# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-864**

# MEDICAL REVIEW(S)

5/22/07

Deputy Office Director Memorandum

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|---|---|
| NDA: | 21-864 |
| Tradename: | Lybrel™ |
| Indication: | Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception |
| Dosage Form/Route: | Tablet/Oral |
| Drug/Dose: | 90 µg levonorgestrel/ 20 µg ethinyl estradiol – daily continuous administration |
| Applicant: | Wyeth Pharmaceuticals, Inc. |
| Complete Response received: | August 22, 2006 |
| Major Amendment received: | December 22, 2006 |
| PDUFA Goal Date: | May 22, 2007 |
| Date of Memorandum: | May 22, 2007 |
| Regulatory Action: | Approval |

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**1.0 Background and Regulatory History**

With this Complete Response, Wyeth is seeking approval of a combination oral contraceptive product (Lybrel) with a dosing regimen that consists of daily continuous administration of levonorgestrel (LNG) and ethinyl estradiol (EE). The drug product proposed by Wyeth contains a lower dosage of the progestin drug component, LNG (90 µg), and the same dose of the estrogen drug component, EE (20 µg), as found in the approved drug product Alesse® (100 µg of LNG and 20 µg of EE).

There are currently two other extended cycle contraceptive products on the US market. They are Seasonale and Seasonique. The Seasonale regimen contains LNG 150 µg/EE 30 µg administered on days 1-84, followed by placebo on days 85-91 (hormone free period or HFP). The Seasonique regimen differs from Seasonale only in that the placebo is replaced with tablets containing 10µg of EE.

The original application for NDA 21-864 was submitted on May 27, 2005. Additional clinical information was submitted on March 6, 2006. The March submission was declared a major amendment, resulting in an extension of the PDUFA goal date to June 27, 2006. On June 27, 2006, an Approvable letter was sent to Wyeth containing the following deficiencies and proposed **resolutions**:

"The application does not contain sufficient stability data to support approval of the product manufactured using the revised [redacted] method. b(4)
**Submit 3 months of real time and accelerated stability data on the three lots of drug product manufactured by the revised [redacted] method."**

"Clinical issues remain unresolved. The three primary areas of concern are the pregnancy rate demonstrated in the US trial, the discontinuation rate, and the unpredictable bleeding pattern. Taken together, these three areas of concern create a questionable risk/benefit ratio for Lybrel. **Therefore, we plan to convene a public meeting to receive input from external contraceptive experts and other stakeholders. We believe that this discussion is needed prior to making a final decision regarding the approvability of your application."**

On August 22, 2006, a Complete Response (CR) was received from Wyeth to address the Division's concerns that were communicated in the June 27, 2006 Approvable Letter. In this submission, Wyeth acknowledged the Division's plans to convene a public meeting to receive input from external experts and other stakeholders regarding the clinical issues expressed in the Approvable letter and also included new information to address the CMC deficiency. On December 22, 2006, Wyeth submitted a major amendment including additional information to resolve CMC issues. The PDUFA goal date was thereby extended to May 22, 2007, from the original goal date of February 22, 2007. The information in the CR and major amendment was sufficient for the CMC team to recommend approval.

A public meeting, in the form of a meeting of the Advisory Committee for Reproductive Health Drugs, was held on January 23 and 24, 2007. This meeting discussed current issues which influence the consideration for approval of hormonal contraceptives. The clinical issues of concern which were cited in the June 27, 2006 Approvable Letter were discussed. The deliberations of the Expert Advisors and their responses to the queries of the Division of Reproductive and Urologic Products provided important and relevant information that allowed me to make a decisive evaluation of the clinical issues raised by the data contained in the original submission of NDA 21-864.

It should be noted that the review team (primary medical officer and medical team leader) did not conclude that Lybrel should be approved. I believe that the data submitted with NDA 21-864 provide substantial evidence of the efficacy of Lybrel when used as labeled. The review team disagrees. We do not dispute that Lybrel is safe.

In my June 2006 memorandum in support of the Approvable Action, I stated that "I disagree with the reviewers on many points. However, because their analyses and opinions raise important issues related to women's health, specifically, contraceptive issues, I believe a public forum including outside contraceptive experts and other stakeholders should be convened to further discuss this application."

After attending the January meeting of the Advisory Committee and reviewing the transcripts, I believe that I gained support for the original positions expressed in my June 2006 memo. I now recommend Approval of Lybrel for the reasons elaborated in this memorandum.

I have attempted to summarize the review team's opinions and comments (section 3.0) followed by my responses (section 4.0) to their concerns. One should read their complete memoranda to best understand their positions.

## 2.0 Clinical Contents of NDA 21-864

Two one-year, Phase 3, multicenter, open-labeled studies were submitted with the NDA to support the efficacy and safety of Lybrel™. They were Study 0858A2-313-NA (Canada and the US) and Study 0858A2-315-EU (Europe).

### 2.1 Study 313NA

This was a single-armed study that included healthy women aged 18-49 who were sexually active, at risk of becoming pregnant, and willing to rely upon the LNG 90 μg/EE 20μg continuous use product as their only method of contraception for the duration of the 13–cycle study. Subjects were enrolled from 80 sites in North America (Canada and the US). The study was conducted from February 2003 through September 2004. Two thousand four hundred and two (2,402) subjects were enrolled and 2,134 subjects took at least 1 dose of study drug. Of the 2,134 subjects who took at least 1 dose of study drug, 77% (1646 subjects) were Caucasian, 10.17% (217) were Black, 8.81% (188 subjects) were Hispanic, 1.55% (33 subjects) were Asian, and 0.23% (5 subjects) were identified as other. Forty-three percent (43%) had never been pregnant and 79% were non-smokers. The mean age was 28.8 years, and 1,762 subjects were 35 years of age or younger at the start of enrollment (population used for efficacy calculation). The mean weight and mean body mass index were 70.38 ±16.83 kg and 26.04±6.07 kg/$m^2$, respectively, in the enrolled population.

2.11 Contraceptive Efficacy

The primary endpoint for the evaluation of oral contraceptives has traditionally been the Pearl Index (PI). The Pearl Index is defined as "pregnancies per 100 woman-years of use." It is computed by dividing the number of "on-treatment" pregnancies by the number of at-risk 28-day treatment cycles or pill packs distributed, and multiplying the value by 1300. The effectiveness of a contraceptive can be represented by the Pearl Index (a proportion), and the 2-sided 95% confidence intervals (CI) of the point estimate.

The denominator of the Pearl Index, for studies 313NA and 315 EU consisted of the number of 28-day treatment cycles taken by the study subjects except for those cycles during which:

1. Backup contraception was used (or unknown);
2. Three (3) or more consecutive days of pill were missed, either
   - During current pill pack, or
   - The missed consecutive days spanned the previous pill pack into the current pill pack, ending in current pill pack (current pill pack was to be excluded), or
   - What should have been the start of study drug of the first pill pack only if the subject started taking her first pill on day 4 or later from the start of her menses;
3. Five (5) or more total days of pills were missed in any pill pack;
4. Prohibited medication was taken within a time frame that could affect contraceptive efficacy;
5. The subject was not sexually active (or unknown); or
6. For subjects who became pregnant, any pill pack that began after the Estimated Date of conception (EDC).

For the studies in the submitted NDA, the "on-treatment" pregnancies (numerator of the

PI) was defined as the number of pregnancies in which conception occurred between the start of the study drug through 14 days ( see discussion of this issue in section 4.1 of this document) following the last dose of study drug. Generally the primary analysis for efficacy is the PI calculated for subjects 35 years old and younger population at entry. Women over 35 are primarily included for evaluation of safety. The inclusion of the over 35y/o women in the PI calculation will usually result in a lower PI because of the lower fecundity of this population. The total number of on-treatment pregnancies in Study 313-NA was 23 (all in 35 y/o and under). Using a total of 12,572 pill packs or 28-day treatment cycles (see Table 1), the calculated PI for 313NA is **2.38 (95% CI: 1.51, 3.57).**

**Table 1**

**Number (%) of Pill Packs (i.e., 28-Day Cycles) Excluded from Pearl Index Analyses of Contraceptive Efficacy by Reason: Subjects Aged 35 years or Younger---Sponsor's Table 9.1.2-2**

| Reason | Number (%) |
|---|---|
| Pill packs included | 12,572 ( 82) |
| Pill packs excluded[a] | 2681 ( 18) |
| Backup contraception used (or unknown) | 1393 ( 9) |
| Missed ≥ 3 consecutive pills | 87 (< 1) |
| Missed ≥ 5 pills total in any 1 pill pack | 106 (< 1) |
| Prohibited medication | 222 ( 1) |
| Not sexually active (or unknown) | 1008 ( 7) |
| Pregnant before pill pack start | 16 (< 1) |

a: A pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason for exclusion applied was excluded.

