February 2006 stating that there was no new safety information to report for the Loestrin 24 product. In the update, the Applicant stated that no additional preclinical or clinical studies were ongoing and that no new safety data had been obtained since submission of the original NDA.

Medical Officer's Comments Regarding Overall Safety

- *The data from Clinical Trial PR-30903 do not raise any concerns about the safety profile of Loestrin 24. In the clinical trial there were no reports of deaths, thrombotic or thromboembolic adverse events, or serious adverse events of concern. Adverse events that were associated with premature discontinuation of treatment or were commonly*

reported also do not raise any safety concerns. These adverse events were the same as those that would be expected in a clinical trial of a combination oral contraceptive.

- *Although the clinical trial safety database for Loestrin 24 contains less than 10,000 x 28-day treatment cycles, it exceeds the minimum total number of 28-day treatment cycles (i.e., > 3,600) requested by the Division for this product as discussed earlier in the section "Regulatory Background." This reduced safety database is acceptable for this product because (a) the daily dose of NETA (1 mg) and EE (20 μg) are identical to the approved 21-day drug product Loestrin 1/20 and (b) the total cumulative monthly dose of NETA and EE associated with the use of Loestrin 24 is less than that associated with the use of Loestrin 1.5/30. Furthermore, the safety of the 2 active ingredients at the dose levels found in Loestrin 24 is well established based on over 25 years of use.*
- *Review of the FDA's AERS database for deaths and serious thrombotic adverse event reports associated with the use of Loestrin 1/20 and Loestrin 1.5/30 did not raise any safety concerns as described earlier*
- *In summary, the safety profile for Loestrin 24 is acceptable for a combination oral contraceptive product.*

LABELING

The Applicant's original proposed product labeling was extensively revised by the Division. No special claims were made concerning the bleeding profile for Loestrin 24. The Clinical Study section of the label states the number of women enrolled, treatment cycles of exposure, number of on-treatment pregnancies, and the Pearl Index for Loestrin 24. The routine class labeling portion of the label was completely updated. Final proposed labeling submitted by the Applicant on February 17, 2006 was acceptable.

NON CLINICAL REVIEW ISSUES

Toxicology and Preclinical Pharmacology

There were no new nonclinical studies submitted in support of this application. Norethindrone acetate and ethinyl estradiol are well known chemical entities, and there are no novel inactive ingredients. The Toxicology team leader (Dr. Lynnda Reid) stated the following in her review: "*From a Pharmacology/Toxicology viewpoint, NDA 21-871 is recommended for Approval.*" Her recommendation for labeling was "*Labeling for Carcinogenesis, Mutagenesis, Impairment of Fertility; Pregnancy and Nursing Mothers will be identical to the label for Loestrin® Fe 1/20 Tablets.*"

Chemistry (CMC)

The Chemistry Reviewer (Dr. Rajiv Agarwal) recommended the following: "This NDA may be approved from the CMC point of view." There were no chemistry recommendations for Phase 4 (post-marketing) commitments, agreements, and/or risk management steps.

Clinical Pharmacology and Biopharmaceutics

In her review of NDA 21-871, the primary Clinical Pharmacology Reviewer (Dr. Kim) stated the following: "*The Office of Clinical Pharmacology / Division of Clinical Pharmacology 3 (OCP/DCP-3) has reviewed NDA 21-871 submitted on April 18, 2005. The overall Human*

Pharmacokinetic Section is acceptable. Labeling comments outlined in the Clinical Pharmacology section and the drug-drug interactions have been accepted by the sponsor."

Statistics

Shahla Farr, MS, Division of Biometrics 2, made the following conclusions and recommendations in her statistical review of NDA 21-871:

*"**Conclusions and Recommendations**. Based on the data provided by the sponsor, from the statistical standpoint, Norethindrone Acetate 1 mg/Ethinyl Estradiol 20 mcg Oral Tablets (Loestrin-24) seems adequately effective for the prevention of pregnancy. A total of 12 pregnancies were reported to have occurred in the clinical trial; 10 in 24-day regimen, and 2 in the 21-day arm. However, 5 of the 10 pregnancies in the Loestrin 24 arm were not assessed as having occurred while the subjects were on treatment with Study Drug. In the Modified Intent-to-Treat (MITT) population, the 21-day treatment arm had 2 occurrences of pregnancies in a total of 873 28-day treatment cycles, resulting in a Pearl Index (PI) of 2.98 (95% CI from 0.27 to 10.8). The Loestrin-24 treatment arm had a total of 5 pregnancies in a total of 3,565 28-day treatment cycles, resulting in a Pearl Index of 1.82 (95% CI from 0.51 to 4.36); if the one unconfirmed pregnancy is considered, there were 6 pregnancies, resulting in a Pearl Index of 2.19 (95% CI from 0.77 to 4.63), also demonstrating acceptable efficacy compared to the 21-day Loestrin, with a PI of 2.98. However, the 24- day regimen's 95% Confidence Intervals for the PI using either 5 or 6 pregnancies overlap with the 21- day regimen: with 5 pregnancies (0.51, 4.36) vs. (0.27, 10.8), and with 6 pregnancies (0.77, 4.63) vs. (0.27, 10.8). Therefore, we cannot conclude that one treatment is significantly better than the other."*

Team Leader Comment

- *Approved labeling does not include any comparative claims.*

Division of Surveillance, Research, and Communication Support

The Division of Surveillance, Research, and Communication Support (DSRCS) made the following comments based on its review of product labeling: *"(1) The format and content of the proposed PPI are acceptable from a patient comprehension perspective. The Flesch-Kincaid reading level is 7.6 and the Flesch reading ease is 67%. (2) Avoid the use of all UPPER CASE letters to emphasize statements or important information. Upper case lettering is difficult to read. Use upper and lower case letters and, bold or increase the font size for word or statement emphasis. The tradename and headings are the exception to this recommendation and may be in all upper case letters.*"

Team Leader Comment

- *The use of upper case lettering will be reduced as part of the process for revising class labeling for combination oral contraceptive products.*

Division of Medication Errors and Technical Support (DMETS)

DMETS made the following recommendations/comments in their consultation of August 19, 2005:

1. *DMETS does not recommend the use of the proprietary name Loestrin® 24.*
2. *DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.*
3. *DDMAC finds the name Loestrin 24 acceptable from a promotional perspective.*

After extensive discussions involving the Applicant, DMETS, and the Division, agreement was reached on the acceptability of "**Loestrin 24 Fe**" for the tradename. Carton labeling (e.g., font sizes, statement locations, and choice of lettering colors) was also extensively revised in accordance with the recommendations of DMETS.

Division of Drug Marketing, Advertising, and Communications

In their consultation of September 8, 2005, the Division of Drug Marketing, Advertising, and Communications (DDMAC) made several suggestions regarding labeling revisions. All recommendations were considered in the Division's extensive revisions and incorporated in product labeling where appropriate.

Division of Scientific Investigation

No study center inspections were conducted by the Division of Scientific Investigation (DSI). After his preliminary review of the NDA submission, the primary Medical Reviewer concluded that such inspections were not warranted for this application.

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

/s/

Scott Monroe
2/17/2006 03:07:34 PM
MEDICAL OFFICER

Daniel A. Shames
2/17/2006 04:27:40 PM
MEDICAL OFFICER

Appears This Way
On Original

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-871
Submission Code	N-000
Letter Date	April 15, 2005
Stamp Date	April 18, 2005
PDUFA Goal Date	February 17, 2006
Reviewer Name	Daniel Davis, MD
Review Completion Date	February 15, 2006
Established Name	Norethindrone acetate and ethinyl estradiol tablets, USP and ferrous fumarate tablets
Trade Name	Loestrin® 24 Fe
Therapeutic Class	Hormonal Contraception
Applicant	Warner Chilcott Company, Inc.
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	1 tablet daily (24 active tablets followed by 4 placebo tablets)
Indication	Prevention of pregnancy
Intended Population	Women of reproductive age

TABLE OF CONTENTS

TABLE OF TABLES

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that Loestrin 24 Fe (hereafter called Loestrin 24) be approved for the following indication: prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special postmarketing risk management activity is recommended.

1.2.2 Required Phase 4 Commitments

There are no required or recommended Phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests of the Applicant.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The development program consisted of a single (6-month) open-label, randomized, active-controlled, multicenter study – PR-03903, involving 32 sites in the U.S. The program was designed to study the safety and efficacy of 1 mg norethindrone acetate [NETA] + 20 mcg ethinyl estradiol [EE]) tablets (hereafter called Loestrin 24) administered for 24 days followed by ferrous fumerate (placebo) tablets for four days in 28-day cycles. The objective was to complete six 28-day cycles of treatment in at least 600 women. The safety and efficacy of Loestrin 24 also was compared to that of Loestrin 1/20 (a combination oral contraceptive [COC] approved in 1973) that contains the same doses of NETA and EE but with a dosing regimen that consists of 21-days of active tablets followed by 7 days of ferrous fumerate (placebo) tablets.

A total of 1,159 potential subjects were screened for the study; of these, 938 women met the entrance criteria for the study, provided informed consent, and were randomized in a 4:1 ratio to one of the two treatments (24-day active dosing regimen or 21-day active dosing regimen, respectively). Seven hundred fifty-one (751) subjects were randomized to the Loestrin 24 group, and 187 subjects to the Loestrin 1/20 group; 743 subjects actually received Loestrin 24 and 186 subjects received Loestrin 1/20. Study visits were at screening, randomization, and after treatment Cycles 1, 3, and 6.

Twenty-two (22) percent of the Loestrin 24 group (168 subjects) and 24% of the Loestrin 1/20 group (45 subjects) failed to complete all aspects of the study protocol. The reasons for early termination of subjects were very similar in the two treatment groups. For the Loestrin 24 group, sixty three subjects (8.4%) were lost to follow-up, 46 subjects (6.1%) discontinued due to adverse events, 24 subjects (3.2%) withdrew consent, 4 subjects (0.5%) discontinued because of lack of efficacy, and the remaining 31 (4.1%) were withdrawn for minor protocol violations or other reasons.

The modified intent-to-treat (MITT) population, the population that was evaluated for contraceptive efficacy, comprised 705 subjects in the Loestrin 24 group, and 181 in the Loestrin 1/20 group. The Completed Subjects population was defined as the subset of the MITT subjects who completed at least

161 days (6 cycles) of treatment. This included 580 subjects (77%) in the Loestrin 24 treatment group, and 141 subjects (75%) in the Loestrin 1/20 treatment group.

In addition to the single Phase 3 trial, two small pharmacokinetic (PK) studies were performed to determine (1) the overall PK profile for Loestrin 24 for one treatment cycle and (2) the effect of food on these PK parameters.

1.3.2 Efficacy

Prevention of pregnancy. The primary efficacy objective of this study was to assess the contraceptive effectiveness of Loestrin 24 in preventing pregnancy. In this study, among 705 women with 3,565 evaluable cycles of treatment, there were 5 pregnancies that occurred while on treatment with Loestrin 24. The cumulative risk (based on a Life Table analysis) of becoming pregnant while taking Loestrin 24 was estimated at 0.9% in the first 6 cycles of use.

The Pearl Index, based on a total of 5 well documented pregnancies and defined as the number of pregnancies per 100 women-years of use, was 1.82 (95% CI 0.59-4.25) for women of all ages considering only cycles for which no backup contraception was used. If the one unconfirmed pregnancy is also counted as an on-treatment pregnancy, the Pearl Index becomes 2.19, which is still an acceptable index. In the 579 women who were 18 to 35 years of age, there were 4 confirmed pregnancies in 2,909 evaluable cycles of treatment during which no backup contraception was used. The Pearl Index was estimated at 1.79 (95% CI 0.49-4.57) for this subset of women. These results are comparable to the pregnancy rates reported with COCs in clinical studies previously submitted to the Division for approved products. In the comparative Loestrin 1/20 group, 2 women became pregnant in 873 cycles of treatment. The Pearl Index for Loestrin 1/20 was 2.98, although this finding is not as meaningful because of the small number of evaluable treatment cycles and the wide confidence interval around the point estimate.

