CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-683

MEDICAL REVIEW(S)

Medical Officer's Original Summary of NDA 20-683

1. NDA 20-683
M. O. Review 1

Submission Date: March 27, 1996
Safety Update received: October 7, 1996
Review Completed: February 26, 1997

Drug Name: Levonorgestrel/ethinyl estradiol

Proposed Trade Name: Alesse™

Chemical Name: levonorgestrel: (-)-13-ethyl-17-hydroxy-18, 19-dinor-17alpha-pregn-4-en-20-yn-3-one
ethinyl estradiol: 19 norpregna-1,3,5 (10)-trien-20-yne-3, 17diol, (17alpha)

Sponsor: Wyeth-Ayerst Laboratories
P.O. Box 8299
Philadelphia, PA 19101

Pharmacologic category: Estrogen/progestogen

Proposed Clinical Use: Oral contraceptive

Dosage and Route of Administration: 20 mcg ethinyl estradiol and 100 mcg levonorgestrel----Orally

NDA Drug Class: 3S

Related Drugs: Other approved oral contraceptives including similar products Nordette and Triphasil

Related Reviews: See Nordette (NDA 18-782) approved May 10, 1982 and Triphasil (NDA 19-192) approved November 1, 1984

2. Table of Contents:

3. Material Reviewed: Volumes 1.1, 1.21, 1.22-1.28, 1.30-1.31, 1.34-1.35

4. Chemistry/Manufacturing Controls: See Chemist review

5. Pharmacology/Toxicology: See Pharmacologist review

6. Clinical Background:

6.1 Oral contraceptives (OC's) are one of the most effective methods of widely available contraceptives. Worldwide, more than women take oral contraceptives annually. One out of every four sexually active women of reproductive age uses oral contraceptives in the US, making the use of OC's the preferred method of contraception for over women in the US alone. Method effectiveness (which defines effectiveness when a contraceptive is used ideally) for OC's is between % for the combined estrogen-progestogen pill. However, such ideal conditions are never encountered clinically and use effectiveness actually ranges from as low as % to as high

as)% in some selected populations. The [redacted]% comes primarily from data obtained from family planning clinics not associated with the usual clinical trial setting. This information can be found in the book published by Trussell and Kost.

Presently, there are a number of oral contraceptives on the market in the US, and most prescribed preparations contain either norethindrone or levonorgestrel (and its racemic mixture--norgestrel) as the progestogen and ethinyl estradiol as the estrogen. A few products contain mestranol as the estrogen. In addition, there are other marketed or about to be marketed progestogens, norethindrone acetate, ethynodiol diacetate, norethynodrel, desogestrel and norgestimate. The estrogenic components are identical in terms of their hormonal activity, however, there are some subtle differences in the progestogens. The differences are primarily in the metabolic effect of the progestogens on lipids and possible differences in their androgenicity. However, it is unclear whether these metabolic changes are clinically significant.

Essentially, contraceptive effectiveness of different OC's are similar enough to make them indistinguishable within the sizes of trials typically conducted. Thus, different sponsors have a difficult time distinguishing their specific products from others. Because of such uniformity, sponsors have tried to distinguish their products by differences in safety and adverse reactions, such as irregular bleeding, total hormone doses, etc. Most of these differences are supposedly based on the amount and side-effects of the various progestogens used in the combination pills. The focus of this NDA is to generate sufficient clinical data to support an NDA for an OC containing previously approved contraceptive steroids in the same ratio as a marketed product, but in lower doses of the components. According to FDA's 1987 OC Clinical Guidelines, clinical data for 600 women completing six months of treatment with such a preparation is sufficient to support an NDA. [The proposed 100 mcg/20 mcg formulation has the same 5-to-1 ratio as LNG-to-EE as Nordette (150 mcg/30 mcg).] Accordingly, the clinical program was designed to provide data for at least 600 women who completed 6 or more cycles of use.

6.2 Important information from related IND's and NDA's

Multiple NDA's have been approved with either levonorgestrel or norgestrel as the progestogen since Ovral (norgestrel 0.5 mg and 0.05 mg ethinyl estradiol) was approved in June 1968. The racemic mixture, Nordette (levonorgestrel 0.15 mg and ethinyl estradiol 0.30 mg) was approved in July 1982.

6.3 Foreign experience

Wyeth-Pharma obtained marketing approval in Germany for a sugar-coated LNG/EE 100 mcg/20 mcg formulation on January 8, 1992. As of February 15, 1996 this product has not been marketed in Germany.

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

The sponsor conducted two Phase II open-labeled, multiple dose, single-center clinical pharmacology studies to evaluate the effect of LNG/EE 100 mcg/20 mcg on ovulation. One study used a 21-day treatment regimen (protocol 858A-201-US) and the second study a 24-day treatment regimen (protocol 858A-202-US). In study 858A-201-US 25 subjects between the age of 20 and 35 years of age were enrolled for a total of 5 cycles (3 treatment cycles). Ovulation was inhibited in 67 of 73 treatment cycles observed. During treatment, 4 subjects ovulated, 2 in both cycles 3 and 4 and 2 other subjects in cycles 4. Overall, mean progesterone levels were suppressed during treatment cycles 2 to 4. Mean maximum 17-beta estradiol levels varied from cycle to cycle, particularly in cycles 3 and 4. In study 858A-202-US 24 subjects between the age of 18 and 34 years of age were enrolled for a total of 5 cycles (3 treatment cycles). Ovulation was inhibited in all but 1 of the 69 treatment cycles observed in 23 of the 24 subjects. Mean maximum progesterone and mean maximum 17-beta estradiol levels were suppressed during treatment cycles 2 through 4.