The Advisory Committee members expressed the view that "the Pearl Index, although providing simplicity, is a less desirable analysis method in almost all circumstances. Life table analysis should be standard." The pregnancy rate calculated by the life table analysis for subjects aged 35 years and younger in trial 313NA **is 2.39 (95% CI: 1.57, 3.62)**

2.12 Discontinuations

Of 2,134 subjects who took one dose of the study drug, 921 (43.2%) completed the study. There were 1,213 (56.8%) subjects who discontinued for various reasons (Table 2). Three-hundred and sixty-three 363 (17%) subjects discontinued due to an adverse event (AE). Of these 363 subjects, 181 discontinued due to a bleeding related AE.

**Table 2**

**The Primary Reasons for Discontinuations Sponsor's Table 8.1.1-1**

| Reason | LNG 90 µg/EE 20 µg Continuous-Use Regimen |
|---|---|
| Total | 2134 (100) |
| Completed | 921 (43.2) |
| Discontinued[a] | 1213 (56.8) |
| Accidental pregnancy | 19 (0.9) |
| Adverse event[b] | 363 (17.0) |
| Discontinuation of study by sponsor | 102 (4.8) |
| Investigator request | 11 (0.5) |
| Lost to follow-up | 223 (10.4) |
| Planning pregnancy | 19 (0.9) |
| Protocol violation | 140 (6.6) |
| Subject request | 336 (15.7) |

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.

a: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.

b: Total includes subject 313-091-8311, who did not have a specific event identified on the case report form. Adverse event was listed on the termination record for this subject but no event was specified and no adverse event was identified on the adverse event case report form as the reason for withdrawal.

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2.13 Cycle Control (analysis of patterns of intermenstrual bleeding, breakthrough bleeding, spotting, and the absence of withdrawal bleeding)

The sponsor used the following definitions for vaginal bleeding in the two studies:

- Bleeding: sanitary protection was required;
- Spotting: some bleeding but no sanitary protection was required; and
- Amenorrhea: no bleeding or spotting during the period of interest.

One of the reasons for the development of a continuous use oral contraceptive is that a subject could have sustained amenorrhea or at least significantly reduced vaginal bleeding in order that such bleeding would not interfere with her daily activities. In addition, some believe that by eliminating menses on a monthly basis the symptoms relating to hormone fluctuation during natural menses such as headache, cramping, bloating, emotional disorders could be lessened and thus improve a woman's quality of life.

Table 3 indicates the bleeding pattern of women in 313NA. At cycle 6, 555 (39.6%) of subjects remaining in the trial were amenorrheic. By this time, the number of subjects in the trial had decreased from 2,134 to 1,403.

At cycle 13, 505 (58.7%) of subjects remaining were amenorrheic. At this point in the study, however, more than half of subjects were no longer in the study.

Table 3
Incidence of Amenorrhea and No Bleeding per Pill Pack (28-day cycle). Sponsor Table 9.4.2.2.1-1

| Pill Pack | n | Amenorrhea [a] n (%) | No Bleeding (With or Without Spotting) n (%) |
|---|---|---|---|
| LNG 90 µg/EE 20 µg Continuous-Use Regimen | | | |
| 1 | 2048 | 48 ( 2.3) | 124 ( 6.1) |
| 2 | 1947 | 450 ( 23.1) | 936 ( 48.1) |
| 3 | 1671 | 446 ( 26.7) | 878 ( 52.5) |
| 4 | 1545 | 502 ( 32.5) | 927 ( 60.0) |
| 5 | 1469 | 540 ( 36.8) | 943 ( 64.2) |
| 6 | 1403 | 555 ( 39.6) | 929 ( 66.2) |
| 7 | 1220 | 546 ( 44.8) | 864 ( 70.8) |
| 8 | 1173 | 600 ( 51.2) | 891 ( 76.0) |
| 9 | 1144 | 601 ( 52.5) | 870 ( 76.0) |
| 10 | 1070 | 584 ( 54.6) | 841 ( 78.6) |
| 11 | 1014 | 597 ( 58.9) | 821 ( 81.0) |
| 12 | 977 | 604 ( 61.8) | 816 ( 83.5) |
| 13 | 860 | 505 ( 58.7) | 679 ( 79.0) |

Abbreviations: LNG = levonorgestrel; EE = ethinyl estradiol.
a: Amenorrhea = no bleeding or spotting.

**2.2 Study 315EU**

Study 0858A2-315-EU was a two-armed, open label comparative trial of the LNG 90 µg/EE 20µg continuous use regimen (Lybrel™) vs. a cyclic regimen of LNG 100 µg/EE 20µg for 21 days and placebo on days 22 to 28. The comparator is marketed in the European Union (EU) as Loette® and as Alesse® in the US. Healthy women aged 18-49 who were sexually active, at risk of becoming pregnant and willing to rely upon the study drug as their only method of contraception for the duration of the 13 x 28-day cycle study were eligible for enrollment. Subjects were enrolled from 44 sites in Europe. The study was conducted from March 2003 to October 2004.

Six hundred and fifty-one (651) subjects were randomized and 641 subjects took at least 1 dose of study drug (323 in the LNG 90 µg/EE 20µg continuous use regimen and 318 in LNG 100 µg/EE 20µg cyclic regimen). Of the 641 subjects, 96.4% (618) were Caucasian, 1.4% (9) were Black, 0.8% (5) were Asian and 1.4% (9) of subjects were identified as other. The mean age was 27.35 years. There were 544 subjects in the study population who were 35 years or younger at the time of enrollment. The mean weight and mean body mass index were 63.8 and 22.74 kg/m$^2$, respectively. Sixty-one percent (61%) had no prior pregnancies. Seventy and five tenths percent (70.5%) reported that they were non-smokers.

2.21 Contraceptive Efficacy

A total of 2,564 (89%) pill packs (28-day cycle equivalents) in the continuous-use regimen and 2,733 (88%) pill packs in the cyclic regimen were included in the Pearl Index analyses for 544 subjects who were aged 35 years or younger at the beginning of this study.

The number of pill packs excluded from the Pearl Index calculation is summarized by treatment group and reason for exclusion in Table (4)

Table 4

Number of (%) of Pill Packs (28-day Cycle Equivalents) Excluded from the Pearl Index by Reason for Subjects Aged 35 Years or Younger at Start of Study. Sponsor's Table 9.1.2-1

| | LNG 90 µg/EE 20 µg (n = 2881) | LNG 100 µg/EE 20 µg (n = 3116) |
|---|---|---|
| Total pill packs included | 2564 ( 89) | 2733 ( 88) |
| Total pill packs excluded[a] | 317 ( 11) | 383 ( 12) |
| Backup contraception used | 107 ( 4) | 204 ( 7) |
| Missed ≥ 3 consecutive pills | 16 (< 1) | 21 (< 1) |
| Missed ≥ 5 pills total in any pill pack | 16 (< 1) | 16 (< 1) |
| Prohibited medication | 2 (< 1) | 15 (< 1) |
| Not sexually active or unknown | 195 ( 7) | 158 ( 5) |

a: A pill pack may have been excluded for more than 1 reason. Only the pill packs to which these criteria apply were excluded.

There was one pregnancy (including days 1-14 post treatment), in the continuous regimen (see Table 5) in the 2564 28-day at risk treatment cycles. Therefore the calculated PI for the continuous regimen was **0.51 (95% CI: 0.01, 2.82). The life table analysis is 0.51 (95% CI: 0.07, 3.57).**

There were 3 pregnancies (see Table 5) in the 2,733 28-day cycles among the cyclic regimen treated women which results in a PI of **1.43 (95% CI: 0.29, 4.17).**

Table 5
Summary of the Four Pregnancies in Study 315-EU. Sponsor's Table 9.4.2.1-1

| Subject Number | Classification | Total Duration on Study Medication | Estimated Date of Conception (Relative Day) |
|---|---|---|---|
| | **LNG 90 µg/EE 20 µg Continuous** | | |
| 315-001-0013 | Not classified[a] | 364 | Posttreatment (6 days) |
| | **LNG 100 µg/EE 20 µg Cyclic** | | |
| 315-026-1147 | Method failure | 245 | 211 |
| 315-034-2252 | User failure | 189 | 179 |
| 315-034-2247 | User failure | 294 | 289 |

a: Not classified for the Pearl Index. Subject was compliant with respect to taking study drug within 30 days of EDC (including the posttreatment portion of that 30 day period, when study drug was not taken), and was classified as a method failure for the life table.

2.22 Discontinuations

Overall, 176 (27%) of subjects discontinued from the study: 107 (33%) subjects in the continuous use treatment group and 69 (22%) in the 21-day cyclic regimen (p<0.001). The primary reasons for discontinuations are summarized in the following Table 6.