Menstrual cycle bleeding patterns. A secondary efficacy objective of the Phase 3 study was to compare the incidence of intracyclic bleeding (IB) between Loestrin 24 and Loestrin 1/20. It was anticipated by the Applicant that the overall bleeding profile (several parameters of bleeding/spotting) for Loestrin 24 would be better than that of Loestrin 1/20.

The mean number of intracyclic bleeding/spotting days in Cycles 2 through 6 (spanning 140 days) was 6.31 for Loestrin 24 compared to 7.31 for Loestrin 1/20 ($P = 0.311$). Other bleeding endpoints that were assessed included total bleeding days, days and intensity of withdrawal bleeding, and incidence of amenorrhea. None of these parameters were significantly different across the 2 treatment groups. **It is this reviewer's opinion that no labeling claims for a better or superior overall bleeding profile or for any individual bleeding parameter may be made in association with use of the Loestrin 24 product. The overall bleeding profile for Loestrin 24 certainly does not appear to be any worse than that of the approved Loestrin 1/20, and the overall bleeding profile for Loestrin 24 is acceptable and safe.**

1.3.3 Safety

The integrated summary of safety (ISS) for this product included data from two small Phase 1 pharmacokinetic studies and one 6-cycle Phase 3 study. The primary clinical database for the safety analysis was derived from all treated subjects in the Phase 3 study: 929 subjects (743 on Loestrin 24), representing approximately 5,000 women cycles of total exposure to tablets containing 1 mg NETA + 20 mcg EE (with over 4,000 women months of treatment on Loestrin 24 evaluable for safety). The safety data that were recorded during the course of the trial included adverse events, physical and gynecologic examination findings, vital signs and laboratory results. The safety data from the two Phase 1 studies were also included, but this involved only 18 women for one cycle of treatment.

There were no deaths in any of the 3 studies. There were 3 serious adverse events (SAEs) in subjects in the Phase 3 study, all in the Loestrin 24 group. One woman had a partial thyroidectomy, one had a thyroid cancer, and one had a back injury. None were considered to be related to study drug and no SAE led to discontinuation from the study. Thus, the reported SAEs in the study did not raise a safety concern.

Over 75% of subjects in both the Loestrin 24 group and the Loestrin 1/20 group completed the study. The reasons for discontinuing early (dropouts) were very similar in the two treatment groups. For the Loestrin 24 group, 63 subjects (8.4%) were lost to follow-up, 46 subjects (6.1%) discontinued due to adverse events, 24 subjects (3.2%) withdrew consent, 4 subjects (0.5%) discontinued because of lack of efficacy, and the remaining subjects were withdrawn for protocol violations or other reasons. In the group that withdrew because of an adverse event, there were no deaths or SAEs.

A total of 46 subjects (6.1%) in the Loestrin 24 group and 13 subjects (7.0%) in the Loestrin 1/20 group discontinued due to an AE. Most of the AEs were classified as being possibly or probably related to drug. All but 3 were mild or moderate in intensity. None were serious. The most common AEs that led to discontinuation in 32 of the 46 Loestrin 24 subjects were:

- Abnormal bleeding- 10 subjects (10/46 = 22%)
- Nausea- 6 subjects (13%)
- Mood change-6 subjects (13%)
- Dysmenorrhea- 4 subjects (9%)
- Edema/weight gain- 3 subjects (6.5%)
- Increased blood pressure- 3 subjects (6.5%)

The other AEs that led to discontinuation in 1 or 2 subjects were fatigue, contact lens problems, premenstrual syndrome, amenorrhea, breast discharge, rash, syncope, acne, abdominal pain, irritable bowel symptoms, yeast infection, and headache.

Adverse events occurring in at least 1% of subjects overall by body system, preferred term, and treatment group were listed by the Applicant. The five most commonly reported adverse events in the Loestrin 24 group were headache (6.3%), vaginal candidiasis (6.1%), upper respiratory tract infection (5.1%), nausea (4.6%), and dysmenorrhea (4.4%). Other common AEs experienced by at least 1.9% of the Loestrin 24 group included the following in descending order: breast tenderness (3.4%), abnormal Pap, sinusitis, and vaginitis (all 3.1%), acne (2.7%), urinary tract infection (2.4%), mood change (2.2%), vomiting and metrorrhagia (both 1.9%). None of these occurrences was unexpected and they did not raise a safety concern.

Very few hematology and chemistry findings were considered to be abnormal by the investigator in either treatment group. Three subjects in the Loestrin 24 group had triglyceride levels that were definitely elevated at the end of the 6-month study; follow-up values (16 and 39 days later) were obtained in 2 of the women and were found to be considerably lower. The same two subjects also had elevated cholesterol values (range of 249-297) at baseline and at end of study. In the smaller Loestrin 1/20 group there was one woman with a slightly elevated triglyceride level of 169 [reference range 36-144].

Blood pressure, pulse and weight were measured at screening and after Cycles 1, 3, and 6. Changes from baseline in mean systolic and diastolic blood pressure and heart rate were small. No clinically significant changes were noted. Mean changes in weight for the Loestrin 24 and Loestrin 1/20 groups were 0.8 and 0.6 pounds, respectively.

The safety data was limited primarily by the length of the Phase 3 study (only 6 months) and the relatively small number of cycles of exposure (~4,000 compared to ≥ 10,000 for a "new" hormonal contraceptive product). These limitations, agreed to by the Division, are acceptable as Loestrin 24 is not a new molecular entity and the two active ingredients, norethindrone acetate and ethinyl estradiol, have

been well established over the past 35 years as safe in the daily doses being used in this NDA submission as well as at a higher daily doses consisting of 1.5 mg NETA + 30 mcg EE (Loestrin 1.5/30).

The overall conclusion of this reviewer is that Loestrin 24 is safe and no Phase 4 commitments or special postmarketing studies are indicated.

1.3.4 Dosing Regimen and Administration

Each pack provides a dosing regimen consisting of 24 active tablets containing 1 mg norethindrone acetate and 20 micrograms of EE followed by 4 placebo tablets containing ferrous fumarate. The regimen and dosing for Loestrin 24 is not flexible. The oral tablet should be taken at the same time each day for 28 consecutive days and then the next package of 28 pills started. The tablets may be taken without regard to meals or food. Labeling gives clear instructions on what to do if 1, 2, or more pills are not taken as directed.

1.3.5 Drug-Drug Interactions

No special drug-drug interaction studies were performed for this product. The label, however, does have a section under **Precautions** (part of class labeling) that addresses this issue for all combination hormonal contraceptive products.

1.3.6 Special Populations

Gender. Loestrin 24 tablets are intended only for women at risk for pregnancy.

Race. No special populations were required or studied for the NDA submission. Although the Phase 3 clinical study enrolled 70.5% Caucasians, 10% Hispanics, and 15% African-Americans, the effect of race on the safety and efficacy of Loestrin 24 was not specifically evaluated. There is no evidence from previous combination oral contraceptive NDAs reviewed by the FDA or from the medical literature to suspect that the safety or efficacy of combination estrogen/progestin oral contraceptive products differ significantly based on the race of the user.

Renal and Hepatic Impairment. No studies were conducted in subjects with renal or hepatic impairment.

Pediatric Studies. No additional pediatric studies are required. It is generally accepted that the safety and efficacy profiles of combination oral contraceptives are similar in post-menarchal adolescents and in women ≥ 18 years of age.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Combination oral contraceptives (COCs) are safe and effective in the prevention of pregnancy. Since the 1970s, because of concern about the safety of hormones, the doses of both the progestin and estrogen hormonal components of COCs have been progressively decreased with little to no diminution of efficacy. Loestrin 1.5/30 and Loestrin 1/20 were first approved by the FDA April 30, 1973. Each was marketed as a 28-day product with 21 active pills followed by 7 "placebo" pills containing ferrous fumarate. However, irregular and unpredictable bleeding (breakthrough bleeding) has been a result of the reduction in dose from 1.5 mg NETA/30 mcg EE tablets (Loestrin 1.5/30) to 1 mg NETA/20 mcg EE tablets (Loestrin 1/20). Increased breakthrough bleeding is considered a cause of poor compliance with the use of Loestrin 1/20, the consequence of which can be an unwanted pregnancy. The Applicant hypothesized that extending the duration of active treatment from 21 to 24 days and decreasing the drug-free interval to 4 days might decrease the frequency of spotting in women using this product and lead to better long-term compliance and fewer unplanned pregnancies.

The investigational product Loestrin 24 contains the same daily doses of NETA and EE as Loestrin 1/20 (1 mg NETA/ 20 mcg EE) oral tablets that are administered for 21 days. Loestrin 24, however, is administered for 3 additional days during each cycle (24 versus 21). In designing the Phase 3 trial for Loestrin 24, it was presumed that the investigational product would be at least as effective as the approved product Loestrin 1/20 in preventing pregnancy through a combination of mechanisms including ovulation inhibition and qualitative changes in the cervical mucus. It was also assumed that since each tablet of the investigational product contains less NETA and EE than found in Loestrin 1.5/30 tablets and the total cumulative monthly dose of each steroid, is less than with Loestrin 1.5/30, the investigational product (Loestrin 24) would be at least as safe as the approved product Loestrin 1.5/30.

2.2 Currently Available Treatment for Indications

There are currently over 50 approved combination oral contraceptive products available in the U.S. Both generic and original versions exist. Many of the products contain the same two hormones, norethindrone (or norethindrone acetate) and ethinyl estradiol, as are found in the Loestrin 24 and Loestrin 1/20 products.

2.3 Availability of Proposed Active Ingredients in the United States

Norethindrone acetate (NETA) and ethinyl estradiol (EE) have been used in many different combination hormonal contraceptive products in the U.S. for over 35 years. Therefore, there is an extensive amount of experience and data concerning the safety and efficacy of these two active ingredients in varying doses and regimens. The safety profile of NETA is generally considered to be among the best of all the progestins used in COCs.

2.4 Important Issues With Pharmacologically Related Products

The most important issue is safety rather than contraceptive effectiveness. In particular, although thromboembolic events (pulmonary embolism, DVTs, strokes, and myocardial infarcts) are rare, they are serious and important. The more common side effects and adverse events are not as important because they are reversible and usually not medically serious.

2.5 Presubmission Regulatory Activity

There were 4 significant clinical agreements reached during the presubmission period:

1. Pre-IND teleconference held 9-17-03: The proposed clinical program was deemed to be adequate for the evaluation of safety and efficacy of the new dosing regimen with pregnancy prevention as the primary endpoint. The Division expected that at least 600 women will complete 6 cycles of treatment.
2. Letter from the Division, 12-11-03: Not all of the 600 subjects who complete 6 months of treatment need to be $\leq$ 35 years of age.
3. Pre-NDA meeting held 11-15-04: The Pearl Index should be calculated for the comparator product and for the subgroup of Loestrin 24 women age 18-35 using only cycles in which no backup contraception was used. A 2-sided 95% confidence interval should be used for all Pearl Indices.
4. The issue of bleeding assessment was discussed on September 17, 2003. As a result of this discussion and meeting minutes dated October 29, 2003 and clarified on December 11, 2003 and March 5, 2004, protocol changes were made to allow the prospective statement of a primary bleeding assessment target (total days of intermenstrual bleeding in Cycles 2-6) as a secondary objective of the study.

2.6 Other Relevant Background Information

There are no other major areas of concern.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

There are no product microbiology issues. For the CMC review, the biggest issue was the Trade name for the product. The use of the word "new" and the number 24 in the Trade name were discussed with the Division of Medication Errors and Technical Support (DMETS) and the Applicant. Final agreement was reached on the Trade name Loestrin® 24 Fe (norethindrone acetate/ethinyl estradiol and ferrous fumarate tablets).

The manufacturing and stability of the product were determined to be acceptable by Raj Agarwal, the chemistry reviewer. The reviewer recommended that the NDA be approved from the CMC point of view. There were no recommendations for Phase 4 (Post-Marketing) Commitments.