The sponsor also conducted a pharmacokinetics study 858A-101-US in 22 subjects. LNG (100 mcg) and EE (20 mcg) appeared to accumulate after multiple doses over 21 days. LNG AUC was increased by % , due in part to increased EE-induced SHBG binding. EE AUC was % higher than after single doses, consistent with a $t_{1/2}$ of 18 hr. This study was conducted with the aqueous film-coated (AFC) levonorgestrel/ethinyl estradiol which is proposed for marketing in the US.

6.5 Other relevant background information (meeting, commitments)

On December 28, 1993, Wyeth-Ayerst submitted a clinical development plan for a 21-day regimen of LNG/EE 100 mcg/20 mcg to FDA for review and comment. The Phase III clinical trial was proposed and accepted. In addition, two studies of the effects of the study drug on ovarian activity were proposed, one with a 21-day regimen and the other with a 24-day regimen. Follicle size and progesterone levels were discussed February 8, 1994 in relationship to defining ovulation. Wyeth-Ayerst agreed to adopt the criteria for defining ovulation, by this reviewing medical officer, of 10-mm follicle size and progesterone level greater than 2 ng/mL.

7 Description of Clinical Data Sources (both IND and non-IND)

7.1 This study was conducted under IND The development plan provided for the submission of an NDA based on clinical data from at least 600 women who had completed 6 months of use. One ongoing multi-center Phase III clinical trial , provides the primary evidence for the efficacy and safety of Alesse. The clinical database derived from this study and presented in this NDA included data from 1,477 women with a total of cycles of experience; 792 of these women completed 6 cycles of use. The sponsor submitted a Safety Update on October 10, 1996.

The Safety Update database includes an additional 188 women, with a total of cycles of experience. The combined total of cycle experience is cycles in 1,665 subjects.

7.2 This dosage was previously studied in Brazil and the results were published in 1974. A group of 438 subjects were observed for cycles of medication with the combination of 100 mcg LNG/20 mcg EE. One pregnancy was reported during the study (Pearl index 0.3). The incidence of spotting and of breakthrough bleeding during treatment was % of the total cycles, respectively.

8 Clinical Study

8.1 Trial # 858-A-301-USA

8.1.1 The objective of this study was to determine the efficacy and safety of a 21-day regimen of the monophasic oral contraceptive combination LNG 100 mcg and EE 20 mcg.

8.1.2 Design

This efficacy and safety study was designed as an outpatient, multi-center, open-labeled trial using a single treatment group. Approximately 1, 750 subjects (1,500 in the United States and 250 in Canada) were anticipated to be enrolled when the protocol was written. Each subject could participate for approximately 36 cycles or until the study was terminated or the subject withdrew or was withdrawn. Enrollment was to be discontinued when 600 subjects, who had data evaluable for efficacy, completed 6 cycles of treatment.

8.1.3.1 Protocol

Subjects who satisfied the following inclusion criteria and did not meet any of the exclusion criteria were admitted to the study.

Inclusion Criteria:

- Healthy women of legal age who wished to use a combination OC were eligible for the study. Smokers were to be under the age of 35 years. There was no upper limit for healthy non-smokers.
- All subjects except for post-abortal and non-nursing postpartum subjects must have regular (21 to 35) cycles for the 3-month period preceding enrollment.
- Post-abortal and non-nursing postpartum subjects must have had a normal spontaneous menses before enrollment. Study medication was begun on day 1 of the second spontaneous menses.
- Subjects must have been at risk of becoming pregnant.
- In the opinion of the investigator, the subject would comply with the protocol.
- Subjects were to give signed informed consent.

Exclusion Criteria:

A history or the presence of any of the following prevented enrollment:

- Thrombophlebitis or thromboembolic disorders
- Known or suspected clotting disorders
- Cerebrovascular or coronary artery disease or myocardial infarction
- Malignancy
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding (within the past six cycles)
- Benign or malignant liver tumor that developed during the use of OC's or other estrogen-containing products
- Hyperlipidemia, hypercholesterolemia defined as fasting blood cholesterol greater than 6.26 nmol/L (260 mg/dL)
- Diabetes mellitus
- Migraine
- Increased frequency or severity of headaches during previous estrogen or OC therapy
- Severe depression
- Chronic renal disease
- Known hypersensitivity to estrogens and/or progestogens
- Neuro-ocular disorders (eg, optic neuritis and retinal thrombosis)
- Cholestatic jaundice
- Failure of efficacy of OC treatment
- Persistent noncompliance with taking medication
- Serious adverse experiences with OC use
- Malabsorption due to disease or surgery

The presence of any of the following prevented enrollment:

- Breast feeding
- Impaired liver function or disease
- Known or suspected pregnancy
- Hypertension, whether treated or untreated Hypertension was defined as elevated sitting blood pressure > 90 mm Hg and/or > 140 Hg systolic.
- Cervical cytologic smear of Papanicolaou (Pap) class III or greater or a Bethesda System report of low-grade squamous intraepithelial lesion (SIL) or greater
- The use of injectable or implantable estrogens, progestogens, or androgens during the 6-month period before enrollment
- Known or suspected alcoholism or drug abuse

Study Procedures:
At the pre-study visit, a complete history, including gynecologic, obstetric, and smoking history, was obtained for each subject. In addition, a physical examination, a laboratory safety screen, a cervical cytological smear, and a serum chorionic gonadotropin (hCG) pregnancy test were done. The physical examination included examination of the breasts, a pelvic examination, ocular funduscopy, and neurologic examinations. Height, weight, and sitting blood pressure were also recorded. The presence of inclusion criteria and the absence of exclusion criteria were verified on the case report form (CRF), and the subject's birth date and race were recorded.