Table 6
Number (%) of Subjects who Discontinued from the Study by Primary Reason. Sponsor Table 8.1.1-1

| Reason | LNG 90 µg/EE 20 µg n = 323 | LNG 100 µg/EE 20 µg n = 318 | Overall p-Value[a] |
|---|---|---|---|
| Total[b] | 107 (33.1) | 69 (21.7) | 0.001** |
| Accidental pregnancy[c] | 0 (0.0) | 3 (0.9) | 0.122 |
| Adverse event | 72 (22.3) | 31 (9.7) | <0.001*** |
| Investigator request | 1 (0.3) | 2 (0.6) | 0.621 |
| Lost to follow-up | 5 (1.5) | 2 (0.6) | 0.451 |
| Planning pregnancy | 3 (0.9) | 3 (0.9) | 1.000 |
| Protocol violation | 9 (2.8) | 11 (3.5) | 0.656 |
| Subject request | 17 (5.3) | 17 (5.3) | 1.000 |

a: p-Value obtained from the Fisher exact test (2-tail).
b: Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
c: One (1) accidental pregnancy in the LNG 90 mg/EE 20 mg group occurred with an EDC 6 days after the last dose of study drug and therefore, did not discontinue early from the study.
* Statistical significance at the .05, .01, .001 levels is denoted by *, **, ***, respectively.

The difference between treatment groups in the total discontinuations rate is attributable to a difference in withdrawals because of adverse events (p <0.001). Adverse events are the most frequent reason for discontinuation of study drug.

Forty- seven (47) of 72 (65.2%) of the continuous group and 12 of 31 (38.7%) of the cyclic group reported adverse events related to bleeding disorders (menorrhagia,

metrorrhagia, uterine hemorrhage and vaginal hemorrhage).

2.23 Cycle Control

The following Tables (7A, 7B) report the bleeding patterns in the continuous and cyclic group for study 315EU.

Table 7A

Summary of Bleeding Pattern in Continuous Group by Pill Pack Number and Percentage of Subjects. Sponsor Table 9.4.2.2.1-1

| | | | Total | | | | |
|---|---|---|---|---|---|---|---|
| Pill Pack | n | Amenorrhea | Bleeding (With No Spotting) | Spotting (With No Bleeding) | Bleeding and/or Spotting | Bleeding (With or Without Spotting) | No Bleeding (With or Without Spotting) |
| LNG 90 µg/EE 20 µg Continuous | | | | | | | |
| 1 | 317 | 14 ( 4.4%) | 43 ( 13.6%) | 14 ( 4.4%) | 303 ( 95.6%) | 289 ( 91.2%) | 28 ( 8.8%) |
| 2 | 307 | 100 ( 32.6%) | 17 ( 5.5%) | 70 ( 22.8%) | 207 ( 67.4%) | 137 ( 44.6%) | 170 ( 55.4%) |
| 3 | 292 | 79 ( 27.1%) | 16 ( 5.5%) | 68 ( 23.3%) | 213 ( 72.9%) | 145 ( 49.7%) | 147 ( 50.3%) |
| 4 | 281 | 87 ( 31.0%) | 13 ( 4.6%) | 80 ( 28.5%) | 194 ( 69.0%) | 114 ( 40.6%) | 167 ( 59.4%) |
| 5 | 271 | 103 ( 38.0%) | 9 ( 3.3%) | 70 ( 25.8%) | 168 ( 62.0%) | 98 ( 36.2%) | 173 ( 63.8%) |
| 6 | 264 | 97 ( 36.7%) | 11 ( 4.2%) | 71 ( 26.9%) | 167 ( 63.3%) | 96 ( 36.4%) | 168 ( 63.6%) |
| 7 | 240 | 95 ( 39.6%) | 7 ( 2.9%) | 70 ( 29.2%) | 145 ( 60.4%) | 75 ( 31.3%) | 165 ( 68.8%) |
| 8 | 236 | 117 ( 49.6%) | 4 ( 1.7%) | 57 ( 24.2%) | 119 ( 50.4%) | 62 ( 26.3%) | 174 ( 73.7%) |
| 9 | 228 | 119 ( 52.2%) | 2 ( 0.9%) | 54 ( 23.7%) | 109 ( 47.8%) | 55 ( 24.1%) | 173 ( 75.9%) |
| 10 | 226 | 118 ( 52.2%) | 5 ( 2.2%) | 51 ( 22.6%) | 108 ( 47.8%) | 57 ( 25.2%) | 169 ( 74.8%) |
| 11 | 222 | 115 ( 51.8%) | 5 ( 2.3%) | 55 ( 24.8%) | 107 ( 48.2%) | 52 ( 23.4%) | 170 ( 76.6%) |
| 12 | 220 | 124 ( 56.4%) | 3 ( 1.4%) | 54 ( 24.5%) | 96 ( 43.6%) | 42 ( 19.1%) | 178 ( 80.9%) |
| 13 | 210 | 111 ( 52.9%) | 4 ( 1.9%) | 55 ( 26.2%) | 99 ( 47.1%) | 44 ( 21.0%) | 166 ( 79.0%) |

In the continuous group, at cycle 6, 97 of 264 (36.7%) of the remaining subjects are amenorrheic. At cycle 13, 111 of 210 (52.9%) of the remaining subjects are amenorrheic (table 7A).

Table 7B

Summary of Bleeding Pattern in Cyclic Group by Pill Pack Number and Percentage of Subjects. Sponsor Table 9.4.2.2.1-1

| | | | Total | | | | |
|---|---|---|---|---|---|---|---|
| Pill Pack | n | Amenorrhea | Bleeding (With No Spotting) | Spotting (With No Bleeding) | Bleeding and/or Spotting | Bleeding (With or Without Spotting) | No Bleeding (With or Without Spotting) |
| LNG 100 µg/EE 20 µg Cyclic | | | | | | | |
| 1 | 308 | 0 ( 0.0%) | 45 ( 14.6%) | 4 ( 1.3%) | 308 (100.0%) | 304 ( 98.7%) | 4 ( 1.3%) |
| 2 | 296 | 3 ( 1.0%) | 69 ( 23.3%) | 8 ( 2.7%) | 293 ( 99.0%) | 285 ( 96.3%) | 11 ( 3.7%) |
| 3 | 290 | 2 ( 0.7%) | 54 ( 18.6%) | 11 ( 3.8%) | 288 ( 99.3%) | 277 ( 95.5%) | 13 ( 4.5%) |
| 4 | 292 | 4 ( 1.4%) | 56 ( 19.2%) | 16 ( 5.5%) | 288 ( 98.6%) | 272 ( 93.2%) | 20 ( 6.8%) |
| 5 | 284 | 1 ( 0.4%) | 47 ( 16.5%) | 15 ( 5.3%) | 283 ( 99.6%) | 268 ( 94.4%) | 16 ( 5.6%) |
| 6 | 281 | 2 ( 0.7%) | 58 ( 20.6%) | 6 ( 2.1%) | 279 ( 99.3%) | 273 ( 97.2%) | 8 ( 2.8%) |
| 7 | 267 | 6 ( 2.2%) | 54 ( 20.2%) | 10 ( 3.7%) | 261 ( 97.8%) | 251 ( 94.0%) | 16 ( 6.0%) |
| 8 | 266 | 3 ( 1.1%) | 53 ( 19.9%) | 17 ( 6.4%) | 263 ( 98.9%) | 246 ( 92.5%) | 20 ( 7.5%) |
| 9 | 262 | 5 ( 1.9%) | 49 ( 18.7%) | 17 ( 6.5%) | 257 ( 98.1%) | 240 ( 91.6%) | 22 ( 8.4%) |
| 10 | 254 | 1 ( 0.4%) | 45 ( 17.7%) | 8 ( 3.1%) | 253 ( 99.6%) | 245 ( 96.5%) | 9 ( 3.5%) |
| 11 | 255 | 4 ( 1.6%) | 46 ( 18.0%) | 6 ( 2.4%) | 251 ( 98.4%) | 245 ( 96.1%) | 10 ( 3.9%) |
| 12 | 255 | 5 ( 2.0%) | 42 ( 16.5%) | 10 ( 3.9%) | 250 ( 98.0%) | 240 ( 94.1%) | 15 ( 5.9%) |
| 13 | 229 | 3 ( 1.3%) | 44 ( 19.2%) | 23 ( 10.0%) | 226 ( 98.7%) | 203 ( 88.6%) | 26 ( 11.4%) |

Data for the 12 subjects with bleeding data at pill packs 14 and 15 are not shown.

Table 7B is included only to illustrate a typical bleeding pattern observed in a cyclic regimen.

## 3.0 Primary Medical Officer and Medical Team Leader Comments and Conclusions

This section (3.0) includes direct quotes and synopses of comments by the primary medical officer and medical team leader (referred to as the review team) for this product. These comments were written in support of the June 27, 2006 Approvable Action before the January 2007 Advisory Committee meeting. The thinking of the review team has not changed substantially since the Advisory Committee. I have attempted to fairly summarize their views regarding salient issues as expressed in their respective reviews of Lybrel. The reader is referred to the memoranda of the review team for the complete representation of their arguments.