3.2 Animal Pharmacology/Toxicology

Because the Loestrin 1/20 product and many other COCs containing NETA and EE have been on the market with extensive use since the 1970s, there was no indication for additional animal studies. This was discussed and agreed to at meetings between the Applicant and the Division on 9-17-03 (Question 3 asked about the need for further pharmtox studies and the Division concurred that none were needed). At the 11-15-04 pre-NDA meeting the same question was again asked: Does the Agency concur that both norethindrone acetate and ethinyl estradiol are well known chemical entities and no new pharmacology and toxicology information need be provided? The Division concurred. The final NDA review by the pharmtox team leader Lynnda Reid, PhD, states that no further pharmtox studies are needed for Loestrin 24 and that the preclinical studies performed for norethindrone and ethinyl estradiol prior to this product's development are sufficient for this product.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The development program consisted of a single abbreviated open-label, randomized, active-controlled, multicenter Phase 3 study – PR-03903, involving 32 sites in the U.S and two pharmacokinetic studies. The Phase 3 study was designed to evaluate the 24-day active tablet dosing regimen instead of 21 days of dosing with active tablets using the approved product (Loestrin 1/20). To that end, the objective was to complete 6 28-day cycles of treatment in at least 600 women using the new product.

The protocol was discussed with the Division of Reproductive and Urologic Drug Products during a Pre-IND teleconference on September 17, 2003. As a result of this discussion and meeting minutes dated October 29, 2003 and clarified on December 11, 2003 and March 5, 2004, protocol changes were made to allow the prospective statement of a primary bleeding assessment target (total days of intermenstrual bleeding in Cycles 2-6 as a secondary endpoint), and to count women over 35 toward the target number of 600 subjects and evaluable safety cycles of treatment.

4.2 Tables of Clinical Studies

As agreed between the Division and the Applicant there was only one 6-month Phase 3 clinical study required for this NDA submission. The study is outlined in the efficacy section of this review.

4.3 Review Strategy

First, the proposed label and integrated summaries of safety (ISS) and efficacy (ISE) for the single clinical trial were read. Previous meeting minutes and agreements between the Division and Applicant were reviewed. Consultations from DMETS (Trade Name review), DDMAC (PI review), and DSRCS (PPI review) were requested and received. Then the clinical reviewer and biometrics reviewer Shahla Farr discussed the important statistical issues to be explored and the number of pregnancies that occurred before, during and after treatment. There were no major chemistry or biopharmaceutical issues. Individual reviews were then completed by the various disciplines and the final label agreed upon between the Division and the Applicant.

Reviewer's comment:

The issues raised by the consultations with DMETS, DDMAC, and DSRCS were shared with the Applicant and resolved. Further details are found in section 9.4 of this review.

4.4 Data Quality and Integrity

All the 32 clinical sites were in the U.S. Two of the 32 sites did not enroll any subjects. The clinical reviewer determined that site inspections were not warranted; there did not appear to be any sites that had data on enrollment, percentage dropouts, AEs, pregnancies, etc. that were clear outliers. The product to be approved contains a very low-dose estrogen (20 mcg EE) oral contraceptive tablet that was originally approved in 1973 and has had a very good safety profile. The new regimen proposed in the NDA represents a minor change [24 active pills instead of 21] from the currently approved tablet and regimen. In addition, a similar higher dose product, Loestrin 1.5/30 (norethindrone 1.5 mg, 30 mcg EE), approved in April 1973 and still marketed also has had a good safety profile.

4.5 Compliance with Good Clinical Practices

The study was carried out in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines: International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, the Guideline for Good Clinical Practice, and the Declaration of Helsinki, Edinburgh version (2000).

4.6 Financial Disclosures

The statements on financial disclosures were reviewed. The principal investigator (PI) at a — site stated on the financial disclosure that the PI owned 5,000 shares of Galen stock @ $50 per share; the — site (— screened — women, enrolled —), and — completed. This enrollment represented — of the total number of women who completed the study; this reviewer concluded that any results from this one center would not significantly change the analysis or conclusions of the clinical review of the NDA.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Two pharmacokinetic (PK) studies were submitted with the NDA.

Study PR-01804 was a single-center, multiple-dose, non-blinded, single-treatment, single-period, pharmacokinetic study designed to characterize the plasma EE and NETA pharmacokinetic profiles and sex hormone binding globulin (SHBG) concentrations following multiple-dose administration of Loestrin 24 tablets to healthy female volunteers under fasting conditions for one full cycle. The study enrolled 18 healthy, non-smoking, non-pregnant female volunteers with no concomitant medication use in the previous 14 days. The 18 subjects had a median (range) age of 27 (18–35) years, a median (range) weight of 59.4 (45.3–75.2) kg. Twelve subjects were Caucasian, 5 were Hispanic and one was Asian. There were no unexpected findings compared to the previously determined Loestrin 1/20 PK profile. The Clinical Pharmacology section of the Physician Label accurately reflects the findings of this study.

PR-01904 was a single-center, randomized, balanced, single-dose, 2-treatment, 2-period, 2-sequence crossover food-effect study designed to assess the effect of food on ethinyl estradiol and norethindrone bioavailability following oral administration of a single Loestrin 24 tablet. The study enrolled 18 healthy, non-smoking, non-pregnant female volunteers with no concomitant medication use in the previous 14 days. The study determined that there was no significant effect of food on the bioavailability of EE and NETA. The label for Loestrin 24 Fe tablets states that they may be administered without regard to meals or food.

The two PK studies were reviewed by Myong-Jin Kim, Pharm.D. The recommendation is that the overall Human Pharmacokinetic Section of the NDA submission is *acceptable*. No Phase 4 commitments are recommended.

5.2 Pharmacodynamics

No pharmacodynamic studies were performed.

5.3 Exposure-Response Relationships

Steady state with respect to NETA was reached by Day 17, and steady state with respect to EE was reached by Day 13. For SHBG, steady state was reached after 9 days. Additional PK parameters are

given in detail in the biopharm review by Myong-Jin Kim, Pharm.D., and in the Clinical Pharmacology section of the physician label.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Loestrin® 24 is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive for contraception.

6.1.1 Methods

The incidence of pregnancy was the primary efficacy outcome measure in this NDA. All suspected pregnancies were carefully evaluated and documented as to the estimated date of conception (EDC). The methods used to define the EDC and the actual results of these assessments, information about bleeding and drug intake (reconciled with diary data), information about concomitant medications (reconciled with information in the CRF), and final diagnoses were recorded. Upon confirmation or exclusion of pregnancy, all required information was documented on the Suspected Pregnancy CRF page.

6.1.2 General Discussion of Endpoints

Efficacy was assessed by evaluating the pregnancy rate in terms of the Pearl Index and Life Table methods. Only cycles in which subjects used no alternative methods of contraception were used to calculate the Pearl Index.

The incidence of pregnancy was the primary efficacy outcome measure in the clinical study. Efficacy was analyzed in the Modified Intent-to-Treat (MITT) population of all treated subjects who were evaluated for pregnancy, either positive or negative, at least once after beginning the study medication. All pregnancies that occurred during the study and within 30 days after the end of the treatment phase were assessed to determine whether the pregnancies occurred while subjects were using the study medications. Pregnancies that were found to have an estimated date of conception (EDC) prior to the onset of treatment or more than 14 days after the end of drug intake were not counted as on-treatment pregnancies. All other pregnancies were considered as an occurrence during treatment. The primary efficacy analysis was the pregnancy rate expressed in terms of the Pearl Index, defined as the number of pregnancies per 100 women-years of use.

6.1.3 Study Design

This was an open-label, randomized, active-controlled, multicenter study in sexually active women, age 18 to 45, at risk of becoming pregnant. The treatment phase included six (6) 28-day cycles. Randomization was 4:1 for the study product Loestrin 24 versus the comparator product Loestrin 1/20. The active pills in both regimens were identical and each tablet contained norethindrone acetate 1 mg and ethinyl estradiol 20 mcg. The difference was that during each 28-day treatment cycle, Loestrin 24 had 24 active pills and 4 placebo (ferrous fumarate) pills, while Loestrin 1/20 had 21 active pills and 7 placebo (ferrous fumarate) pills.

The inclusion criteria were the following:

1. Age $\geq$ 18 and $\leq$ 45 years of age.
2. At risk of becoming pregnant (currently involved in an active, heterosexual relationship).
3. Negative serum pregnancy test.

4. Regular cycles with a usual length of 21-35 days with a variability of +/– 3 days (subjects who were recently post-partum or post-abortion must have had at least 2 normal cycles).
5. Body mass index of $\leq$35 kg/m^2.
6. Willing to use the study drug as their only method of contraception (subjects who were on oral, intra-vaginal or transdermal combination hormonal contraceptives were switched directly to study medication).
7. Signed an informed consent.

Exclusion criteria follow:

1. Used hormonal contraception via the following routes and during the specified time frames: (1) progestational implants, progestin, estrogen, or estrogen/progestational injectable drug therapy within 3 months; (2) intrauterine device within 3 months.
2. Abnormal Pap smear suggestive of low grade squamous intraepithelial lesion (LGSIL) or worse (enrollment of subjects with an atypical squamous cells of undetermined significance [ASCUS] interpretation was to be discussed with the Applicant prior to randomization).
3. Currently nursing.
4. Any disease or condition that compromises the function of the body systems, and could result in altered absorption, impaired metabolism, excessive accumulation or altered excretion of the study medication.
5. Known or suspected premalignant or malignant disease (excluding successfully treated skin cancers), or a history of steroid-dependent malignancy, including malignant melanoma.
6. Severe systemic disease that could have interfered with the conduct of the study or the interpretation of the results.
7. Abnormal baseline laboratory values that were considered clinically significant.
8. History of any of the following manifestations of cardiovascular disease: myocardial infarction, coronary artery bypass graft surgery, percutaneous angioplasty, or more than 50% angiographic narrowing of a coronary artery.
9. Congestive heart failure (CHF).
10. Uncontrolled hypertension defined as sitting systolic blood pressure (BP) of $\geq$ 160 mmHg or diastolic BP of $\geq$ 95 mmHg.
11. History of stroke or transient ischemic attacks (TIA).
12. Thrombophlebitis or thromboembolic disorder, or a history of these conditions, or a known or suspected genetic component.
13. Treatment with anticoagulants (heparin or warfarin).
14. Uncontrolled thyroid disorders.
15. History during pregnancy or estrogen use of cholestatic jaundice, severe pruritus, or deterioration of otosclerosis.
16. Insulin-dependent diabetes mellitus.
17. Porphyria.
18. Increased frequency or severity of headaches that include migraines during previous estrogen therapy.

19. History of drug addiction or alcohol abuse (within the last 2 years).
20. Current or significant past history of depression.
21. Participation in another clinical trial within 1 month, or use of an investigational drug within the last 3 months, prior to study entry.
22. Smoking >15 cigarettes/day and >35 years of age.
23 Untreated chlamydia infection.

Reviewer's comment:

The inclusion and exclusion criteria used for the Phase 3 study are standard for a COC trial. The Division has encouraged sponsors to enroll women older than 35 years of age even though fecundity is reduced in this population. The reason is primarily for safety data, because it is common knowledge that COC products are used in this older reproductive-age patient population as well as in younger women.

Study assessments and procedures:

A summary of study assessments and procedures and the time points at which they were to be performed during the study are presented in Table 1.

Table 1. Study Assessments and Procedures

Assessment	Screening	Randomization	Interim Visits		Final Visit*	Follow-up†
Visit	**1**	**1A**	**2**	**3**	**4**	
Day‡	**-14**	**1**	**28 (Cycle 1)**	**84 (Cycle 3)**	**168 (Cycle 6)**	**182-196**
Subject information and informed consent	x					
Demographic data / exclusion and inclusion criteria	x					
Medical and medication history	x					
Gynecological history	x					
Physical examination	x				X	
Gynecological examination	x				X	
Chlamydia test	x					
Pap smear	x				X	
Blood pressure, heart rate, weight	x		x	x	X	
Pregnancy test	x§	x§	x	x	X	x
Serum chemistry, hematology and urinalysis	x				X	
Randomization		x				
Medication and diary cards dispensed		x	x	x		
Diary cards and medication returned			x	x	X	
Adverse events			x	x	X	
Concomitant medication			x	x	X	
Compliance Assessment			x	x	X	
End of study evaluation					X	
Telephone/visit follow-up						x

* If the subject was prematurely withdrawn from the trial, all evaluations described under Final Visit 4 were performed at the time of withdrawal.