Each subject began taking study medication on the first day of her menstrual cycle in cycle one. Subjects who were currently taking another OC began the study medication on the first day of their withdrawal menses. Each tablet was to be taken at approximately the same time of each day. The subject was to take one LNG/EE 100 mcg/20 mcg tablet for 21 days of each cycle, followed by one placebo tablet taken daily for 7 days. On completion of a pill-pack, the subject continued to the next pill-pack.

Subjects were given diary cards on which to record the number of pills taken each day. They were instructed to take a missed tablet as soon as they remembered. If two consecutive tablets were missed, the subject was to return the first missed tablet to the investigator at the next visit and take the second missed tablet immediately. Subsequent tablets were to be taken at the usual time. Missing three or more consecutive tablets of active medication constituted a protocol violation (noncompliance). If this circumstance was reported to the investigator during the cycle of occurrence, the subject was to be dropped from the study and instructed to use an alternate form of contraception.

Subjects were seen for follow-up visits during the second and fourth treatment cycles, and every third cycle thereafter. At each visit, weight and sitting blood pressure were measured and the daily diary card was reviewed.

Subjects were to report any amenorrheic cycles immediately and a pregnancy test was performed. Subjects were encouraged to report any other unusual occurrences by telephone or at their next visit. If necessary, the study nurse contacted subjects by telephone to ensure compliance. Extra visits with the physician were arranged, if indicated. All information was recorded on the CRF's.

Concomitant therapy:
Concomitant medications were generally prohibited during the study without the knowledge and permission of the investigator.

Prescription medications other than those listed below as prohibited could be used to treat intercurrent medical conditions at the discretion of the investigator. All concomitant prescription medication information, including dates of use, was recorded on the CRF.

The following medications were prohibited during the course of the study:

- Sex hormones (except those given in this study)
- Any anticonvulsant medications
- Other forms of contraception including condoms
- Chronic use of an anti-infective that alters the intestinal flora (i.e. for more than 10 days)
- Drugs for which the labeling requires the simultaneous use of a contraceptive (e.g. Accutane)
- Any use of rifampin

Treatment was stopped and a subject removed from the study because of pregnancy; other reasons for discontinuation were subject request, protocol violation, or medical indications.

The physical examination, laboratory safety screen, and cervical cytologic smear(Pap smear) were repeated during cycle 7 (visit 4) and every 6 cycles, thereafter, for the duration of the study.

8.1.3.2 Endpoints

Efficacy was determined on the basis of the number of pregnancies that occurred during the study and whether the subjects who became pregnant had taken their tablets correctly. Any subject, without withdrawal bleeding, after completing a pack of tablets, was to be given a pregnancy test. If the subject was pregnant, investigators were to supply any additional information that would help in estimating the date of conception. Pregnant subjects were to be followed up until the pregnancy was terminated or until delivery. Information on the status of the infant at birth was to be recorded.

Cycle control was evaluated by analyzing cycle characteristics such as duration and intensity of withdrawal bleeding and the incidence of breakthrough bleeding/spotting and amenorrhea. Primary definitions are as follows:

A. A withdrawal bleeding episode was a sequence of 1 or more days of spotting and/or bleeding that began on or after day 22 (during the 7-day drug-free interval), and included all spotting and bleeding between days 22 and 28. The episode could continue into the first 4 treatment days of the next pill pack if there was bleeding on days 27 or 28. and ended when there were 2 consecutive days without bleeding.

B Breakthrough bleeding and/or spotting, after cycle 1, was defined as bleeding and/or spotting on pill-days 5 to 21 inclusive or on pill-pack days 1 to 4 inclusive if preceded by 2 consecutive days without bleeding or spotting.

C. Amenorrhea is the absence of any bleeding or spotting during the entire 28-day medication cycle, except in cycle 1. Amenorrhea in cycle 1 excluded the initial menstrual bleeding.

8.1.3.3 Statistical considerations

The emphasis in this non-comparative study was on descriptive statistics, rather than on the testing of a hypothesis.

Use effectiveness was evaluated by using the **Pearl index** and **Life-table** methods. Cycles for a subject in which extra contraceptive protection was used were deleted from the calculation of the Pearl Index and the life-table analysis, and all subsequent cycles for that subject were also deleted from the life-table method analysis. Cycles in which active study medicine was missed for 3 or more consecutive days and all subsequent cycles were also excluded from the life-table analysis.

Cycle control was characterized by cycle length, latent period, length of menses, and incidence of bleeding patterns.

The primary consideration with vital signs and laboratory values was to identify individual out-of-range changes of clinical importance.