**3.1 Contraceptive efficacy:** The review team believes that, historically, it was accepted that effectiveness for combination oral contraceptive drug product would be established with demonstration of a Pearl Index (method + user failure) of less than 1. In 1975, the Division (then HFD-510) took the issue of approval for Ovcon35 to the Reproductive Health Advisory Committee (AC). At issue was the Pearl Index (1.36) of this combination oral contraceptive containing lower amounts of norethindrone (400 μg) and ethinyl estradiol (35 μg) compared to other conventional combination oral contraceptive products of that time. Following discussions at that AC meeting, the review team believes that a cut-off for Pearl Index of 1.5 to establish effectiveness was adopted and that over the years as the doses of progestin and estrogen anticipated to suppress ovulation have been lowered, the Division-accepted cut-off value for the Pearl Index was allowed to rise to 2.

The review team further believes that during the earlier days of combined oral contraceptives when the drug products consisted of high doses of the estrogen and progestin components, the Division (then HFD-510) determined that because there were so few method failure pregnancies that in order to have reasonably sized clinical trials, effectiveness would be determined by a failure rate (i.e. pregnancy rate) that considered both method and user failures. User failure rates were limited to patients who followed the protocol with minor violations (as in this protocol subjects who missed greater or equal to three consecutive pills or five in a single pill pack were discontinued and their cycles not counted). As the determination was made that oral contraceptives were safe to use into the perimenopausal years (up to age 50), it was decided that effectiveness should be determined not in all women (i.e. up to age 50), but in the sub-group of women who have higher fecundity and are thus at greater risk. Therefore, evaluation of effectiveness was limited to the population of women less than or equal to age 35.

As determined in the primary "proof of efficacy" study, Study 0858A2-313-NA, in women less than or equal to age 35, Lybrel™ has a Pearl Index (method plus user failure pregnancies) of 2.38 (95% CI 1.51, 3.57). The review team states that "When judged against the cut-off value for Pearl Index less than or equal to 2.0, the point estimate and 95% upper bound limit are clearly outside of the limit contemporarily used by the Division to determine effectiveness. In addition, the high proportion of contraceptive failures that are a result of "method failures" is disturbing."

As far as efficacy, it is unclear to the review team as to why there is a difference in the Pearl Index between the US (PI 2.38) and European (PI 0.51) trials. Possible explanations are better patient compliance and lighter weight of the subjects in the European population. It should also be noted that the European trial was less ethnically diverse. The

primary reviewer states that "In conclusion, while the sample size of this small comparative study is *not large enough to assess pregnancy rates*, from an efficacy standpoint, it would appear that women who take Lybrel are not at a greater risk of pregnancy than Alesse."

The sponsor proposed an analysis that would have combined the results of the two trials with a resultant lower PI than in 313NA alone. This analysis was rejected by the review team because they believed that neither the protocol nor the proposed meta-analysis and its statistical plan was proposed by the sponsor a priori, the trial populations were different, and 315EU "was clearly under-powered in terms of a US contraceptive trial."

In the medical team leader's, May 2007 memorandum she states "that even after the contributions made with the discussions at the Hormone Contraceptive General AC (Jan. 2007 AC), I remain concerned that an acceptable level of efficacy (in my opinion) was not demonstrated with the Lybrel application."

**3.2 Discontinuations:** The review team believes that the discontinuation rate from 313NA is the highest that they can find among contraceptive trials for 20 to 30 mcg pills. (Table 8).

Table 8

Study Discontinuation Rates (%) for 20-30 mcg dose OCs

| LN90 EE20 | Alesse * LN 100/ 20EE | Lo-Estrin NET 100 20EE | Mircette DES0 150/EE20 10EE (days 2428) | Cyclessa DESO 100/125/150 EE25 | Ortho TriCyclenLo NORGES 180/215/250 EE25 | Nordette LN150 EE30 | Seasonale LN150 EE30 | YAZ 20DESO 20EE | Lo-Estrin/24* NETA100/ EE20 |
|---|---|---|---|---|---|---|---|---|---|
| 56.8 | 9.0 | 25.6 | 47.0 | 18.2 | 25.6 | 28.8 | 40.6 | 5.6 | 22 |

*6-month cycle trial, some of these discontinuation rates have been complied in more recent comparative trials used to supplement approval of lower dose COCs

The primary reviewer states that;

"The previous highest discontinuation rate presented in a clinical trial was that of Mircette® at 47.0%. Other products range between a low of 5.6% (Yaz®) to 25.6% for Loestrin® and Ortho TriCyclenLo®. All of these products contain 20-25mcg of EE. Note that the discontinuation rate of Lybrel™ is 56.8%."

Of note, the primary reviewer did not take into account the Seasonale rate of 40.6%.

The primary reviewer states in his memorandum of May 2007 that "there is an unacceptable discontinuation rate."

**3.3 Cycle Control:** The review team has concerns regarding the lack of cycle control in the form of irregular bleeding and spotting in subjects using Lybrel. The medical team leader states that in her June 2006 Approvable memo that:

"It is difficult to assess the bleeding associated with one drug product relative to that demonstrated in a separate trial for another product. Various sponsors have utilized different measures to discuss bleeding. However, the extended and continuous cycle regimens would appear to have more unanticipated bleeding than the cyclic regimens which are designed to have an approximately 28-day withdrawal bleed. As stated at the outset of this Discussion section, in addition to providing effective contraception, this product was intended to provide sustained amenorrhea. In the study report for Study 0858A2-313-NA, the Sponsor states "In addition to inhibition of menses, the LNG 90 µg/EE 20 µg continuous use regimen is intended to reduce all types of bleeding and spotting.".

The question is should a Sponsor who purports that their product provides sustained amenorrhea and reduces all types of bleeding and spotting be required to provide the evidence that demonstrate this? My response to this question is yes. The clinical trial data did not demonstrate sustained amenorrhea. At cycle one, 98% of subjects had bleeding and/or spotting. By cycle 13, 40% of subjects had bleeding and/or spotting. While one can say that the percentage of subjects with bleeding and/or spotting improved from cycle 1 to cycle 13, a product that demonstrates 40% of women to have bleeding and/or spotting at one year certainly does not represent sustained amenorrhea or reduced bleeding and spotting.. Another concern to think about is whether with "real world" use, the poor cycle control might lead women to discontinue this drug product thereby increasing the exposure of these women to unintended pregnancies."

The medical team leader further states that:

"In this reviewer's opinion, the enormous public health impact of unintended pregnancies linked to discontinuations of oral contraceptives because of poor cycle control argues heavily against approval of a product with questionable cycle control.

In summary, I agree with the primary clinical reviewer for Lybrel™ and recommend that this product not be approved because of a demonstrated lack of efficacy and poor cycle control. Short of new clinical trial data in the US population which demonstrate an acceptable overall (user failure + method failure) Pearl Index and method failure Pearl Index, I do not believe that the Sponsor can satisfy the doubts regarding the efficacy of this product."

The primary medical officer states in his May 2007 memorandum that Lybrel provides"poor cycle control."

## 4.0 Deputy Office Director Comments and Conclusions

I believe that the January 2007 meeting of the Reproductive Health Drugs AC was important because there has been no public discourse sponsored by FDA for some time that has addressed contraceptive issues and provided guidance to sponsors regarding analyses and conduct of contraceptive trials which may have been inconsistent or evolved due to changing science over the years.

After attending the January AC meeting and reviewing the transcripts, I now recommend Approval for reasons stated below.

**4.1 Contraceptive efficacy:** The reviewers maintain that the PI of 2.38 from study 313 is too high to allow approval of Lybrel because a PI above 2 or perhaps 1.5 indicates that a oral contraceptive is not efficacious.

In my June 2006 memorandum I concluded that "there is no clear regulatory guidance or precedent regarding efficacy standards in the form of the upper limit of the point estimate (or 95% confidence intervals) of PI as calculated from the data derived from contraceptive trials. Furthermore, the point estimate of the PI in trial 313NA is lower than other approved products. In addition, since most contraceptive trials are single armed relying on historical controls, I do not believe one cannot determine whether a PI of 2.38 calculated from data in one trial represents superior, equivalent, or inferior effectiveness compared to another trial in which a product's PI is determined to be 2 or even 1.5."

Discussions from the January 2007 AC meeting addressed these issues and the messages were quite clear. There was a strong consensus that comparisons of efficacy across single armed trials were inappropriate and that, if efficacy comparisons were necessary between products, an active controlled trial should be conducted. The Advisors were asked specifically " For historically controlled trials, should evaluation of pregnancy rate be based only upon the point estimate, the upper bound of the 95% confidence interval around that point estimate, or both? There was extensive discussion of this issue on both days and the Advisors believed that "that arbitrary limits be avoided in order to promote the widest range of new contraceptive products being developed and brought to the market."