† Subjects were contacted/seen within 2-4 weeks of end of treatment to determine if they had a withdrawal bleed, and if ongoing AEs were resolved. If the subject did not have a withdrawal bleed, a pregnancy test was done.

‡ Visits 2 and 3 may be +/- 7 days of Day 28 and Day 84, respectively. Visit 4 was performed only after all active medication had been taken.

§ Serum and urine pregnancy tests were performed at Visit 1; urine pregnancy test was performed at Visit 1A.

Data Source: Page 18 of Applicant's integrated summary of efficacy (ISE).

6.1.4 Efficacy Findings

Enrollment and Disposition:
The disposition of subjects enrolled in this study is shown in Table 2.

Table 2. Subject Disposition

Subject Disposition	Loestrin 24	Loestrin 1/20	Overall
Randomized subjects	751	187	938
Treated subjects	**743 (98.9)**	**186 (99.5)**	**929 (99.0)**
MITT subjects	705 (93.9)	181 (96.8)	886 (94.5)
Subjects evaluable for IB Cycles 2-6	550 (73.2)	136 (72.7)	686 (73.1)
Completed subjects(*)	**580 (77.2)**	**141 (75.4)**	**721 (76.9)**
Discontinued early	**168 (22.4)**	**45 (24.1)**	**213 (22.7)**
Lost to follow-up	63 (8.4)	16 (8.6)	79 (8.4)
Adverse event	46 (6.1)	13 (7.0)	59 (6.3)
Withdrawal of consent	24 (3.2)	8 (4.3)	32 (3.4)
Lack of efficacy	4 (0.5)	2 (1.1)	6 (0.6)
Protocol violation	1 (0.1)	0 (0.0)	1 (0.1)
Other reasons	30 (4.0)	6 (3.2)	36 (3.8)

(*)The Completed Subjects population was defined as the subset of MITT subjects who completed at least 161 days of treatment based on the amount of drug returned or retrieved diaries
Note: percentages are relative to all randomized subjects
Data Source: Report RR-10104.0, Section 14.1, Table 14.1.2.1, Table 14.1.2.2, and Table 14.1.2.3

A total of 1159 potential subjects were screened for the study; of these, 938 women met the entrance criteria for the study, provided informed consent, and were randomized in a 4:1 ratio to one of two treatments. Seven hundred fifty-one (751) subjects were randomized to the Loestrin 24 group, and 187 subjects to the Loestrin 1/20 group. Nine of the randomized subjects later returned all of the dispensed study medication unused, so that 929 subjects were considered to have received treatment: 743 subjects received Loestrin 24 and 186 subjects received Loestrin 1/20.

Twenty-two percent (22.4%) of the Loestrin 24 group (168 subjects) and 24.1% of the Loestrin 1/20 group (45 subjects) failed to complete all aspects of the study protocol. The reasons for early termination of subjects were similar in the two treatment groups. In the Loestrin 24 group, 63 subjects (8.4%) were lost to follow-up, 46 subjects discontinued due to adverse events (6.1%), 24 subjects (3.2%) withdrew consent, 4 subjects (0.5%) discontinued because of lack of efficacy, and the remainder (31 subjects. 4.1%) were withdrawn for protocol violations or other reasons.

Thus, 583 subjects (77.2%) completed the study in the Loestrin 24 group, and 142 subjects (75.4%) completed the study in the Loestrin 1/20 group. The MITT population, evaluable for efficacy, comprised 705 subjects in the Loestrin 24 group, and 181 in the Loestrin 1/20 group. The Completed Subjects population was defined as the subset of the MITT subjects who completed at least 161 days (6 cycles) of treatment. This included 580 subjects (77.2%) in the Loestrin 24 treatment group, and 141 subjects (75.4%) in the Loestrin 1/20 treatment group.

Reviewer's comment:

Because the women were randomized and taking similar COC products, the percentage of women who dropped out, completed, and completed without protocol violations are very similar in the 2 groups. No significant outliers were identified in the enrollment and disposition of subjects.

Summary of Pregnancy Outcomes

There were 8 women who were found to be pregnant during screening and were therefore not randomized. Seventeen women were found to be pregnant after randomization. The case report forms for these 17 pregnancies were carefully reviewed. Table 3 shows this reviewer's evaluation of the 17 pregnancies.

Table 3. Timing of Pregnancy in the Trial (All Treated Subjects)

Pregnancy Timing	Loestrin 24 (N =705)	Loestrin 1/20 (N =181)	Reviewer Comments
During treatment	**5**	**2**	
Before treatment	2	0	These are well documented
>14 days post treatment	1	0	Discussed below
Never took treatment	5	1	These are well documented
Unknown (unconfirmed)	1	0	Discussed below
TOTALS	14	3	

Data Source: Compiled by clinical reviewer from Applicant's ISE (pg. 27-33) and the individual case report forms.

Pregnancy >14 days post treatment:

Subject 012/014 was randomized on 4-19-04 and began taking study drug on 4-29-04. She was next seen on 5-19-04 when a urine pregnancy test was negative and study drug for Cycles 3 and 4 was dispensed per protocol. She failed the next interim Visit 3 because she left the area unexpectedly and was eventually seen on 10-29-04 when a urine pregnancy test was positive. She had a period starting 8-21-04 after completing pill pack # 4 on 8-18-04, and her last menstrual bleeding started on 9-11-04. A sonogram on 10-30-04 showed a 6 week-5 day gestation with an estimated conception date of 9-27-04 which was during her second cycle off the study drug. The pregnancy occurred approximately 40 days after her last study pill was taken.

Reviewer's comment

This subject was given only 4 cycles of study drug and therefore could not have taken the drug longer than 8-18-04. Her diary cards also confirm this finding. A sonogram demonstrated a 6 week-5 day gestation which is an accurate time to estimate a date of conception (EDC). The EDC was determined to be 9-11-04 by the Applicant and 9-27-04 by this reviewer. In any case, the pregnancy occurred > 14 days after stopping study drug and should not be counted as a pregnancy while on treatment.

Pregnancy Unconfirmed:

Subject 022/011, age 24, was randomized to treatment with Loestrin 24 on 3-12-04 and began taking study drug on 3-18-04. She was classified as "lost to follow-up" when she did not return for a final visit on 9-1-04. On 12-28-04 she came to the clinic and returned her diaries which indicated she took study drug until 8-3-04 (Cycle # 5 completed). The diary card for Cycle 6 was not returned and the record does not state her last menstrual period. She thought she became pregnant after stopping study drug, but this was not confirmed by any lab tests or pelvic examination; the patient failed to keep her appointment for an ultrasound (to confirm the pregnancy and EDC) and was subsequently lost to follow-up. The Applicant has not counted this subject as a confirmed pregnancy while on treatment.

Reviewer's comment:

It is clear from the returned diary cards that this subject took the study drug during all of July and started a light withdrawal period on August 02-04 (Day 27). If she had conceived anytime during the month of July, she would have been at least 24 weeks pregnant when she turned in her diary cards on 12-28-04. It is difficult to believe that a pregnancy would not be fairly evident in such a case, although the exact gestational dates would be uncertain. The date of her last menses and whether she took the pills for Cycle 6 are not clear from the CRF. In any case, it appears unlikely to this reviewer that she conceived while on the study drug (Loestrin 24).

Pearl Index calculations (which follow below) have been done with and without this possible pregnancy for the sets of all women and women age 18-35. When this unconfirmed pregnancy is included as an on-treatment pregnancy, a worst case scenario, the Pearl Index is 2.19 which is still in an acceptable range for this reviewer.

Pregnancy before or during treatment:

The CRFs for the Loestrin 24 subjects with 7 pregnancies classified by the Applicant as having conception dates before or during treatment were reviewed carefully by this reviewer. The data show that 2 pregnancies were definitely conceived prior to the start of active treatment and 5 occurred while on active treatment. A summary of the pregnancies that are considered to have occurred while on treatment or within 14 days of treatment for all subjects treated in the clinical trial is seen in Table 4.

Table 4. On-Treatment Pregnancy Data (All Subjects)

ID Number (Site/Subject)	Demographic Data (age, race, parity)	Treatment Group	Conception Cycle #	Sonogram Gestational dates	Reviewer Comment
016/040	28 Cauc G2P2	Loestrin 1/20	# 5	9+ weeks	
017/008	24 Afr Am G2P1	Loestrin 1/20	# 1 (~Day 21)	7 weeks	Weight- 220 #
013/001	37 Hisp G1Ab1	Loestrin 24	# 1 (~Day14)	6 weeks	
015/005	30 Afr Am G1Ab1	Loestrin 24	# 3	6+ weeks	Weight- 191 #
017/031	20 Cauc G0P0	Loestrin 24	# 2	6 weeks- empty sac	
027/006	24 Afr Am G0P0	Loestrin 24	Post # 6	8 weeks	Conception ~6 days after last pill
028/004	35 Hisp G3P3	Loestrin 24	Early # 4	8.5 weeks	Started Cycle 4 ~ 1 week late

Data Source: Clinical Reviewer table compiled from individual CRF data.

Reviewer's comment:

There are no clear patterns here. The estimated dates of conception (EDC) were spread throughout the 6 treatment cycles. The age range was from 20 to 37; the ethnicity included Caucasians, African-Americans and Hispanics. All the confirming sonograms were performed between 6-9 weeks gestation which is an accurate time to determine an EDC. It appears that subject 027/006 probably conceived ~6 days after she took the last pill of Cycle 6, and subject 028/004 probably conceived early in Cycle 4 because she started her pills for Cycle 4 one week later than per protocol. In any case, all of these listed pregnancies are included in the Pearl Index calculations for the two respective treatment arms.

Pearl Index calculations:

Using the MITT population, the Applicant's Table 5 below shows the Pearl Index for all Loestrin 24 subjects and for subjects age 18-35. Only cycles for which no alternative method of contraception was used are included in the Pearl Index calculation; otherwise, the Pearl Index would be slightly lower because additional cycles would be included in the denominator.

Table 5. Pregnancy Outcomes and Pearl Index: Loestrin 24 and Loestrin 1/20 MITT Populations

	Loestrin 24 All Ages N = 705	Loestrin 24 Age 18-35 N = 579	Loestrin 1/20 All Ages N = 181	Loestrin 1/20 Age 18-35 N = 151
Number of pregnancies	5	4	2	2
Number of women-cycles of treatment*	3565	2909	873	709
Pearl Index	**1.823**	**1.788**	**2.978**	**3.667**
95% Confidence Interval**	0.592 - 4.251	0.487 – 4.572	0.36 - 10.73	0.44 - 13.20

* Only cycles for which no alternative method of contraception was used are included
** Confidence intervals are calculated using exact confidence intervals for binomial estimation of p, where p= (Number of pregnancies/Number of cycles)
Data Source: Report RR-10104.0, Section 14.2, Table 14.2.1

Reviewer's comment:

It is generally believed that the longer a contraceptive method is used, the lower the Pearl Index will become because the more fertile women and women with poorer compliance will have either become pregnant or have dropped out. The clinical trial was only 6 months in duration as agreed to between the Applicant and the Division. Had the trial been longer, the Pearl Index values would probably have been slightly lower. This reviewer agrees with the Applicant's above number of pregnancies and the calculations for the Pearl Indices.

If the one unconfirmed pregnancy in a 24 year old woman is included, however, making a total of 6 pregnancies in the MITT population who used Loestrin 24, then the Pearl Index becomes 2.19, which is still acceptable. If the unconfirmed pregnancy is included in the MITT population, age 18-35 inclusive, who used Loestrin 24, the Pearl Index is 2.23. For the 125 Loestrin 24 subjects older than 35, the Pearl Index is 1.99 with 1 pregnancy in 655 evaluable cycles of use.

The Pearl Index for the comparator Loestrin 1/20 product was 2.98, although this finding is not as reliable because there were only 873 evaluable cycles of use in 181 women.