8.1.4 Results

The first subject was enrolled on April 9, 1994. A total of 1,477 subjects had been enrolled in the study and provided cycles of exposure as of the data cutoff date of June 30, 1995. Enrollment was to be terminate when 600 subjects completed 6 cycles each. However, enrollment is continuing in order to recruit subjects for special sub-studies. A total of 415 (28%) subjects were withdrawn from the study for any reason. A summary of the number of subjects entering and discontinuing during each treatment cycle by the cutoff date of June 30, 1995 is given in the following table. Because of the ongoing nature of the study, the number of subjects entering a cycle minus the number of subjects who discontinued during one cycle may not equal the number of subjects who entered the next cycle.

Table 1 Summary Tabulation of Subjects Beginning and Discontinuing Each-Pill Pack Cycle

Sponsor's table 5.1.1

Pill-pack Cycle	Subjects Beginning	Subjects Discontinuing
1	1477	89
2	1244	82
3	1140	45
4	910	51
5	839	20
6	798[a]	36
7	438	32
8	378	14
9	319	14
10	120	17
11	88	6
12	79	2
13	19	2
14	11	3
15	8	1
16	2	1

[a] 797 subjects had completed 6 cycles of treatment (ie, took ≥ 19 active pills during cycle 6) as of the cutoff date of June 30, 1995.

Protocol violations on admission, but before the subject took study mediation, were the reason for withdrawal of 25 subjects (1.6%). This is shown in the following table:

Table 2 Discontinuance Due to Protocol Violations On Admission

Sponsor's table 5.1.2A

Categorized Reason for Discontinuation	Number (%) of Subjects (n = 1477)
Abnormal laboratory values	10 (<1)
Excluded medical condition	8 (<1)
Pregnancy	3 (<1)[a]
Other protocol violations	4 (<1)

a One additional subject (301B5-018) had a positive pregnancy test because she had a terminated pregnancy 2 months before she started study medication. Prior to receiving study drug, a pregnancy test was negative. She was not discontinued from the study.

After beginning to take the study medication, a total of 57 (3.9%) subjects were withdrawn because of protocol violations. This is summarized in table 3:

Table 3 Protocol Violations During Study For Which Subjects Discontinued

Sponsor's table 5.1.2B

Categorized Reason for Discontinuation	Number (%) of Subjects (n = 1477)
Excluded medical condition	2 (<1)
Noncompliance Missed Pills Backup contraception	 29 (2) 7 (<1)
Prohibited concomitant medication	5 (<1)
Other protocol violations	14 (1)

An additional 333 (23%) subjects discontinued treatment for reasons other than protocol violations. This is shown in Table 4.

Table 4 Reasons for Discontinuations Other Than Protocol Violations

Sponsor's table 5.1.3

Categorized Reason for Discontinuation	Number (%) of Subjects (n = 1477)
Other medical event	131 (9%)[a]
Subject request	84 (6%)
Lost to follow-up[b]	69 (5%)
Withdrawn by sponsor[c]	27 (2%)
Pregnancy desired	13 (<1%)
Pregnancy	5 (<1%)
Release from study[d]	2 (<1%)
Investigator's choice[e]	2 (<1%)

[a]Two additional subjects listed adverse events with discontinuation as an outcome (Table 9.3.3). One was categorized as a protocol violation, and a termination record was not received by the cut-off for the other.

[b] Subjects who failed to return or who moved.

[c] Included 25 subjects from sites that were closed before study completion.

[d] One subject left the country and 1 provided contradictory comments about migraine.

[e] Investigator believed that subject was non-compliant or unable to comply with drug regimen.

Not all of the cycles for the subjects included in the evaluations were valid for efficacy and cycle control analysis. Table 5 gives the number of cycles valid for each type of evaluation. The reasons reported are in sections 7.1.1, 7.2.1 and 8.1 of the sponsor's NDA.

Table 5 Summary of Cycles Valid for Evaluation

Type of Evaluation	Number of Pill-pack Cycles
Life-table analysis	(98.8%)
Pearl Index	(98.0%)
Cycle Control	(95.5%)
Safety	(100.0%)

[a] all subjects, all cycles

The sponsor summarized cumulative continuation rates, and monthly and cumulative withdrawal rates, which were adjusted for loss-to-follow-up. The continuation rate at cycle 3 was 0.9167, at cycle 6 the continuation rate was 0.8306, at cycle 9 the continuation rate was 0.7235 and at cycle 12 the continuation rate was 0.6125.

Data were collected for 1,477 subjects, ages 17 to 49 years of age. More than half (61%) of subjects were using another oral contraceptive (OC) in the cycle before starting LNG/EE (switchers). Only 5.3% of the subjects had never used OC's in the past. Sixty-one percent of subjects were switchers from other OC's, 28.6% were former users, 5.1% were recent users, and 5.3% were never users.

Demographically, the mean age of subjects was 27.0 ± 6.0 years, with a range of age from Approximately 87% (n = 1285) of subjects were white, 5.1% (n = 75) were black, and 7.9% (n = 117) were classified as other. The mean weight was 66.4 ± 14.8 kg, with a range of kg. The mean parity was 1.0 ± 1.3 children. Further breaking down parity, 46.9% of subjects had 0 parity, 23.4% had a parity of 1, 15.8% had a parity of 2, 7.4% had a parity of 3, and 4.7% had parity greater than 3.

Forty-five percent (45%) of subjects received some type of concomitant medication during the study. The most common categories of concomitant medications were beta-lactam antibacterials/penicillins (11%) and non-steroidal anti-inflammatory/antirheumatic products (7%). Antibiotics were taken for longer than 10 days by 122 subjects during the study. However, only 1 subject was withdrawn as a protocol violator because of extended use of an antibiotic (Ceclor).