The review team rejects the inclusion of trial 315EU in a combined analysis in order to calculate the PI for Lybrel. They also dismissed this trial altogether in terms of supporting efficacy.

I believe that the data from 315EU adds very important supportive information regarding the efficacy of Lybrel. This is especially true because 315EU is an active controlled trial. When the Advisors were asked "Is there a role for active controlled trials" They unanimously answered in the affirmative (YES = 19 NO =O Abstain =0 Total = 19). When asked about the selection of comparator, one of the choices suggested was "a direct comparator, which would have a similar formulation to the proposed product but differ in one aspect (e.g., a different dose of estrogen or a different progestin)." This is the case with 315EU. Lybrel contains a lower dosage of the progestin drug component, LNG (90 µg), and the same dose of the estrogen drug component, EE (20 µg), as found in the approved drug product Alesse® (100 µg of LNG and 20 µg of EE).

Trial 313NA includes about 12,500 cycles in the single continuous treatment arm. Trial 315EU includes about 2,500 cycles in each of the continuous and cyclic treatment arms. Both trials are one year in length (13, 28-day cycles). I do not agree with the review team's assertion that Trial 315 EU is "underpowered." The point estimate and spread of the two-sided 95% confidence intervals reveals the precision of the trial results, regardless of the number of cycles.

While it is problematic to pool the data from trial 315EU and 313NA, I believe that trial 315EU lends strong supportive evidence for the effectiveness of Lybrel. The conduct of trials 315 EU and 313NA were essentially the same. There are population differences that have been mentioned previously but it is also true that all trials differ from each other to

some degree in terms of population and that is why randomized controlled trials are the best method to compare treatments.

The PI for Lybrel in trial 315EU is **0.51 (95% CI: 0.01, 2.82)** and the PI for the cyclic comparator, Alesse (an approved US product) is **1.43 (95% CI: 0.29, 4.17)** indicating that the contraceptive efficacy of Lybrel is comparable to Alesse. The review team asserts that the data indicate very disparate efficacy results for Lybrel, in terms of PI, between 313NA and 315EU. While the point estimate of the PI of Lybrel is higher in 313NA [**2.38 (95% CI: 1.51, 3.57)**] compared to 315EU [**0.51 (95% CI: 0.01, 2.82)**] there is significant overlap between the 95% confidence intervals, therefore the assertion that the efficacy results between 313EU and 315NA are quite different is statistically unsupported.

Much of the concern of the review team regarding the efficacy of Lybrel is based on information on other contraceptive products from cross trial comparisons. Aside from the issues discussed above there are other issues related to trial conduct that may affect efficacy (PI) results in contraceptive trials. Some of these are:

- Differing methods of determining the estimated date of conception (EDC). These methods have become more accurate recently.
- Populations that may differ by such factors as age, weight, compliance, and ethnicity.
- Dose of the product. Lybrel is a low dose product (20μg vs. 30-35μg EE).

The AC members were asked "Should the Division approve lower-dose products that have apparent decreased efficacy and possible decreased risk of serious adverse events as compared to higher-dose products (e.g., 20 pg estrogen vs. 30-35 pg estrogen contraceptive products)?"

The general opinion of the committee was yes. They expressed the view that 20 ug ethinyl estradiol oral contraceptives are still more effective than some marketed, non-hormonal means of contraception (e.g. spermicides, condoms or diaphragms)...The bottom line is that the risks versus benefits need to be conveyed to the patient.

- Variable methods of calculating the PI

Factors that exclude some cycles in the PI calculation such as lack of sexual activity, condom use, pill compliance issues, etc. need to be considered.

There are several factors that determine which pregnancies are, in fact, "on treatment." Should a pregnancy be included in the calculation of the PI only if it occurs during the period that the pills are actually being ingested or should the pregnancy be included in the calculation if the EDC occurs 14 or 7 days after pill ingestion is stopped per protocol (posttreatment)? In general, the AC supported the idea that pregnancies should not be counted after the contraceptive effects have worn off.

I believe that the physiologic alterations affected by Lybrel as demonstrated in phase 2 trials would support counting pregnancies only until 7 days after cessation of treatment. One could further argue, however, that eliminating the pregnancies that occur 1-7 days posttreatment from the calculation of the Pearl Index is also appropriate.

Regarding study 313NA, there were 2 pregnancies 7 to 14 days posttreatment and 2 pregnancies between 1 -7 days posttreatment. I calculated the PI as 2.17 if one discounts the pregnancies which occurred 7-14 days post treatment. If one further discounts the pregnancies that occurred between 1 and 7 days posttreatment, the PI is 1.96.

There was much discussion regarding these issues at the AC meeting. I would refer the reader to the transcript for further elucidation of the thoughts of the Advisors.

**4.2 Cycle control:** The reviewers state that "the cycle control, in the form of sustained amenorrhea, for this continuous use oral contraceptive is poor." I stated in my June 2006 Approvable memo that "My opinion is that the determination of whether cycle control is adequate (or poor) should be made by the woman and her health care provider. As the trials submitted with this NDA progressed, an increasing proportion of women become amenorrheic or reported spotting not requiring any sanitary protection. It is difficult to compare bleeding between trials and certainly even more difficult to compare cyclic and continuous products."

The Advisors were asked during the January 2007 AC meeting "How should the Division assess the impact of unscheduled bleeding on product acceptability?" In response "The committee felt that the FDA should approve products based on their demonstrated safety and efficacy and allow the patient and clinician to determine acceptability..."

In a related question the AC members were asked "In reviewing extended regimens, how should the Division balance a decrease in scheduled bleeding against an increase in unscheduled bleeding?" The response was that "The committee felt the FDA does not need to balance these issues; rather they need to provide the relevant information to patients and clinicians in labeling."

When asked "If the modified or extended dosing regimen does not expose a women to a greater daily or monthly quantity of either hormonal component of an approved and marketed otherwise identical product, does a Sponsor need to meet any criteria other than the criteria for efficacy and safety required for a traditional 21/7 product?" The consensus of he committee was "no."

**4.3 Discontinuations**

The primary and secondary medical reviewers state that "The discontinuation rate of 56.8% is the highest rate the Division has reviewed in regards to a combination oral contraceptive." The review team is referring to study 313NA. The discontinuation rate in 315EU was 33% (22% in the cyclic arm). It may well be that discontinuation rates for extended cycle regimens are higher than for traditional cyclic regimens. In the case of extended cycle products, I suspect that if women are expecting little or no vaginal bleeding, they may become discouraged and drop out of the trial because the desired effect is not achieved. It is relevant to note that trials for both oral and parenteral Progestin only contraceptives, which are know to cause significant "unanticipated bleeding", also have discontinuation rates of this order. The discontinuation rates for the two approved extended cycle regimens, which are taken continuously for 84-days (approximately 3-cycles) as opposed to an indefinite continuous use product such as Lybrel, are 40% for Seasonale and 50% for Seasonique.

Finally, one must remember that caution should be exercised in making cross-trial comparisons regarding discontinuation rates for some of the same reasons that were mentioned regarding cross trial comparisons of Pearl Indices. (See section 4.1)

**4.4 General Conclusion:** The medical team leader states "I agree with the primary clinical reviewer for Lybrel and recommend that this product not be approved because of demonstrated lack of efficacy and poor cycle control...In this reviewer's opinion, the enormous public health impact of unintended pregnancies linked to discontinuations of oral contraceptives because of poor cycle control argues heavily against approval..."

I do not believe that Lybrel has a "demonstrated lack of efficacy" for the reasons that I discussed in section 4.1.

This product provides a specific alteration in cyclical bleeding that many women perceive as positive. It should be determined by the woman and her health care provider after reviewing the facts related to the discontinuations, bleeding patters, and Pearl Index as to whether or not the risks and benefits are appropriate.

## 5.0 Regulatory Action and Labeling

### 5.1 Regulatory Action

Because I conclude that Lybrel is safe and effective for the intended use, I will Approve NDA 21-864. The Acting Director of the Division of Reproductive and Urologic Products (DRUP) concurs with this action.

DRUP has recently initiated a policy of requesting that Applicants for new hormonal contraceptive products conduct a post-approval study to assess thrombotic risk if the new product contains either a new molecular entity or has a dosing regimen that differs significantly from previously approved products. Lybrel is taken daily, without any break in dosing, and therefore represents a new dosing regimen for a combination oral contraceptive. Wyeth has agreed to conduct a post-approval claims database safety study to compare the risk for thromboembolic risks in users of Lybrel compared to the risk in users of cyclic combination oral contraceptives. The study will be of sufficient size to exclude a 2-fold increase in risk.