The Applicant calculated the 6-cycle cumulative pregnancy rate for Loestrin 24 using the Life Table method for all subjects and subjects age 18-35. The calculation was done using (1) the 5 pregnancies occurring while on-treatment and (2) adding in the one unconfirmed pregnancy in the 24 year old subject. The following Applicant Table 6 shows the results.

Table 6 6-Cycle Cumulative Pregnancy Rates for Loestrin 24

	Subject Population		
	All subjects- 5 pregnancies	All subjects- 6 pregnancies*	Subjects- age 18-35 5 pregnancies*
Number of subjects (N)	703	703	577
6-month Pregnancy Rate	0.90%	1.06%	1.13%

* Includes one unconfirmed pregnancy
Data Source: Applicant's ISE and Amendments # 13 and # 17 to the NDA.

Reviewer's comment:

Using the above Life Table analysis by the Applicant and counting only 5 pregnancies, the cumulative pregnancy rate was 0.90% in the 703 evaluable women on Loestrin 24 after the end of the 6-month treatment period. When the 1 unconfirmed pregnancy is added to the analysis, the cumulative pregnancy rate becomes 1.06% at the end of the 6-month treatment period. When only subjects age 18-35 are considered and the one unconfirmed pregnancy is also included (a worst case scenario), the pregnancy rate becomes 1.13%. The three different cumulative pregnancy rates are acceptable, especially when considering that only 4 of the 6 pregnancies occurred during per protocol use of Loestrin 24 and 1 potential pregnancy was unconfirmed.

6.1.5 Clinical Microbiology

No clinical microbiology was required for this NDA submission.

6.1.6 Primary Efficacy Conclusions

The primary objective of this study was to assess the efficacy of Loestrin 24 in preventing pregnancy. In this study, among 705 women with 3,565 evaluable cycles of treatment, there were 5 pregnancies that definitely occurred while on treatment with Loestrin 24 or within 14 days of stopping treatment. Depending on the subject population, the cumulative risk of becoming pregnant while taking Loestrin 24 was estimated between 0.9% and 1.13% in the first 6 cycles of use.

The Pearl Index for Loestrin 24, defined as the number of pregnancies per 100 women-years of use was estimated at 1.82 for women of all ages considering only cycles for which no backup contraception was used. If the one unconfirmed pregnancy is also counted as an on-treatment pregnancy, then the Pearl Index becomes 2.19, which is still an acceptable index.

In the 579 women who were 18 to 35 years of age, there were 4 confirmed pregnancies in 2,909 evaluable cycles of treatment. The Pearl Index was estimated at 1.79 per 100 women-years of use for this subset of women. If the one unconfirmed pregnancy in a 24 year old woman is counted as an on-treatment pregnancy, then the Pearl Index is increased from 1.79 to 2.23, which is still an acceptable index. These results are comparable to the pregnancy rates reported with COCs in many previous clinical studies submitted to the FDA for presently approved COCs. In the comparative Loestrin 1/20 group, 2 women became pregnant in 873 cycles of treatment. The Pearl Index was 2.98, although this finding is not as meaningful because of the small number of evaluable treatment cycles and the wide confidence interval around the point estimate.

6.2 Secondary Efficacy Endpoint

A secondary objective of the Phase 3 study was to compare the incidence of intracyclic bleeding (IB) between Loestrin 24 and Loestrin 1/20. It was anticipated by the Applicant that the overall bleeding profile (several parameters of bleeding/spotting) for Loestrin 24 would generally be better than that of Loestrin 1/20.

6.2.1 Methods

The secondary efficacy variables were the descriptive parameters of bleeding/spotting. Data for the bleeding parameters were derived from subject diaries, and bleeding/spotting analyses were performed by pre-defined criteria calculated for each subject. All parameters of bleeding were summarized using descriptive statistics by reference period and cycle, treatment group, age cohort, user status (switcher vs. new start), and overall. Statistical comparisons were performed between the Loestrin 24 treatment group (by age cohort, by user status, and combined), and the Loestrin 1/20 treatment group with regard to incidence of withdrawal bleeding, incidence of intracyclic bleeding (IB), number of IB episodes, number

of IB days, and number of bleeding/spotting episodes. In all cases the statistical comparisons were made using Cochran-Mantel-Haenszel (CMH) statistics (row mean scores), stratified by investigational site.

Each subject recorded the presence and intensity of bleeding daily in a diary using the terms none, light, normal, and heavy, defined by protocol as seen in Table 7.

Table 7. Definitions of Bleeding Intensity

Bleeding intensity	Definition
None	No vaginal bleeding
Light	Less than associated with normal menstruation relative to the subject's experience
Normal	Like normal menstruation relative to the subject's experience
Heavy	More than normal menstruation relative to the subject's experience

Data Source: Applicant's ISE, page 19.

Each subject also recorded daily whether any bleeding required the use of sanitary protection other than panty liners. Bleeding that was described as light, and requiring no more than the use of a single pad or tampon for sanitary protection was classified as spotting. All other bleeding of any intensity was classified as bleeding as shown in Table 8.

Table 8. Further Bleeding/Spotting Definitions

		BLEEDING INTENSITY		
		Light	**Normal**	**Heavy**
Use of sanitary protection	**None***	Spotting	Bleeding	Bleeding
	1 pad or tampon	Bleeding†	Bleeding	Bleeding
	More than 1	Bleeding	Bleeding	Bleeding

* Including panty liners
† The protocol specified light bleeding with use of only 1 pad or tampon to be treated as spotting. This definition was revised in the analysis after discussion with the FDA.
Data Source: Applicant's ISE, page 20.

Reviewer's comment:

The definition of spotting here is rather strict: spotting was defined as light bleeding requiring no sanitary protection. All other possibilities were defined as "bleeding." This definition is fine as it does not allow for underreporting of bleeding (conditions where bleeding might be reported as spotting or go unreported).

Terms that were used to define further the descriptive parameters of bleeding/spotting are described in Table 9.

Table 9. Descriptive Parameters of Bleeding/Spotting

Term	Definition
Bleeding (spotting) day	A diary day in which the subject reported bleeding (spotting).
Bleeding (spotting) episode	A set of consecutive bleeding (spotting) days preceded and followed by at least 2 bleed/spot-free diary days. One or more single isolated bleed/spot-free days could be included in a single episode. An episode was considered a bleeding episode if it included at least one bleeding day.
Withdrawal bleeding episode	The first bleeding episode (1) starting after the last day of active drug intake during a treatment cycle and up to the 2nd day of the next treatment cycle, or (2) starting within 4 days prior to the last day of active drug intake during the treatment cycle and continuing at least through the first day after the end of active drug intake in the treatment cycle.
Intracyclic bleeding (spotting) (IB) day	Any bleeding (spotting) day not included in a withdrawal bleeding episode.
Intracyclic bleeding (spotting) (IB) episode	A bleeding episode composed of intracyclic bleeding (spotting) days.

Data Source: Applicant's ISE, page 22.

The duration of a bleeding (spotting) episode was defined as the number of days from the first to the last day of the episode, inclusive, including single isolated bleed-free (spot-free) days. The intensity of the bleeding (spotting) episode was defined as the maximum intensity (see Table 8) of the component bleeding (spotting) days, with 1=light, 2=normal, and 3=heavy.

The 6-cycle study period was divided for the purpose of analysis into two 84-day reference periods each of 3 treatment cycles. The first reference period started on the first day of study medication, which was Day 1 of the first treatment cycle. The onset day of an intracyclic bleeding episode was counted from Day 1 of the treatment cycle. The onset day of a withdrawal bleeding episode was counted from the last day of the treatment cycle (Day 0 of withdrawal).

The following parameters of bleeding were calculated for each subject, by cycle, by reference period, and overall:

- Incidence of withdrawal bleeding (yes/no); incidence of amenorrhea
- Average duration of withdrawal bleeding
- Maximum intensity of withdrawal bleeding
- Average intensity of withdrawal bleeding (0=none, 1=light, 2=normal, 3=heavy)
- Average composite score for overall intensity (duration times average intensity)
- Median onset day of withdrawal bleeding
- Incidence of IB (yes/no)
- Number of IB episodes
- Number of bleeding episodes

- Number of spotting-only episodes
- Maximum duration of IB episodes
- Maximum duration of bleeding episodes
- Maximum duration of spotting-only episodes
- Maximum intensity of IB episodes
- Number of IB days
- Number of bleeding days, spotting-only days and all bleeding/spotting days

6.2.2 General Discussion of Endpoints

The evaluation for the bleeding parameters with the use of Loestrin 24 was very complete as can be seen in the list of 16 parameters noted above. The issue of bleeding assessment was discussed with the Applicant on September 17, 2003. As a result of this discussion and meeting minutes dated October 29, 2003 and clarified on December 11, 2003 and March 5, 2004, protocol changes were made to allow the prospective statement of a primary bleeding assessment target (total days of intermenstrual bleeding in Cycles 2-6) as a secondary endpoint. However, in the label for this product no specific claim is being made for an improved bleeding profile while taking Loestrin 24.

6.2.3 Study Design

The overall clinical study design is discussed in section 6.1.3 and the methods for evaluating the bleeding parameters are discussed in section 6.2.1. The frequency of clinic visits and the use of a daily diary provided adequate collection of data to assess the various secondary endpoints for the product's bleeding profile.

6.2.4 Secondary Efficacy Findings

A summary of exposure to study medication for the All Randomized population is presented in Table 10, showing the number and percent of subjects who completed 1 cycle of treatment, 2 cycles, 3 cycles, etc. Within each cycle, more than 95% of subjects who began the cycle completed all doses for that cycle. Five hundred eighty-four (584) subjects (77.8%) completed all 6 treatment cycles in the Loestrin 24 treatment group; 142 subjects (75.9%) in the Loestrin 1/20 group completed all 6 cycles. The mean number of completed cycles was 5.36 for Loestrin 24 and 5.25 for Loestrin 1/20. This allowed for over 4,400 cycles in the combined two groups that were evaluated for bleeding/spotting parameters.

Table 10. Summary of Exposure to Study Medication (All Randomized Subjects)

Number of Treatment Cycles Completed (>14 days of active treatment)	Loestrin 24 N=751	Loestrin 1/20 N=187
0	8 (1.1%)	1 (0.5%)
1	40 (5.3%)	12 (6.4%)
2	16 (2.1%)	6 (3.2%)
3	30 (4.0%)	13 (7.0%)
4	21 (2.8%)	1 (0.5%)
5	6 (0.8%)	4 (2.1%)
6	584 (77.8%)	142 (75.9%)
Unknown	46 (6.1%)	8 (4.3%)
N	705	179
Mean (SD)	5.36 (1.52)	5.25 (1.60)

Data Source: Report RR-10104.0, Section 14.3, Table 14.1.6.1

Reviewer's comment:

To be evaluable for bleeding parameters a subject needed to complete an entire 28 days of product use, complete the diary for that cycle of use, and turn in the diary at the next clinic visit. For the Loestrin 24 group there were over 3,500 cycles of exposure and for the comparator Loestrin 1/20 group over 900 cycles that were evaluable for bleeding. This exposure allowed for an acceptable evaluation of the bleeding parameters, especially for Loestrin 24.

6.2.4.1 The Incidence of Intracyclic Bleeding (IB)

The incidence of intracyclic bleeding for the MITT population, including only subjects who were evaluable for IB in the given cycle, is summarized in Table 11.

Table 11. Incidence of Intracyclic Bleeding (MITT Subjects Evaluable for IB)

Cycle(s)	Loestrin 24 N=705	Loestrin 1/20 N=181	P-value
***Cycles 2 through 6**	317/550 (57.6)	82/136 (60.3)	0.546
Cycle 1	262/693 (37.8)	62/176 (35.2)	0.574
*Cycle 2	224/637 (35.2)	51/160 (31.9)	0.452
*Cycle 3	190/622 (30.5)	40/153 (26.1)	0.298
*Cycle 4	147/598 (24.6)	39/145 (26.9)	0.700
*Cycle 5	148/578 (25.6)	40/143 (28.0)	0.681
*Cycle 6	139/572 (24.3)	35/139 (25.2)	0.875

Numbers shown are number of subjects with IB / number of subjects evaluable for IB, and percent of subjects with IB. *P* values use CMH statistics adjusting for investigational site.
***Cycles of primary interest (because Cycle 1 is considered as an adjustment cycle).**
Data Source: Report RR-10104.0, Section 14.3, Table 14.2.2.1.1

Reviewer's comment:

In the Loestrin 24 treatment group, 35% of subjects experienced at least one episode of intracyclic bleeding in the second cycle of treatment. The rate declined gradually with each successive treatment cycle until at Cycle 6, the rate was 24%. The rates in the Loestrin 1/20 treatment group

were very similar; there were no statistically significant differences observed between treatments in the rate of incidence of intracyclic bleeding and no special claims may be made by the Applicant.