In addition, 1 subject had a positive tuberculin skin test with a negative chest x-ray. She started taking rifampin 19 days before she was withdrawn from the study. She was withdrawn from the study because receiving rifampin was a protocol violation.

Subjects took LEG/EE 100ug/20ug tables for 21 days, followed by 7 placebo tablets, during 6,391 (81.2%) of cycles of use. A subject who missed a pill was instructed to take two pills on the following day. One or more pills were missed during 1,479 (18.8%) of the — cycles. A total of 29 (2%) subjects who missed three or more pills were withdrawn from the study because of noncompliance (Sponsor's table 5.1.2B- not reproduced).

Efficacy Results:
One hundred forty-one subjects had a total of 150 cycles excluded from the calculation of the Pearl index. These included cycles during which backup contraception was used (31 cycles) and cycles in which 3 or more consecutive active pills were missed (136 cycles). There were 17 cycles with both violations.

A total of 5 pregnancies were attributed to treatment failure occurred during the efficacy cycles and were used to compute the Pearl index. Based on 13 cycles per year, the Pearl index was 0.84 women.

$$\text{Pearl Index} = \frac{5 \times 1300}{7{,}720} = 0.841$$

Individual pregnancies summarizes were reviewed in detail, including last normal menstrual periods, active taking of oral conceptive pills and documentation with pelvic ultrasound. Data from these pregnancies appears accurate. Four additional subjects who were pregnant before receiving study medications (prestudy) and 5 other subjects who become pregnant after missing more than 3 consecutive day of medication or stopping study mediation (return to fertility) had their history summaries reviewed (including date of pregnancy test, OC use, and ultrasound when warranted) and were found to be consistent with a non-treatment method of failure.

Another method to establish the **use-effectiveness** of an oral contraceptive is the Life-table analysis. In table **S2** at the end of this review, the number of accidental pregnancies is shown over 16 cycles. Review of this table shows that 5 pregnancies occurred in cycles 4, 5, 6, 8 and 9. At cycle 6 the cumulative pregnancy rate via Life table analysis is 0.0041, meaning 0.4 women/women years of use became pregnant. By cycles 9 through cycle 12, the cumulative pregnancy rate remains 0.0110, meaning 1.1 women/women years of use became pregnant. These rates are well within the acceptable range.

Other than the pregnancy rate, the next most important parameter in the successful use of OC's, is the amount of bleeding noted in a cycle or "cycle control." Commonly reviewed parameters are: breakthrough bleeding alone, spotting alone, breakthrough bleeding and spotting and breakthrough bleeding and/or spotting. In addition, another important parameter is the absence of bleeding, or amenorrhea. Review of the sponsor's table 8.1 (Vol 1.26), which will not be shown, reveals that 217 subjects, for a total of cycles, were excluded from the cycle control analyses. Of this total, the overwhelming number who were excluded were excluded because of study medication missed or not recorded for 3 or more consecutive days during the pill-pack cycle, or

bleeding data was not recorded for 1 or more days during a pill-pack cycle. Overall, cycles were reviewed for cycle control. Table 6, (sponsor's table 8.2) shows the incidence of breakthrough bleeding and spotting.

Table 6
Incidence (% of cycles) of Breakthrough Bleeding
and Spotting in Selected and Total Treatment Cycles

Cycle	Cycle Valid for Analysis	Breakthrough Bleeding Alone	Spotting	Breakthrough Bleeding and/or Spotting	Breakthrough Bleeding and/or Spotting
1	1411	50 (3.5)	231 (16.4)	149 (10.6)	430 (30.5)
3	1097	51 (4.6)	122 (11.1)	118 (10.8)	291 (26.6)
6	765	33 (4.3)	76 (9.9)	85 (11.1)	194 (25.4)
9	302	10 (3.3)	32 (10.6)	34 (11.3)	76 (25.2)
12	77	3 (3.9)	6 (7.8)	5 (6.5)	14 (18.2)
Total Treatment Cycles (%)	7508	321 (4.3)	905 (12.1)	823 (11.0)	2049 (27.3)

Overall, it can be sen that breakthrough bleeding alone and spotting alone occurred during 4.3% and 12.1% of cycles, respectively. Breakthrough bleeding and spotting occurred during 11.0% of the cycles, while breakthrough bleeding and/or spotting occurred in 27.3% of the cycles. The total incidence of 27.3% of breakthrough bleeding/spotting is quite high and is consistent with a very low dose formulation of estrogen/progestogen. As is usual, with most OC's, the percentages of cycles with breakthrough bleeding and/or spotting were higher during the earlier cycles than in later cycles.

Amenorrhea was reported in 195 cycles. The overall incidence was 2.6% of the total cycles.

The duration of withdrawal bleeding ranged from 1 to 11 (mean = 4.8) days. The withdrawal bleeding period during this monophasic regimen was between 3 and 7 days in 86% of cycles. The mean bleeding intensity was light for the most common episode lengths (between 4 and 6 days). The mean cycle length, excluding cycle 1, was 29.1 days, and 90% of the cycles ranged in duration from 26 to 30 days.

Safety Results:

All adverse experiences, treatment-emergent signs or symptoms (TESS), new intercurrent illnesses, or clinically significant abnormal laboratory finding were entered in the case report forms (CRF). However, only those events that were not present before the study or that worsened during treatment are presented (if treatment-emergent).