### 5.2 Labeling

The Division of Reproductive and Urologic Products and The Office of Drug Evaluation III have worked with the sponsor so that labeling for Lybrel provides clear information regarding the efficacy, bleeding patterns, and discontinuation issues. In this way, women and health care providers can make informed decisions regarding this product. The reader is referred to the complete product labeling for Lybrel. Below are a few examples of how information is conveyed.

*The **Clinical Studies** section clearly and completely describes the efficacy and discontinuation rates in the two phase three clinical trials submitted with the NDA. The efficacy is described in terms of a Pearl Index and life table analysis for both total and method failures.*

**Clinical Studies**

The efficacy and safety of Lybrel were studied in 2 one-year clinical trials of subjects age 18-49. There were no exclusions for body mass index (BMI), weight, or bleeding history.

The primary efficacy and safety study (313-NA) was a one-year open-label clinical trial that treated 2,134 subjects in North America. Of these subjects 1,213 (56.8%) discontinued prematurely, including 102 (4.8%) discontinued by the Sponsor for early study closure. The mean weight of subjects in this study was 70.38 kg. The efficacy of Lybrel was assessed by the number of pregnancies that occurred after the onset of treatment and within 14 days of the last dose. Among subjects 35 years or less, there were 23 pregnancies (4 of these occurred during the interval 1 to 14 days after the last day of pill use) during 12,572 28-day pill packs of use. The resulting total Pearl Index was 2.38 (95% CI: 1.51, 3.57) and the one-year life table pregnancy rate was 2.39 (95% CI 1.57, 3.62). Pill pack cycles during which subjects used back-up contraception or were not sexually active were not included in these calculations. Among women 35 years or less who took the pills completely as directed, there were 15 pregnancies (method failures) resulting in a Pearl Index of 1.55 (95% CI: 0.87, 2.56) and the one-year life table pregnancy rate was 1.59 (95% CI 0.95-2.67).

In a second supportive study conducted in Europe (315-EU), 641 subjects were randomized to Lybrel (n=323) or the cyclic comparator of 100 mcg levonorgestrel and 20 mcg ethinyl estradiol (n=318). The mean weight of subjects in this study was 63.86 kg. The efficacy analysis among women 35 years or less included 2,756 Lybrel pill packs and 2,886 cyclic comparator pill packs. There was one pregnancy in the Lybrel group that occurred within 14 days following the last dose. There were three pregnancies in the cyclic comparator group.

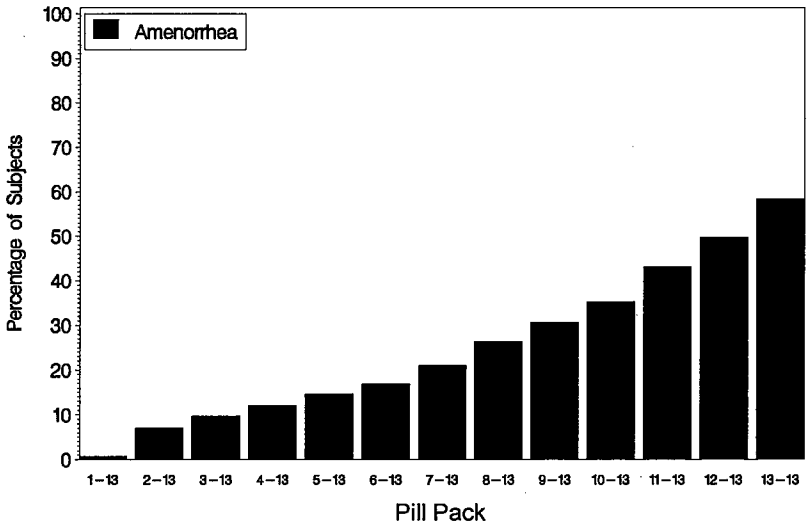
*The material below appears in the **Clinical Studies, Warnings, or Precautions** section and presents data related to amenorrhea and the potential problem that could result in terms of diagnosing pregnancy.*

**Inhibition of Menses (Bleeding Profile)**

The bleeding profile for subjects in Study 313 NA also was assessed. Women with a history of unscheduled bleeding and/or spotting were not excluded from the study.

In those subjects who provided complete bleeding data, the percentage of patients who were amenorrheic in a given cycle and remained amenorrheic through cycle 13 (cumulative amenorrhea rate) was determined (Figure 2).

**Figure 2: Percentage of Subjects with Cumulative Amenorrhea for Each Pill Pack through Pill Pack 13**




The 779 subjects with complete data for all 13 pill packs were used in this cumulative analysis. Subjects were to begin pill pack 1 on the first day of menses.

When prescribing Lybrel, the convenience of having no scheduled menstrual bleeding should be weighed against the inconvenience of unscheduled bleeding and spotting (see **WARNINGS**, 11).

## PRECAUTIONS

### 1. General

Scheduled withdrawal bleeding does not occur with the use of Lybrel, therefore, the absence of withdrawal bleeding cannot be used as a sign of an unexpected pregnancy and as such, unexpected pregnancy may be difficult to recognize. Although pregnancy is unlikely if Lybrel is taken as directed, if for any reason, pregnancy is suspected in a woman using Lybrel, a pregnancy test should be performed.

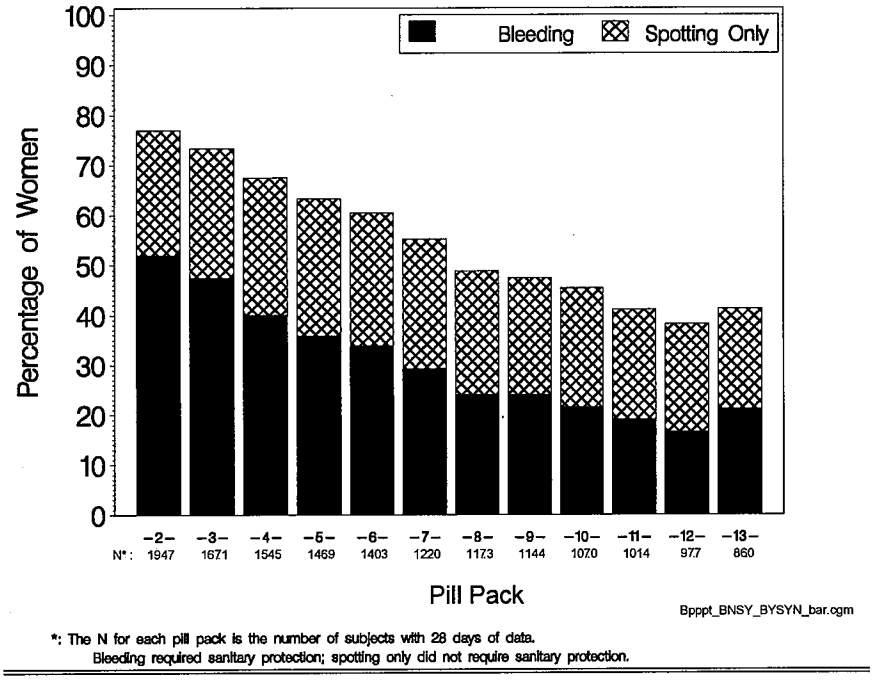
*The following text and graphs address in more detail the bleeding patterns that women can expect with Lybrel*

#### 11. Bleeding Irregularities

When prescribing Lybrel, the convenience of having no scheduled menstrual bleeding should be weighed against the inconvenience of unscheduled breakthrough bleeding and spotting. In Study 313-NA, 385/2,134 (18%) of women discontinued prematurely due to bleeding that was reported either as an adverse event or where bleeding was given as one of the reasons for discontinuation

Figure 4 shows the percentage of Lybrel subjects in study 313-NA by pill-pack who experienced unscheduled bleeding or spotting only (Defined as "No sanitary protection required").

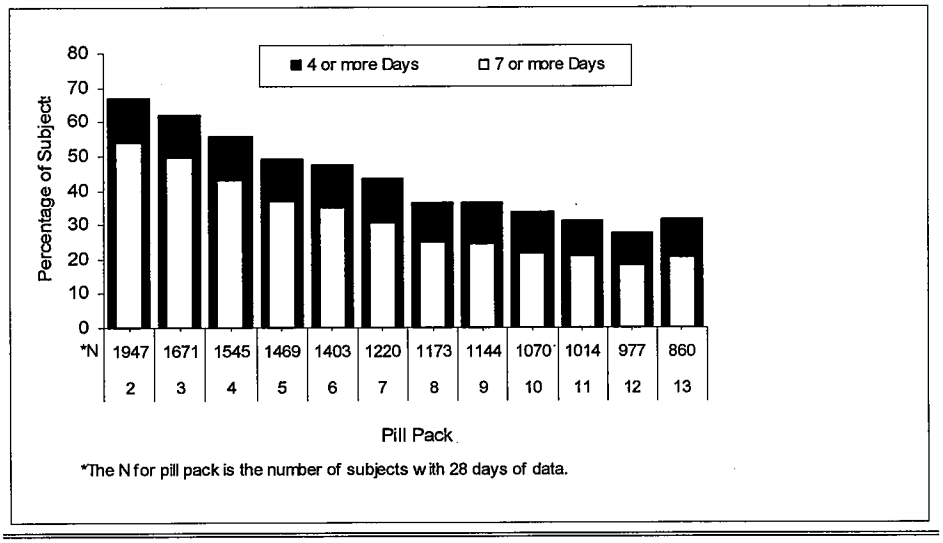
**Figure 4: Percentage of Subjects Reporting Bleeding or Spotting Only per Pill Pack**




*: The N for each pill pack is the number of subjects with 28 days of data.
Bleeding required sanitary protection; spotting only did not require sanitary protection.