The overall incidence of IB was lower among switchers than among new users, and lower among older women than among younger women. For example, in the Loestrin 24 group, the incidence of IB in Cycle 2 was 45% among new users compared to 30% among switchers; it was 36% among women 18 to 35 years old compared to 30% among women 36 to 45 years old. In Cycle 6, the incidence of IB was 29% among new users compared to 22% among switchers, and 26% among the younger women compared to 15% among the older women. These differences are generally expected and were not statistically significant.

6.4.2.2 Number of Intracyclic Bleeding and Spotting Days

The analysis of the number of intracyclic bleeding/spotting days (spotting only and bleeding only) experienced by subjects by cycle and overall for the MITT population is shown in Table 12.

Table 12. Number of Intracyclic Bleeding/Spotting Days (Mean ± SD) (MITT Population)

Cycle	Loestrin 24 N=705	Loestrin 1/20 N=181	*P* value
***Cycle 2 through Cycle 6**	6.31 ± 9.16	7.31 ± 10.51	0.311
Cycle 1	2.12 ± 3.79	1.71 ± 3.20	0.227
Cycle 2	1.81 ± 3.26	2.25 ± 4.32	0.156
Cycle 3	1.44 ± 2.84	1.05 ± 2.15	0.107
Cycle 4	1.18 ± 2.60	1.25 ± 2.62	0.924
Cycle 5	1.09 ± 2.39	1.30 ± 2.63	0.415
Cycle 6	0.95 ± 2.04	1.63 ± 3.54	0.005

P values use CMH statistics adjusting for investigational site.
***Cycles of primary interest (because Cycle 1 is considered as an adjustment cycle).**
Data Source: Report RR-10104.0, Section 14.3, Table 14.2.2.2.1

In the MITT population, the mean number of IB/spotting days experienced by subjects in the Loestrin 24 treatment group from Cycles 2 through 6 was 6.31 compared to 7.31 in the Loestrin 1/20 group. The treatment difference was not statistically significant ($P = 0.311$). The mean number of IB/spotting days by cycle in the Loestrin 24 group declined from 2.12 in Cycle 1 to 0.95 in Cycle 6. In the Loestrin 1/20 group, the mean was 1.71 in Cycle 1 and 1.63 in Cycle 6.

Reviewer's comment:

This reviewer agrees with the overall finding that there was no increase and a suggestion of less intracyclic bleeding and spotting days with Loestrin 24 compared to Loestrin 1/20. In additional subset analyses of the MITT population, the mean number of IB/spotting days was lower among switchers than among new users, and lower among older women than among younger women within a treatment group. For example, the mean number of IB/spotting episodes experienced by subjects from Cycle 2 through Cycle 6 was 1.48 in the Loestrin 24 group and 1.41 in the Loestrin 1/20 group. The average maximum duration of IB/spotting episodes experienced by subjects in the Loestrin 24 treatment group from Cycles 2 through 6 was 3.15 days compared to 3.91 days in the Loestrin 1/20 group.

These treatment differences were not statistically significant and this reviewer's opinion is that they are also not clinically significant. Although it does appear that the Loestrin 24 overall bleeding profile is no worse than the Loestrin 1/20 profile, no labeling claims should be allowed based on any of the bleeding profile parameters.

6.4.2.3 Withdrawal Bleeding

In the Phase 3 study, the first bleeding episode starting after the last day of active drug intake during a treatment cycle and up to the second day of the next treatment cycle, or starting within 4 days prior to the last day of active drug intake during the treatment cycle and continuing at least through the first day after the end of active drug intake in the treatment cycle was defined as a withdrawal bleeding. All other bleeding events were counted as intracyclic bleeding. The incidence of withdrawal bleeding by cycle is summarized in Table 13.

Table 13. Incidence of Withdrawal Bleeding (MITT Population)

Cycle	Loestrin 24 N=705	Loestrin 1/20 N=181	*P*-value
Cycle 1	473/693 (68.3)	129/176 (73.3)	0.183
Cycle 2	441/637 (69.2)	117/160 (73.1)	0.321
Cycle 3	414/622 (66.6)	114/153 (74.5)	0.054
Cycle 4	403/598 (67.4)	98/145 (67.6)	0.890
Cycle 5	380/578 (65.7)	106/143 (74.1)	0.056
Cycle 6	335/572 (58.6)	103/139 (74.1)	0.001

P values use CMH statistics adjusting for investigational site.
Data Source: Report RR-10104.0, Section 14.3, Table 14.2.2.6.1

In the Loestrin 24 treatment group, the percentage of subjects who experienced withdrawal bleeding in each treatment cycle ranged from 58.6% (Cycle 6) to 69.2% (Cycle 2). A higher percentage of subjects experienced withdrawal bleeding in each cycle in the Loestrin 1/20 group, ranging from 67.6% (Cycle 4) to 74.5% (Cycle 3). The difference between treatment groups in the percentage of subjects who experienced withdrawal bleeding was statistically significant only in Cycle 6 (P = 0.001).

Reviewer's comment:

The incidence of withdrawal bleeding with Loestrin 24 ranged from 59-69% which means that from 31 to 41% of the women did not have an expected withdrawal bleeding in one of Cycles 2-6. Although it is generally desirable to have less menstrual bleeding and less intracyclic bleeding/spotting, the absence of bleeding can be worrisome because it is a potential signal for an unplanned pregnancy which must eventually be ruled in or out.

6.4.2.4 Other Bleeding Parameters

The Loestrin 24 group had shorter duration of withdrawal bleeding than the Loestrin 1/20 group (2.42 days vs. 3.06 days averaged over Cycles 2 through 6 in the MITT population, P < 0.001), and a lower composite score for overall intensity of withdrawal bleeding (2.76 vs. 3.68 averaged over Cycles 2 through 6 in the MITT population. The day of onset of withdrawal bleeding appeared to be somewhat later in the Loestrin 24 group compared to the Loestrin 1/20 group; this would be expected, however, given the 3 additional days of active hormonal tablets in the Loestrin 24 subjects.

6.2.6 Secondary Efficacy Conclusions

In summary, compared to Loestrin 1/20, the use of Loestrin 24 yielded numerically fewer total bleeding days overall [4.20 days over 5 cycles], fewer days of withdrawal bleeding [0.64 days per cycle], a higher incidence of amenorrhea [on average, 34.5% vs. 27.5% = approximately 7% more per cycle], and less intense withdrawal bleeds. The mean number of intracyclic bleeding/spotting days in Cycles 2 through 6 (spanning 140 days) was 6.31 for Loestrin 24 compared to 7.31 for Loestrin 1/20 (*P* = 0.311). However,

all of these different parameters, including one less day of intracyclic bleeding/spotting over 140 days, are of doubtful clinical significance. Use of Loestrin 24 for more than 6 cycles was not studied, so no conclusions can be made concerning use longer than 6 cycles. **It is this reviewer's opinion that no labeling claims for a better or superior overall bleeding profile or for any individual bleeding parameter may be made in association with use of the Loestrin 24 product. The bleeding pattern certainly does not appear to be any worse than that of the approved Loestrin 1/20 and the overall bleeding profile for Loestrin 24 is acceptable and safe.**

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated summary of safety (ISS) for this product included data from two completed Phase 1 studies (Studies PR-01804 for PK data and PR-01904 for food effect data) and 1 completed Phase 3 study (PR-03903) with Loestrin 24. The primary data for safety analysis was derived from all treated subjects in the 6-month Phase 3 study. The ISS included safety data from the approximately 929 subjects (743 on Loestrin 24) from Phase 3, representing approximately 5000 women months of total exposure (over 4000 on Loestrin 24). These data include adverse events, physical and gynecologic examination findings, vital signs and laboratory results, which were recorded on CRFs during the course of the trials. The safety data from the two Phase 1 studies was also included, but this involved only 18 women for one cycle of treatment.

7.1.1 Deaths

There were no deaths in any of the 3 studies.

7.1.2 Other Serious Adverse Events

There were 3 SAEs in three separate Loestrin 24 subjects in the Phase 3 study. One woman had a partial thyroidectomy, one had a thyroid cancer, and one had a back injury. None were considered to be related to study drug and none of the SAEs led to discontinuation from the study. Thus, the SAEs in the study did not raise a safety concern. There were no SAEs in the smaller Loestrin 1/20 group.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The number of subjects treated in each group and the reasons for discontinuing the study are given in Table 14. Over 75% of subjects in the Loestrin 24 group and the Loestrin 1/20 group completed all aspects of the study protocol. The reasons for early termination of subjects (dropouts) were similar in the two treatment groups. Seventy-nine subjects (8.4%) were lost to follow-up, 59 subjects (6.3%) discontinued due to adverse events, 32 subjects (3.4%) withdrew consent, 6 subjects (0.6%) discontinued because of lack of efficacy, and the remaining subjects were withdrawn for protocol violations or other reasons.

Table 14. Reasons for Early Discontinuation [Number (%)]

Subject Disposition	Loestrin 24	Loestrin 1/20	Overall
Randomized subjects	**751**	**187**	**938**
Completed subjects(*)	580 (77.2)	141 (75.4)	721 (76.9)
Discontinued early	**168 (22.4)**	**45 (24.1)**	**213 (22.7)**
Lost to follow-up	63 (8.4)	16 (8.6)	79 (8.4)
Adverse event	46 (6.1)	13 (7.0)	59 (6.3)
Withdrawal of consent	24 (3.2)	8 (4.3)	32 (3.4)
Lack of efficacy	4 (0.5)	2 (1.1)	6 (0.6)
Protocol violation	1 (0.1)	0 (0.0)	1 (0.1)
Other reasons	30 (4.0)	6 (3.2)	36 (3.8)

* The Completed Subjects population was defined as the subset of MITT subjects who completed at least 161 days of treatment based on the amount of drug returned or retrieved diaries.
Note: percentages are relative to all randomized subjects,

Data Source: Report RR-10104.0, Section 14, Table 14.1.2.1, Table 14.1.2.2, and Table 14.1.2.3

Reviewer's comment:

The reasons for discontinuing early and the percentages above are expected and acceptable. Overall, in the Loestrin 24 group only 6.1% (46 subjects) withdrew because of an adverse event, and in this group there were no SAEs.

7.1.3.2 Adverse events associated with dropouts

A total of 46 subjects (6.1%) in the Loestrin 24 group and 13 subjects (7.0%) in the Loestrin 1/20 group discontinued due to an AE. Most of the AEs were classified as being possibly or probably related to drug. All but 3 were mild or moderate in intensity. None were serious. The most common AEs that led to discontinuation in 32 of the 46 Loestrin 24 subjects were:

- Abnormal bleeding- 10 subjects (10/46 = 22%) [includes metrorrhagia, spotting, irregular bleeding]
- Nausea- 6 subjects (13%)
- Mood changes-6 subjects (13%) [includes mood change, depression, irritability, and nervousness]
- Dysmenorrhea- 4 subjects (9%)
- Edema/weight gain- 3 subjects (6.5%)
- Increased blood pressure- 3 subjects (6.5%)

The 14 other AEs that led to discontinuation in either 1 or 2 Loestrin 24 subjects were fatigue, contact lens problems, premenstrual syndrome, amenorrhea, breast discharge, rash, syncope, acne, abdominal pain, irritable bowel symptoms, yeast infection, and headache.

7.1.3.3 Other significant adverse events

There were none.