Safety data are presented for 1,477 subjects who began at least one treatment cycle of LEG/EE, resulting in a total of cycles of exposure. Treatment-emergent study events (TESE) were reported for 1,106 (75%) of subjects. TESE that were reported by > 2% of subjects are listed in the sponsor's table 9.2B. A summary of table 9.2B follows. Headache was the most frequent adverse event, occurring in 440 (27%) of subjects; dysmenorrhea occurred in 210 (14%) of subjects; infection occurred in 200 (14%) of subjects (none were considered drug related); pharyngitis occurred in 146 (10%) of subjects; abdominal pain occurred in 134 (9%) of subjects; nausea occurred in 134 (9%) of subjects; metrorrhagia occurred in 123 (8%) of subjects; sinusitis and flu-like syndrome occurred in 6% of subjects; vaginal moniliasis and pain occurred in 5% of patients. Events which occurred between 2% and 4% will not be mentioned except to note that acne occurred in 4% of subjects and vaginitis and urinary tract infections occurred in 3% of subjects. These symptoms are only mentioned because they are infrequently associated with OC's.

Approximately 133 of 1477 subjects discontinued the use of LN/EE due to one or more adverse events. The most frequent reasons for discontinuation were headache and metrorrhagia. It should be noted that all of the following events, which caused the subjects to discontinue medication, were observed in < 1% of subjects. The following conditions have been associated with the use of OC's and are frequently mentioned as causes for discontinuing their use. The condition is stated first, followed by the number: Headache (21), hypertension (7), migraine (3), hypercholesterolemia (5), weight gain (5), depression (8), emotional lability (8), acne (7), amenorrhea (8), dysmenorrhea (4), menorrhagia (6) and metrorrhagia (21). Narrative summaries of these patients, who discontinued the use of this OC, did not show any unusual or unexpected adverse event(s) not usually associated with OC's.

Adequate cervical cytological smears (Pap smears) were obtained in 1435 of 1477 (97%) subjects. One-thousand two hundred forty (84%) had normal Pap smears at baseline. Smears classified as abnormal showed mostly infectious, reactive or reparative changes. Eighty-nine (89) or 6% of the smears were classified as having epithelial abnormalities, the majority of which

(74) or 5% were atypical squamous cells of undetermined significance (ASCUS). Of the epithelial abnormalities, 20 (1%) showed low grade SIL or cervical intraepithelial neoplasia (CIN) I.

Two subjects developed high-grade SIL during the study and were referred for further evaluation and treatment. One subject had an initial Pap smear with ASCUS. Six to 8 months later she progressed to high-grade SIL and underwent a loop electrosurgical excisional procedure (LEEP). She was withdrawn from the study. The second subject had a Pap smear on May 3, 1994 which showed inflammation. On November 12, 1994 a repeat Pap smear showed high-grade SIL. Colposcopy demonstrated severe dysplasia on December 7, 1994 (and this diagnosis mapped to cervical carcinoma for COSTART purposes). As a clarification, some diagnoses in the coding process in COSTART may overlap between the less severe diagnosis, severe dysplasia. and the more severe, Carcinoma in-situ. The patient was referred for LEEP. She was withdrawn from the because of a protocol violation (high-grade SIL).

Laboratory Test
Elevated lipid levels were reported for 6 subjects; 4 were withdrawn because of elevated cholesterol values and 1 because of elevated triglyceride values. One subject, who had an elevated cholesterol level, remained in the study.

One subject had an elevated thyroxine (T_4) at the conclusion of the study. The subject refused follow-up care.

One subject had a positive history of cholelithiasis. Uric acid and liver transamine levels were elevated above baseline values. During the course of drug treatment, a laparoscopic cholecystectomy was done. The patient recovered quickly. This adverse event was classified as possibly related to drug treatment.

Vital Signs and Body Weight Data
More than 97% of the subjects had normal BP (systolic BP $\leq$ 140 mm Hg; diastolic BP $\leq$ 90 mm Hg) at baseline and during treatment. Seven subjects withdrew from the study because of elevated BP.

Five subjects listed weight gain as a reason for discontinuation; 1 additional subject discontinued study medication for personal reasons attributed to weight gain. Of these six subjects who discontinued, one showed an increase of more than % from her pre-study weight. Forty-one (41) subjects gained more than % and there were 17 subjects who lost more than % of their baseline weight. These fluctuations in body weight were not considered clinically important.

SAFETY UPDATE:

The sponsor submitted the safety update report for this product on October 10, 1996. The original cutoff date of June 30, 1995 included all of the efficacy and safety data previously reviewed. That data base included 1,477 women, with a total of cycles of experience; 792 of these women had completed 6 cycles of use. This safety update used a cutoff date of March 29, 1996 and included data from 1,655 women (1,419 in the US and 246 in Canada), with a total of cycles. These data represent an additional 188 enrolled subjects, and approximately a doubling (.cycles) of the total cycles of exposure.

The demographic characteristics of the study population at the NDA cutoff date, and at the safety update data cutoff date, are similar. After 12 cycles, data were available from at least 508 subjects who entered cycle 13.