Figure 5 shows the percentage of Lybrel subjects with complete bleeding data in Study 313-NA who had 4 or more and 7 or more days of bleeding and/or spotting during each pill pack cycle. During Pill Pack 2, 67% of subjects experienced 7 or more days of bleeding or spotting and 54% of these subjects experienced 7 or more days bleeding and/or spotting. During the final cycle of use of Lybrel (Pill Pack 13), these percentages were 31% and 20%, respectively.

**Figure 5: Percentage of Subjects Reporting Greater than 4 or 7 Days of Bleeding and/or Spotting per Pill Pack (Study 313-NA)**




*The N for pill pack is the number of subjects with 28 days of data.

As in any case of bleeding irregularities, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

*Lybrel is a low dose hormonal contraceptive therefore the effects of Lybrel will not last long after the pills are discontinued. This means women must be particularly careful if they miss or discontinue this product. In the prescriber labeling, the following appears:*

**DOSAGE AND ADMINISTRATION**

To achieve maximum contraceptive effectiveness, Lybrel (levonorgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The possibility of ovulation and conception prior to initiation of medication should be considered. Women who do not wish to become pregnant after discontinuation should be advised to immediately use another method of birth control. The dosage of Lybrel is one yellow tablet daily without any tablet-free interval.

It is recommended that Lybrel tablets be taken at the **same time** each day.

*In the patient labeling the following appears:*

THE RIGHT WAY TO TAKE Lybrel IS TO TAKE ONE PILL **EVERY DAY** AT THE **SAME TIME**.

If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss the more likely you are to get pregnant.

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/s/
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Daniel A. Shames
5/22/2007 04:02:15 PM
MEDICAL OFFICER

5/22/06

# Group Leader Memorandum
# Lybrel™

| | |
|---|---|
| **NDA:** | **21-864** |
| **Drug:** | **Lybrel™** |
| **Dosage Form/Route:** | **Tablet/Oral** |
| **Strength:** | **90 µg levonorgestrel/ 20 µg ethinyl estradiol – daily continuous administration** |
| **Applicant:** | **Wyeth Pharmaceuticals, Inc.** |
| **Original Submission Date:** | **May 27, 2005** |
| **Medical Officer Completion Date:** | **March 22 2006** |
| **Date of Memorandum:** | **May 22, 2006** |

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Background and Regulatory History

With this application, the Sponsor is seeking approval for a daily continuous administration regimen of an oral contraceptive drug product combination of levonorgestrel (LNG) and ethinyl estradiol (EE). This is the first continuous administration contraceptive drug product regimen sought. SEASONALE®, an extended cycle (LNG 150 µg/EE 30 µg active drug administered for day 1-84, followed by placebo day 85-91) oral contraceptives regimen received approval on September 5, 2003. The drug product proposed by Wyeth contains a slightly lower dosage of the progestin drug component, LNG (90 µg), and the same dose of the estrogen drug component, EE (20 µg), as found in the approved drug product Alesse® (100 µg of LNG and 20 µg of EE). The continuous combined formulation for Lybrel™ was intended to provide contraception and sustained amenorrhea.

Drug development for the continuous regimen of Lybrel™ was first discussed in a pre-IND meeting for this product held on April 8, 2002. At that meeting, the Division of Reproductive and Urologic Drug Products (Division) recommended that a standard contraceptive study of at least 10, 000 cycles including at least 200 women exposed for 13 cycles would support the indication of contraception for this continuous use product. The Division also informed Wyeth that if other non-contraceptive indications were to be pursued these would have to be discussed in a separate meeting with the Agency.

IND 65, 693 was opened on August 28, 2002. The initial IND contained two studies: a Phase 2 open label study, Study 0858A2- 208-US, to evaluate the effects of the continuous regimen on ovulation and a Phase 3 open label "proof of efficacy" and safety study, Study 0858A2-313-NA

The Division's comments on the protocol for Study 0858A2-313-NA, sent to the Wyeth in a November 8, 2002 correspondence, included the following:

- A coagulation profile that includes platelets, anti-thrombin-3, factor V Leiden, and Proteins C and S should be incorporated into the baseline, Month 6 and the end of treatment assessments
- Monthly pregnancy test (either at home or in the clinic) between the protocol scheduled clinical assessments should be incorporated into the clinical trial to reduce the possibility that a pregnant subject might be exposed to study drug for more than 100 days
- The CRSS sub-study is *purely exploratory* and can not lead to any product claims. If claims are to be obtained, Wyeth should contact the Division of Neuropharmacology for the PMS indication, and the Division of Antiflammatory, Analgesic, and Ophthalmologic Drug Products for the dysmenorrhea indication
- An interim analysis is not acceptable to support an NDA. Data should be not submitted prior to completion and final analysis of the US Phase 3 study
- Because of the extensive number of exclusions, *it is unlikely that an accurate pregnancy rate will be obtained that is consistent with the general population* that will be taking OCs (e.g., certain antidepressants/anxiolytic and antibiotic drugs which are used significantly in the general population are excluded). If these subjects are excluded, a disclaimer may need to be placed in the label stating these subjects were not studied.

On December 5, 2002, Wyeth responded as follows to the Agency's comments of November 8, 2002 on the Phase 3 protocol:

- All subjects in Protocol 0858A2-313-NA will have their platelets levels evaluated at baseline and at the 6 months and 1 year (end of treatment) assessments; Wyeth will assess anti-thrombin 3, factor V Leiden, ad Proteins C and S in a sub-population
- Wyeth will obtain either at home or in the clinic a pregnancy test during each 28-day pill pack
- Wyeth will consult with the other FDA divisions to discuss the data requirements for product claims
- Data on return to menses will be collected in a separate extension study utilizing subjects who choose to participate and who do not elect to use hormonal contraception when they complete Protocol 0858A2-313-NA
- Wyeth reduced the number of exclusion from previous Wyeth clinical trials of oral contraceptives; one exception is the antidepressant/anxiolytic exclusion; this relates to 308 subjects in the CRSS; the antibiotic exclusion is similar to that in the current label for Alesse®. Wyeth proposed to leave the antibiotic exclusion criterion as stated.

On December 30, 2002, Wyeth submitted additional changes to their Phase 3 protocol:

- Return to menses follow-up was removed from the protocol and will be analyzed in an extension study
- Subject participation was changed from 16 months to 13 months for basic and endometrial histology sub-study subjects, and from 18 to 15 months for cycle-related symptom sub-study subjects
- Study duration was changed from 22 to 19 months
- Hemostasis measures have been added to the endometrial histology sub-study for all subjects at visits 1B, 3 and 4A
- Additional endometrial histology sub-study ---prohibited treatment added
- Subjects will receive home urine pregnancy test kits to check for pregnancy during pill packs in which there are no scheduled visits
- CRSS antidepressants/anxiolytic exclusion has changed to prohibit these medications only during the first 84 days of test article use
- Relevant family history was added to the protocol
- Subjects who withdraw from the study early, who are 40 or older and have not had a mammogram in the past six months must have a mammogram at the early termination visit

On April 25, 2003, the Division sent Wyeth a correspondence withdrawing a previous recommendation to perform an extension study to pursue long-term safety and bleeding patterns. DRUP recommended that Wyeth assess return to menses and fertility in subjects that have been treated with LNG 90µg/EE 20µg continuous use regimen for at least one year.

On August 18, 2003, Wyeth submitted a protocol entitled "A Phase 3 Multi-Center Study to Evaluate the Return to Spontaneous Menses for Subjects Receiving Prior Treatment with a Continuous Daily Regimen of Levonorgestrel and Ethinyl Estradiol for Oral Contraception (Study 0858A2-314-NA).

On September 12, 2003, Wyeth submitted a protocol entitled "Multiple Dose Study for the Pharmacokinetics of Levonorgestrel (90µg and Ethinyl Estradiol (20µg) Administered Orally to Healthy Women (Protocol 106-US).