7.1.4 Other Search Strategies

None were indicated.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

A standard case report form was used at each clinic visit. Adverse events were solicited as each visit and were then recorded on the form. Thus, accurate information was recorded for adverse events throughout the clinical trial.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

AEs were coded according to the MedDRA dictionary by body system organ class and preferred term. If an AE was reported more than once for the same subject, the subject was only counted once for the respective AE and assigned the most severe intensity.

7.1.5.3 Incidence of common adverse events

The number (%) of subjects with AEs occurring in at least 1% of subjects overall by body system, preferred term, treatment group, and overall is presented in Table 15. In the Loestrin 24 groups, the five most commonly reported adverse events were headache (6.3%), vaginal candidiasis (6.1%), upper respiratory tract infection (5.1%), nausea (4.6%), and dysmenorrhea (4.4%). The percentages of subjects reporting these events in the Loestrin 1/20 group were similar.

7.1.5.4 Common adverse event table

Table 15. Common Adverse Events [number (%)] by Treatment and Overall

Body System and Preferred Term	Loestrin 24 N= 743 (%)	Loestrin 1/20 N= 186 (%)	Overall N= 929 (%)
Nervous System Disorders			
Headache	47 (6.3)	13 (7.0)	60 (6.5)
Infections and Infestations			
Vaginal candidiasis	45 (6.1)	10 (5.4)	55 (5.9)
Upper respiratory tract infection NOS	38 (5.1)	9 (4.8)	47 (5.1)
Sinusitis NOS	23 (3.1)	4 (2.2)	27 (2.9)
Vaginitis bacterial NOS	23 (3.1)	3 (1.6)	26 (2.8)
Urinary tract infection NOS	18 (2.4)	5 (2.7)	23 (2.5)
Pharyngitis streptococcal	11 (1.5)	2 (1.1)	13 (1.4)
Gastroenteritis viral NOS	8 (1.1)	4 (2.2)	12 (1.3)
Gastrointestinal Disorders			
Nausea	34 (4.6)	6 (3.2)	40 (4.3)
Vomiting NOS	14 (1.9)	1 (0.5)	15 (1.6)
Diarrhea NOS	9 (1.2)	1 (0.5)	10 (1.1)
Dyspepsia	8 (1.1)	2 (1.1)	10 (1.1)
Reproductive System and Breast Disorders			
Dysmenorrhea	33 (4.4)	5 (2.7)	38 (4.1)
Breast tenderness	25 (3.4)	2 (1.1)	27 (2.9)
Metrorrhagia	14 (1.9)	2 (1.1)	16 (1.7)
Pelvic pain	10 (1.3)	2 (1.1)	12 (1.3)
Investigational Findings			
Smear cervix abnormal	23 (3.1)	6 (3.2)	29 (3.1)
Weight increased	15 (2.0)	3 (1.6)	18 (1.9)
Skin and Subcutaneous Tissue Disorders			
Acne NOS	20 (2.7)	5 (2.7)	25 (2.7)
Psychiatric Disorders			
Mood swings	16 (2.2)	5 (2.7)	21 (2.3)
Depression	8 (1.1)	4 (2.2)	12 (1.3)
Musculoskeletal and Connective Tissue			
Back pain	7 (0.9)	3 (1.6)	10 (1.1)
General Disorders			
Fatigue	8 (1.1)	2 (1.1)	10 (1.1)

NOS = Not otherwise specified
Data Source: Report RR-10104.0, Section 14, Tables 14.3.1 and 14.3.2

7.1.6 Less Common Adverse Events

There were no less common AEs (AEs occurring in < 1% of subjects) that were of note or significance among all the reported AEs. For example, there were no DVTs, pulmonary emboli, myocardial infarcts or CVAs.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Hematology and biochemistry samples were collected for all subjects during screening, at the end of the study, and sometimes during treatment. The following parameters were assessed:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count, differential WBC count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC)

- Biochemistry: aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, gamma-glutamyl transferase (GGT), total bilirubin, creatinine, blood urea nitrogen (BUN), calcium, albumin, glucose, inorganic phosphorus, potassium, sodium, total protein, cholesterol, triglycerides, uric acid.

7.1.7.3 Standard analyses and explorations of laboratory data

In the Applicant's ISS, two Loestrin 24 and one Loestrin 1/20 subjects had normal baseline hematology values that according to the site investigator became abnormal between the beginning and end of the study. The abnormalities included the following:

1. Subject 011/006 on Loestrin 24: WBC 13.7 and neutrophil count 10.6
2. Subject 018/005 on Loestrin 24: Platelet count 618,000
3. Subject 006/045 on Loestrin 1/20: Hemoglobin 11.3

Reviewer's comment:

Although the investigator considered these values to be abnormal, the above values are not markedly abnormal and do not raise a safety concern.

In the Applicant's ISS, six Loestrin 24 subjects had chemistry lab values that were deemed by the investigator to be clinically significant. The abnormalities included the following:

1. Subject 011/021 on Day 185: Glucose 49
2. Subject 003/017 on Day 209: Glucose 212
3. Subject 013/028 on Day 197: Cholesterol (total) 242 [normal 128-218]
4. *Subject 001/020 on Day 194: Triglycerides 707 [normal reference range 39-176]
5. **Subject 003/004 on Day 201: Triglycerides 511
6. ***Subject 023/005 on Day 181: Triglycerides 291

*Subject 001/020 had an initial triglyceride level of 191 mg/dL which was elevated to 707 on Day 194. A repeat triglyceride level 16 days later was 178 (lower than her baseline level). This repeat value suggests that the value of 707 reflected a laboratory error or a non-fasting assessment. The subject also had an elevated cholesterol of 297 mg/dL at baseline and 249 at end of study. There were no other chemistry abnormalities.

**Subject 003/004 had an initial triglyceride level of 251 mg/dL which was elevated to 511 on Day 201. A repeat triglyceride level 39 days later was 323, still somewhat higher than her initial level of 251 mg/dL. This subject also had an elevated cholesterol of 252 mg/dL at baseline and 266 at end of study. Other chemistry parameters were normal.

***Subject 023/005 had an initial triglyceride level of 208 mg/dL which was elevated to 291 on Day 212. She was referred to her private physicians for follow-up and no additional information was collected. Her other chemistry values were normal at baseline and end of study.

Reviewer's comment:
The glucose and cholesterol values in the first three subjects above are not unusually abnormal.

An exclusion criterion for trial participation was abnormal baseline laboratory values that were considered clinically significant. This determination was decided by the individual investigators as evidenced by the fact that the three subjects in the Loestrin 24 group who had triglyceride levels that were definitely elevated at the end of the 6-cycle study also had elevated triglyceride values at baseline. Follow-up values (16 and 39 days later) were obtained in 2 of the women and were found to be considerably lower than the values at end of study. The same two subjects also had elevated cholesterol values both at baseline and at end of study (range of 249-297).

One subject in the Loestrin 1/20 group had a slightly elevated triglyceride of 169 [normal reference range 36-144] on Study Day 2; otherwise there were no abnormal triglyceride values in this group.

7.1.7.4 Additional analyses and explorations

None were performed or indicated.

7.1.7.5 Special assessments

None were performed or indicated.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure, pulse and weight were measured at screening and after Cycles 1, 3, and 6. Changes from baseline in mean systolic and diastolic blood pressure and heart rate were small. No clinically significant changes were noted. Mean changes in weight for the Loestrin 24 and Loestrin 1/20 groups were 0.8 and 0.6 pounds, respectively.

Reviewer's comment:
Three subjects (0.40%) in the Loestrin 24 group were discontinued from the trial because of elevated blood pressure. The severity of the adverse event was classified as mild to moderate in these 3 cases and all 3 recovered from the adverse event. In the Loestrin 1/20 group one subject (0.55%) was discontinued because of elevated blood pressure of moderate severity and she recovered.

7.1.9 Electrocardiograms (ECGs)

No ECGs were performed at screening or during the Phase 3 clinical trial. This is acceptable because Loestrin 1/20 and Loestrin 1.5/30 have been marketed in the U.S. since 1973 and there have been no signals for issues relating to cardiac or ECG safety.

7.1.12 Special Safety Studies

None were indicated or performed for this NDA.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There are no known withdrawal or abuse potentials, based on many years of clinical usage, associated with of COCs containing NETA and EE.

7.1.14 Human Reproduction and Pregnancy Data

No additional data was required for this NDA. No fetal or maternal toxicity issues have been identified with either Loestrin 1/20 or Loestrin 1.5/30 since their original approvals in 1973. It is therefore reasonable to conclude that the new Loestrin 24 product will be safe from a human reproductive (fetal toxicity) perspective.

7.1.15 Assessment of Effect on Growth

No assessment has been made. It is generally believed that COCs are safe in young women (adolescents) of reproductive age provided that menarche has occurred.

7.1.16 Overdose Experience

There are no data on overdose for this product. Past experience with other COCs, especially low dose products like Loestrin 1/20, has not shown a problem or safety concern.

7.1.17 Postmarketing Experience

There is no postmarketing experience because the Loestrin 24 product is not approved in any other country. There is extensive postmarketing experience, however, with the 21-day comparator Loestrin 1/20 and with the higher dose Loestrin 1.5/30, as both these products were approved by the FDA in 1973.

Reviewer's comment:

The FDA adverse event reporting system (AERS) was reviewed for reports of death and serious thrombotic adverse events in association with the use of either Loestrin 1/20 or Loestrin 1.5/30. Twenty-four "fatalities" have been reported since May 1980. There were no duplicates reports and 11 cases [2 melanoma cases and 9 unintended pregnancies ("fetal deaths")] were removed from the list, leaving 13 deaths in women of reproductive age over the past 25 years. The primary cause of death in these 13 cases was listed as the following: pulmonary embolism (7), cerebral vascular accident (2), acute myocardial infarct (2), arterial thrombosis (1), and cardiac surgery (1). The product reported for these 13 cases was: Loestrin 1/20 (6), Loestrin 1.5/30 (2), and exact dose not specified (5).

This number of fatalities spanning 25 years of Loestrin use is well within the expected range of deaths associated with the use of a combination hormonal contraceptive. The review of the FDA AERS database does not raise any safety concerns in terms of fatal SAEs associated with the use of both Loestrin products (1/20 and 1.5/30) from 1980 through January 31, 2006.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The two pharmacology studies involved only 18 women exposed to a maximum of 24 active pills. In the Phase 3 6-month clinical trial, 743 women were treated and used Loestrin 24 for a minimum of 15 days up to a maximum of 6 cycles (168 days). No fetal or maternal toxicity issues have been identified with either Loestrin 1/20 or Loestrin 1.5/30 since their original approvals in 1973. It is therefore reasonable to conclude that the new Loestrin 24 product will be safe from a human reproductive (fetal toxicity) perspective.

In the Loestrin 24 group over 75% of the 743 subjects completed all 6 cycles of treatment and there were a total of 3,565 cycles evaluable for contraceptive efficacy. In the women ages 18-35 using Loestrin 24 there were 2,909 evaluable cycles. For the smaller, comparative Loestrin 1/20 group, over 75% of the 186 subjects completed all 6 cycles and there were a total of 873 cycles evaluable for contraceptive efficacy. It was agreed with the Division that this would generally be an adequate number of subjects for evaluation of contraceptive efficacy and safety for this NDA submission.

Reviewer's comment:
The extent of exposure during the 6-cycle trial was adequate for an assessment of safety for this product. As noted earlier the total amount of hormones per cycle is slightly greater than that found with the use of Loestrin 1/20 and less than with Loestrin 1.5/30. Both the approved products have had an acceptable safety profile since their approval in 1973.

7.2.1.2 Demographics

Demographic and background characteristics are summarized by treatment for the All Treated population in Table 16 below.