A total of 763 (45.8%) subjects had been withdrawn from the study for any reason at the March 29, 1996 data cutoff date. The four primary reasons for discontinuing in the study were "other medical event" 213 (13%), subject request 173 (10%), lost to follow-up 138 (8%) and protocol violation during the study 112 (7%). Incorporated in this total of 213 (13%) subjects are subjects who reported adverse events on their CRF. Review of sponsor's Table 6 (Volume 1) shows no AE which occurred more than 2% at any time. The urogenital system had the highest cumulative percentage of subjects discontinuing at 5%. Of this total, 2% discontinued use of this OC because of metrorrhagia and 2% discontinued due to headache. All other AE's were 1% or less.

There were 9 subjects who became pregnant after the cutoff date of June 30, 1995. Four (4) of these subject were classified as treatment failures. With an additional cycles and four additional pregnancies, the Pearl's index would decrease slightly to 0.78, with a corresponding decrease in the Life table analysis value. A decreasing pregnancy rate has typically been shown with other similar low-dose OC studies with continued use, and this is reflected in this study.

Seven subjects were hospitalized during the new reporting period. Two of the 7 subjects, were hospitalized for reasons considered by the investigator to be possibly related to treatment. Subject was hospitalized for a biopsy of the left breast. The result her pathology report indicated ductal hyperplasia with papillomatosis and focal adenosis without atypia.

Subject had an acute myocardial infarction and was withdrawn from the study on March 19, 1996.

Breakthrough bleeding alone and spotting alone occurred during 4.0% and 11.1% of cycles, respectively. Breakthrough bleeding and spotting occurred during 10.1% of the cycles, while breakthrough bleeding, spotting or both occurred during 25.2% of the cycles. The percentage of cycles with breakthrough bleeding, spotting, or both are very similar to the original data base.

Amenorrhea occurred in 1.9% of the cycles. Withdrawal bleeding and cycles length were

Special Studies:
The sponsor conducted 4 special studies: an endometrial biopsy study, a lipid study, a carbohydrate study and a coagulation study. These studies will be briefly summarized:

a. The endometrial biopsy study included 27 subjects who had undergone biopsy before treatment and at least one biopsy during or after treatment as of a data cutoff date of March 15, 1996. Twenty-four(24) or 89% of subjects had a secretory or proliferative endometrium before treatment. During treatment, most specimens were characterized as secretory, proliferative, or hypoplastic. None of the subjects had endometrial hyperplasia.

b. The purpose of the lipid study was to evaluate the effects of a 21-day regimen of this monophasic OC on lipid levels. Twenty-three (23) women had blood samples for lipid determinations, obtained after a fast of at least 15 hours. The samples were obtained twice during the pretreatment cycle, once each during the third and sixth cycles, and every six cycles, thereafter. Statistically significant mean percent increases were seen in triglyceride and apolipoprotein (Apo) B concentrations during cycles 3, 6, and 12, in high density lipoprotein subfractions (HDL_3)-cholesterol (C) values during cycle 6, and in low density lipoprotein (LDL)-C values during cycles 6 and 12. No significant mean percent changes were seen in total-C, HDL-C, HDL_2-C, and $ApoA_1$.

c. The purpose of the carbohydrate study was to evaluate the effects of a 21-day regimen of this monophasic OC on carbohydrate metabolism. Carbohydrate metabolism studies included a 3-hour oral GTT with insulin determination with a 75-g loading dose of glucose. Tests were done during the prestudy period, once each during the third and sixth treatment cycles, and every 6 cycles, thereafter. Completed data were available for 15 subjects during cycles 3 and 6 of treatment. Except for a mean increase in the 30-minute glucose value at cycle 6, there were no statistically significant changes from the baseline in glucose or insulin values for 13 subjects with completed data through cycle 6, excluding 2 subjects because of extreme variability of the on-treatment insulin results.

d. The purpose of the coagulation study was to evaluate the effects of this 21-day regimen OC on coagulation. Blood samples for coagulation assays were obtained once during the pretreatment cycle, once each during the third and sixth cycles, and every six cycles thereafter. Blood samples during the pretreatment period were obtained during cycle days 17 and 26. Blood samples during treatment were obtained during tablet days 15 and 21. An additional sample was obtain 4 to 6 weeks after the end of therapy between cycle days 17 and 26, if the subject was not receiving oral, implantable, or injectable contraceptive therapy. Results are available for 11 subject who had data through cycle 6. Significant mean decreases were observed in the anticoagulant factors, antithrombin III antigen and protein S activity total antigen, during cycle 6. In contrast, there were increases in the fibrinolytic factors, plasminogen antigen and activity, during cycles 3 and 6. There were

significant mean increases in PTT and in the ratio of PTT to that of concurrent controls during cycle 3. Significant increases were seen in thrombin/antithrombin III (TAT) complexes during cycle 3 only, and in the fibrin split products(D-dimer), during cycle 6. None of the observed changes in coagulation were considered to be of clinical importance.

Other safety assessments in the Safety Update:
Before, during, and after the study, the percentage of subjects with normal Pap smears was always greater than %. Epithelial abnormalities that were noted during the study were mostly atypical squamous cells of undetermined significance (ASCUS), with a few indicating low-grade squamous intraepithelial lesion. No microinvasive or invasive cancers were noted at any time throughout the study.

Except for 4 subjects who withdrew because of hypertension, there were no clinically important changes in vital signs or weight of individual subjects during the new reporting period.

The safety profile at the safety data cutoff date of March 29, 1996 is similar to that at the NDA data cutoff date. The study events that most frequently caused subject discontinuation at the safety update data cutoff date were metrorrhagia (2%) and headache (2%). At the time of the NDA cutoff, headache and metrorrhagia had also been the most common study events (1% each) causing subject withdrawal.

One or more TESE has been reported for 1,355 (81%) subjects by the safety update cutoff date of March 29, 1996 and for 1,106 (75%) of 1,477 subjects by the NDA cutoff date of June 30, 1995. Headache, dysmenorrhea, and infection were the most frequent adverse events at each cutoff date. Headache occurred in 30 % of the subjects during the cumulative reporting period and in 27% of the subjects by the NDA cutoff. Dysmenorrhea occurred in 17% of subjects during the cumulative period and in 14% of the subjects as of the NDA cutoff date. Infection occurred in 17% o the subjects during the cumulative reporting period and in 14% of the subjects by the NDA cutoff date.

9 Overview of Efficacy:
Efficacy end points with oral contraceptives are calculated by using the Pearl's index and Life table analysis. Since pregnancy rates are an objective end-point, contraceptive studies have been conducted without controls and in an open-label fashion. The sponsor has submitted adequate data with this NDA to make an evaluation of efficacy.

The sponsor's developmental plan for this submission was based on clinical data from at least 600 women who had completed 6 months of use, in accordance with the Division of Metabolism and Endocrine Drug Products 1987 OC clinical data requirements for products containing reduced amounts of approved steroids in the same ratio as a marketed product. Alesse™ (levonorgestrel 0.100 mg /ethinyl estradiol 0.020 mg) is in the same ratio [5(LN) to 1(EE)] as

other Wyeth-Ayerst products such as Ovral and Lo-Ovral which provide Norgestrel as the progestin, and Nordette (NDA 18-872) which provides levonorgestrel as the progestin, (0.150 mg and ethinyl estradiol 0.030) in the same ratio.

The Pearl index is 0.84. This is acceptable especially when documented by supportive data such as accurate dates of ingestion of contraceptive pills and first trimester ultrasound to document dates of conception. The Life table analysis of cumulative pregnancies is 0.0041. Higher pregnancy rates have been reported with other monophasic products such as desogestrel and norgestimate within the last 7 to 8 years.

9 Overview of Safety:

Cycle Control:

The incidence of breakthrough bleeding alone ranged from % in cycle one to % at cycle 12; spotting alone ranged from % in cycle one to % in cycle 12. Breakthrough bleeding and/or spotting ranged from % in cycle one to % in cycle 12. Overall, in a total of treatment cycles, breakthrough bleeding and/or spotting were noted in 27.3% of cycles. This is a significant frequency of bleeding. In comparison, Desogen, a monophasic OC approved December 1992, containing 30 mcg of EE and 0.15 mg of Desogestrel, was noted to have an 8.1% incidence of breakthrough bleeding and spotting for all cycles. However, it is noted that over time, as with other OC's, the incidence of bleeding and/or spotting decreased with increasing cycles of treatment.

Amenorrhea occurred in 2.6% of the cycles. This is an acceptable incidence and is comparable to Desogen at 1.7% of patients. There were no clear patterns of adverse experiences noted in relationship to other AE's such as headache, infection, dysmenorrhea, abdominal pain or nausea. These AE's have been consistently recorded for other OC'S. Weight gain and vital signs were stable for most patients. Additionally, no unusual trends were noted in the subset of patients who were monitored in the continuation study. The endometrial biopsy study, the lipid study, the carbohydrate study and the coagulation study showed no unusual trends not seen in other low dose OC's. Adverse reaction trends seen in the original NDA were also seen in the continuation study.

In summary, no unusual AE's were seen with Alesse. However, the incidence of breakthrough bleeding and/or spotting is high at 27.3% at cycle six.

11 Labeling Review

In general, the proposed labeling submitted corresponds to the revised Labeling Guidance for Combination Oral Contraceptives dated August 1994. Labeling reviewed includes draft labeling submitted with the NDA and a Labeling amendment submitted on December 20, 1996. The Labeling amendment of December 20, 1996 contains only physician's labeling. There are some minor differences which are not consistent with the Labeling Guidance document and these

Labeling amendment of December 20, 1996 contains only physician's labeling. There are some minor differences which are not consistent with the Labeling Guidance document and these differences should be revised. Only deviations from the Guidance document are specified.

a. Under Adverse Reactions:

b. Brief Patient Insert
the last paragraph in this section has been deleted and should be replaced into the labeling. It reads '

c. Detailed Patient Labeling
under effectiveness of oral contraceptives,
, should be placed in lower case print.

the female condom and cervical cap should be placed with other methods commonly used in the comparison table for typical failure rates for other birth control methods.

under General Precautions, a fifth paragraph should be added. As in the brief PI, the paragraph should read '

12 **Conclusion**

The sponsor has demonstrated, through a multi-center Phase III clinical trial, the safety and efficacy of Alesse (levonorgestrel 100 mcg and ethinyl estradiol 20 mcg) as an oral contraceptive. This oral contraceptive is the same ratio of estrogen:progestogen as a previously approved product, Nordette.

13 **Recommendations**

Approval with labeling revisions (after concurrence from all disciplines once reviews are completed). The sponsor has updated the Pharmacokinetics section and this will be separately reviewed.

The clinical labeling revisions, as stated above, should be incorporated into the final draft labeling.

Phill H. Price, M.D.
February 26, 1997

Concur: HJolson 3/11/97

This review is 23 pages

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