Table 16. Subject Demographic and Background Characteristics

	Loestrin 24 Days (N=743)	Loestrin 1/20 21 Days (N=186)
AGE		
MEAN (STD)	28.7 (6.8)	28.4 (7.0)
MEDIAN	27.3	27.1
RANGE	18.0, 45.7	18.0, 45.8
AGE COHORTS - N (%)		
UNKNOWN	1 (0.1%)	1 (0.5%)
18 - 35	614 (82.6%)	156 (83.9%)
> 35	128 (17.2%)	29 (15.6%)
ETHNIC ORIGIN - N (%)		
ASIAN	17 (2.3%)	8 (4.3%)
BLACK	115 (15.5%)	25 (13.5%)
CAUCASIAN	516 (69.5%)	130 (70.3%)
HISPANIC	77 (10.4%)	18 (9.7%)
NATIVE AMERICAN	2 (0.3%)	0 (0.0%)
OTHER	15 (2.0%)	4 (2.2%)
USER STATUS - N (%)		
SWITCHER	454 (61.1%)	107 (57.5%)
NEW START	289 (38.9%)	79 (42.5%)
HEIGHT (ins)		
MEAN (STD)	64.7 (2.8)	64.9 (2.6)
MEDIAN	65.0	65.0
RANGE	49.0, 73.0	56.0, 71.0
WEIGHT (lbs)		
MEAN (STD)	147.4 (28.4)	150.0 (28.8)
MEDIAN	142.0	143.5
RANGE	90.0, 260.0	101.0, 235.0

Data Source: Report RR-10104.0, Section 14, Table 14.1.4.4

Reviewer's comment:

There are no concerns with the demographic data from the Phase 3 trial. As expected, the Caucasian representation is highest; it is acceptable that there were ~15% African-American and 10% Hispanic women as these percentages are often lower than this in contraceptive clinical trials submitted to the FDA. Approximately 60% of the women switching from another hormonal contraceptive is expected, and the finding that 17% of the women on Loestrin 24 were older than 35 years is acceptable [safety and efficacy data from this older age group is helpful and often missing from contraceptive trials].

7.2.1.3 Extent of exposure (dose/duration)

Table 17. Summary of Exposure to Study Drug (All Randomized Population)

Number of Treatment Cycles Completed (>14 days of active treatment)	Loestrin 24 N=751	Loestrin 1/20 N=187
0	8 (1.1%)	1 (0.5%)
1	40 (5.3%)	12 (6.4%)
2	16 (2.1%)	6 (3.2%)
3	30 (4.0%)	13 (7.0%)
4	21 (2.8%)	1 (0.5%)
5	6 (0.8%)	4 (2.1%)
6	584 (77.8%)	142 (75.9%)
Unknown	46 (6.1%)	8 (4.3%)
N	705	179
Mean (SD)	5.36 (1.52)	5.25 (1.60)

Data Source: Report RR-10104.0, Section 14, Table 14.1.6.1

Reviewer's comment:

In the Loestrin 24 group over 75% of the 743 subjects completed all 6 cycles of treatment resulting in a total of 3,565 cycles evaluable for contraceptive efficacy. In the Loestrin 24 women with ages 18-35 there were 2,909 evaluable cycles. This is an acceptable exposure as agreed to between the Division and the Applicant.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Except for the small number of subjects (18) of the two PK studies, no secondary clinical sources were used to evaluate safety for this NDA review.

7.2.3 Adequacy of Overall Clinical Experience

As agreed to by the Division and the Applicant during the IND phase of development, the overall clinical experience is adequate. The Loestrin 24 product contains 3 more 1/20 tablets than the approved Loestrin 1/20 (21 tablet) product; this represents a 14% increase in total norethindrone and ethinyl estradiol. Compared to the higher dose Loestrin 1.5/30, however, one cycle treatment with Loestrin 24 contains 24% less total norethindrone and ethinyl estradiol.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No special animal and/or in-vitro testing was indicated or required.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing for this NDA was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No special metabolic, clearance, or interaction studies were performed for this NDA. As noted in the Clinical Pharmacology section 5.1, a food effects study was performed with 18 healthy women.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data for this NDA was judged by this reviewer to be adequate and acceptable.

7.2.9 Additional Submissions, Including Safety Update

There were no additional major clinical submissions to the NDA except for an updated label, as requested by the Division and received on 1-26-06. A safety update was submitted on 2-01-06 stating that there was no new safety information to report for the Loestrin 24 product. No preclinical or clinical studies have been ongoing or completed since the original submission of the NDA. No new information on Loestrin 24 has been obtained from a review of the more current scientific literature by the Applicant. In addition, Loestrin 24 is not marketed outside the U.S.; therefore, there is no foreign postmarketing experience to report.

7.3 Summary of Selected Drug-Related Adverse Events, Limitations of Data, and Conclusions

The standard parameters were used to evaluate the overall safety of the hormonal contraceptive Loestrin 24 product. All serious adverse events (SAEs), adverse events leading to discontinuation from the study, and most common adverse events were analyzed. Routine hematology and chemistry labs were obtained at baseline and end of study; vital signs and weight were followed throughout the 6-month study.

The 3 reported SAEs were not related to use of Loestrin 24 and all 3 subjects actually continued in the clinical trial. Of the 751 subjects evaluable for safety in the Loestrin 24 group, 46 (6.1%) of the subjects discontinued due to an AE. Most of the AEs were classified as being possibly or probably related to drug. All but 3 were mild or moderate in intensity. The most common AEs that led to discontinuation in the 46 Loestrin 24 subjects were: abnormal bleeding (10 subjects), nausea (6), mood change (6), dysmenorrhea (4), edema/weight gain (3), and increased blood pressure (3). Overall, the most commonly reported adverse events were headache (6%), vaginal candidiasis (6%), upper respiratory tract infection (5%), nausea (5%), and dysmenorrhea (4%).

Very few hematology and chemistry findings were considered by the individual site investigator to be abnormal. Three subjects in the Loestrin 24 group had triglyceride levels that were definitely elevated at the end of the 6-cycle study; follow-up values (16 and 39 days later) were obtained in 2 of the women and were found to be considerably lower. These same two subjects also had elevated cholesterol values (range of 249-297) at baseline and at end of study. In the smaller Loestrin 1/20 group there was one woman with a slightly elevated triglyceride level of 169 [reference range 36-144].

Blood pressure, pulse and weight were measured at screening and after Cycles 1, 3, and 6. Changes from baseline in mean systolic and diastolic blood pressure and heart rate were small. Mean changes in weight for the Loestrin 24 and Loestrin 1/20 groups were 0.8 and 0.6 pounds, respectively.

No fetal or maternal toxicity issues have been identified with either Loestrin 1/20 or Loestrin 1.5/30 since their original approvals in 1973. It is reasonable to conclude that the new Loestrin 24 product also will have an acceptable safety profile. Although the dosing regimen for Loestrin 24 includes 3 more 1/20 tablets than the approved Loestrin 1/20 (21 tablet) product, representing a 14% increase in total norethindrone and ethinyl estradiol, one cycle treatment with Loestrin 24 contains 24% less total norethindrone and ethinyl estradiol than the higher dose Loestrin 1.5/30 product taken for 21 days.

The safety data was limited primarily by the length of the Phase 3 study (6 months vs. 12 months) and the relatively small number of cycles of exposure (~4,000 vs. 10,000). These limitations, agreed to by the Division and the Applicant, are acceptable as Loestrin 24 is not a new molecular entity and the two active ingredients, norethindrone acetate and ethinyl estradiol, have been well established over the past 35 years as safe in the doses being used.

The overall conclusion is that Loestrin 24 is safe and no Phase 4 commitments or special postmarketing studies are indicated.

7.4 General Methodology

Because this NDA submission required only one Phase 3 clinical trial using a known product but a slightly different dosing regimen, there was no need for the following:

- Pooling Data Across Studies to Estimate and Compare Incidence
- Explorations for Predictive Factors
- Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The regimen and dosing for Loestrin 24 is not flexible. The oral tablet should be taken at the same time each day for 28 consecutive days and then the next package of 28 pills started the following day. Labeling gives clear instructions on what to do if 1, 2, or more pills are not taken as directed.

8.2 Drug-Drug Interactions

No special studies were performed for this NDA application. Class labeling for COCs, however, has a section on drug-drug interactions which will be in the approved label for Loestrin 24.

8.3 Special Populations

No studies were performed in special populations, such as women with renal or hepatic impairment.

Although the Phase 3 clinical study enrolled 70.5% Caucasians, 10% Hispanics, and 15% African-Americans, the effect of race on the safety and efficacy of Loestrin 24 was not specifically evaluated. There is no evidence, however, from previous combination oral contraceptive NDAs or from the medical literature to suspect that the safety or efficacy of oral combination hormonal contraceptives differ significantly based on the race of the user.

8.4 Pediatrics

No special pediatric studies were performed or are required. No subjects in the Phase 3 trial were under age 18. It is generally accepted that the safety and efficacy profiles of combination oral contraceptives are similar in post-menarchal adolescents compared with women $\geq$ 18 years of age.

8.5 Advisory Committee Meeting

No Advisory Committee meeting was indicated or held.

8.6 Literature Review

A review of relevant medical literature was not indicated.

8.7 Postmarketing Risk Management Plan

The Applicant did not provide a postmarketing risk management plan and none is recommended by this reviewer.

8.8 Other Relevant Materials

The AERS database was reviewed for all fatalities associated with the use of Loestrin 1/20 and Loestrin 1.5/30 since 1980. There were no other special materials that were relevant for the review of this NDA application. The label originally submitted with the NDA was not current for the extensive class labeling portions of the label. Upon request from the Division, the Applicant submitted an updated proposed label on 1-26-06.

9 OVERALL ASSESSMENT

9.1 Conclusions

The NDA 21-871 submission is complete and adequate for clinical review. Based on the clinical review of the data included in the NDA submission and the extensive clinical experience with two very closely related COCs (Loestrin 1/20 and Loestrin 1/30), the reviewer's conclusion is that Loestrin 24 is safe and effective for prevention of pregnancy in women of reproductive age.

9.2 Recommendation on Regulatory Action

The reviewer recommends that Loestrin 24 Fe be approved for the following indication: prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special postmarketing risk management activity is recommended.

9.3.2 Required Phase 4 Commitments

There are no recommended Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests of the Applicant.

9.4 Labeling Review

The label that was submitted with the NDA contained an outdated version of the class labeling portion of the label. The Applicant was asked on 1-11-06 to revise the label and submit the revisions as soon as possible. The revised version was submitted on 1-26-06 and subsequently reviewed by all disciplines.

No special claims were made concerning the bleeding profile for Loestrin 24. The **Clinical Studies** section of the label states the number of women enrolled, treatment cycles of exposure, number of on-treatment pregnancies, and the Pearl Index for Loestrin 24. The routine class labeling portion was completely updated. There were no major labeling issues except for the Trade name for the product. The issue of using the word NEW and the use and location of the number 24 as part of the Trade name were discussed. After several discussions, Loestrin 24 Fe was submitted by the Applicant as the official Trade name for the product and agreed to by the Division and DMETS.

9.5 Comments to Applicant

There are no comments or recommendations for the Applicant.

10 APPENDICES

10.1 Review of Individual Study Reports

Only one Phase 3 clinical study was submitted with the NDA. The complete review of this study is found in the body of this NDA review.

10.2 Line-by-Line Labeling Review

The major changes that the Division made to the label submitted on 1-26-06 and agreed to by the Applicant are the following:

1. Substitution of the official Trade name Loestrin 24 Fe
2. Revisions to the Clinical Pharmacology sections by Myong-Jin Kim, Pharm.D.; addition of the statement that Loestrin 24 Fe may be administered without regard to meals or food.
3. Revisions to the Clinical Studies section stating facts about the single 6-cycle trial: number of women enrolled and completed, total cycles of treatment, pregnancies occurring on-treatment, and the overall Pearl Index for all subjects (ages 18 to 45).
4. Addition to the Adverse Reactions section, (1) the most common adverse events reported by 2-6% of subjects, and (2) adverse events leading to discontinuation of treatment in 3 or more subjects.
5. Revisions to the Dosage and Administration section in both the Physician and brief and detailed Patient labels to improve the clarity of when (especially during the first cycle of use) and how to take the 28 tablets in each pack (especially if any of the 24 "active" hormone containing pills are missed.

REFERENCES

No references are included in this review.

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
2/15/2006 04:30:11 PM
MEDICAL OFFICER

Scott Monroe
2/17/2006 07:37:41 AM
MEDICAL OFFICER
I concur with Dr. Davis that the safety and efficacy data submitted in NDA 21-871 support approval of Loestrin 24 Fe for the indication of prevention of pregnancy.