On September 30, 2003, Wyeth submitted a change to the Phase 3 protocol. A pulse rate measurement at the standing position was added to the vital signs procedures at screening, on days -1, 13, 27, and at the final evaluation.

On July 28, 2004, Wyeth submitted the following changes to their Phase 3 protocol:

- Changes to the Medical Monitor and Clinical Scientists
- Incorporation of region specific changes, changes specific to endometrial histology sub-study, and Canadian one-year extension study
- "Approximately" has been added to the number of subjects to allow for flexibility
- The number of subjects expected to complete the 3-month sub-study (assuming a 3-month 20% dropout rate) is changed from 165 to 246 (typographical error)
- The definition of return to spontaneous menses was incorporated as stated in study protocol
- Information regarding pregnancies has been enhanced to incorporate the Canadian one-year extension study

On August 6, 2004 Wyeth submitted additional changes to the protocol for Study 0858A2-314, including:

- Medical monitor and emergency contacts changed
- Revisions of the synopsis, concomitant treatment changed to be consistent with the Phase 3 protocol (313-NA)
- Revising the protocol, concomitant treatment, and permitted treatment to be consistent with Phase 3 protocol

On September 10, 2004 Wyeth, requested a Pre-NDA meeting and on September 27, 2004, DRUP confirmed a November 22, 2004 Pre-NDA meeting.

On November 8, 2004 (after completion of the clinical trial), in preparation for a discussion at the pre-NDA meeting, Wyeth submitted a statistical analysis plan for Study 0858A2-313-NA as an information amendment to the FDA. No discussions between Wyeth and the Division on this analysis plan were held. The protocol was never amended to incorporate the statistical analysis plan.

On November 10, 2004 the Pre-NDA meeting scheduled for November 22 was cancelled per the Clinical Team Leader's (Dr. Monroe) request. Per the Regulatory letter canceling the meeting, there were no major program-related issues that warranted a Pre-NDA meeting. b(4)

Wyeth acknowledges that the protocol for Study 0858A2-313-NA was amended three times (their dates February 5, 2003, May 15, 2003 and July 1, 2004). None of these amendments substantially affected the determination of efficacy for Study 0858A2-313-NA.

NDA 21-840 for Lybrel™ was submitted by Wyeth on May 27, 2005. It was administratively filed on July 25, 2005.

Clinical

Two one-year, Phase 3, randomized, multicenter, open-labeled studies were submitted with the NDA to support the efficacy and safety of Lybrel™. Study 0858A2-313-NA was the primary "proof-of-efficacy" study intended to support registration in the United States for the combination of LNG 90 µg/EE 20µg in a continuous use regimen (dispensed as 28-day pill packs). The second study, Study 0858A2-315-NA was planned to support registration in Europe. This study was not presented during the pre-NDA as a "proof-of-efficacy" study for US registration. The protocol for this second study was not presented to the Division for review.

Study 0858A2-313-NA

Efficacy

Study 0858A2-313-NA included 2 sub-studies, a 3-month cycle-related symptom sub-study and an endometrial histology subs-study. Healthy women aged 18-49 who were sexually active, at risk of becoming pregnant, and willing to rely upon the LNG 90 µg/EE 20µg continuous use regimen as their only method of contraception for the duration of the 13–cycle study were eligible for enrollment in Study 0858A2-313-NA if all other qualifying criteria were met. Subjects were enrolled from 80 sites in North America (Canada and the US). The study was conducted from February 2003 through September 2004.

Study 0858A2-313-NA involved the randomization of 2,402 subjects. Per the Sponsor 268 subjects did not take study drug and 2, 134 subjects took at least 1 dose of study drug (including 1, 762 subjects who were age 35 year or younger at the start of the study) and constitute the Intent-to-Treat population. Only the less than or equal to age 35 years of age population was analyzed by the Division for the determination of effectiveness.

Of the 2,134 subjects who took at least 1 dose of study drug, 77% (1646 subjects) were Caucasian, 10.17% (217) were Black, 8.81% (188 subjects) were Hispanic, 1.55% (33

subjects) were Asian and 2.34% (5) subjects) were identified as other. The mean age was 28.8 years and 1,762 subjects (83%) were 35 years of age or younger at the start of enrollment into the study. The mean weight and mean body mass index were 70.38 ±16.83 kg and 26.04±6.07 kg/$m^2$, respectively. Forty two and seven tenths percent (42.7 %) had no prior pregnancies. Seventy Nine and four tenths percent (79.4%) reported that they were non-smokers.

Of the 2,134 subjects who took at least 1 dose of study drug, 1,213 (56.8%) discontinued the study drug prematurely. Adverse events [363 of 1,213 (17%)] and lost-to-follow-up [(223 of 1,213 or (10.4%)] were the primary reasons for discontinuation. Of the 363 (17%) subject who discontinued for adverse events, 181 (49.86% of the adverse events) were attributable to bleeding-related adverse events (this will be discussed later in the review).

Per the study report for Study 0858A2-313-NA (page 39), the primary efficacy variable was the number of "on-therapy pregnancies". Pregnancies were classified as "on-therapy" when the EDC occurred between the start of study drug administration and 14 days after stopping study drug. A pregnancy was considered post-therapy when the EDC was more than 14 days after discontinuation of the study drug. Pregnancy rates were computed by means of the Pearl Index and Life Table methods to determine contraceptive effectiveness. A determination for both analyses were made on all subjects who were randomized and considered to have taken medication as well as on subjects who were 35 years of age or younger at the beginning of the study. For determining effectiveness the latter population was used. From the statistical analysis plan (as described on page 46 of the study report for Study 0858A2-313-NA), the Pearl Index was defined as "pregnancies per 100 women-years of use" and was computed by dividing the number of "on-therapy" pregnancies (EDC occurred between the start of study drug and 14 days after stopping study drug) by number of woman-cycles (or 28-day intervals) of observation, then multiplying by 1300. The Pearl Index was treated as a proportion and 2-sided 95% confidence intervals were computed for the overall values as well as for method and user failures. Only pregnancies that occurred before the last day of study drug were classified as method or user failures. Documented pre-therapy and post-therapy pregnancies were not to be included in the Pearl Index or Life table analyses. Analyses of the Pearl Index and Life Table methods included all pill packs, except for pill packs in which the following criteria applied ( a pill pack may have been excluded for more than 1 reason; only the pill pack to which the reason (s) applied were excluded): backup contraception used (or unknown); three (3) or more consecutive days of pills were missed; five (5) or more total days of pills were missed during a pill pack; prohibited medication (sex hormones, other forms of birth control, any hepatic enzyme-inducing drugs, 14 days of anti-infectives that alter the intestinal flora and drugs requiring the simultaneous use of contraceptives in their labeling); subjects not sexually active (or activity unknown) and subject became pregnant before the start of the pill pack (i.e. any pill pack that began after the EDC was excluded).

A total of 18, 710 cycles were reported for the 2,134 subjects in the total study population. Of the total number of cycles reported, 15, 461 (83%) were included in the Sponsor's analysis of the Pearl Index and 11,295 (60%) were included in the Life Table

analysis of effectiveness. Data from 3,249 cycles (17% of total) were excluded from the calculation of the Pearl Index and data from 7,415 cycles (40% of total) were excluded from the calculation of the Life Table method because the cycle met one or more of the pre-specified exclusion criteria (see preceding paragraph). Only the cycles to which the reason applied were excluded from the analyses of the Pearl Index, and that cycle plus any subsequent cycles were excluded from the life table analyses. The most common reasons for exclusion of a cycle were use of backup contraception (9%) and not sexually active (or sexual activity unknown).

A total of 15, 253 cycles were reported for 1,762 subjects in the subgroup 35 years of age or younger. Of the total cycles reported in this subgroup 12,572 (82% of total cycles) were included in the Pearl Index analysis and 9, 180 (60% of total cycles) were included in the Life Table analysis of effectiveness. The data from 2,681 cycles (18% of total cycles) were excluded from the Pearl Index analysis and 6,073 cycles (40% of total cycles) were excluded from the Life table analysis of the subjects 35 years of age or younger.

The Sponsor's determined that there were 23 accidental pregnancies occurring during the "on therapy" time period (stop of study drug + 14 days). Of these accidental pregnancies, 15 were classified as Method failures, 4 were classified as User failures and 4 were unclassified and happened within the 14 days post discontinuation of study drug. Table 1 presents the Sponsor-identified pregnancies and their classification.

Table 1 – Sponsor-identified Pregnancies during "on-therapy" time period[a]- Study 0858A2-313-NA

| Subject | Pregnancy Classification | Total Duration of Study Drug | Estimated Date of Conception – relative to study drug duration |
|---|---|---|---|
| 313-019-1102 | Method failure[b] | 340 | |
| 313-025-1735 | Method failure[b] | 168 | |
| 313-0303-2210 | Method failure[b] | 74 | |
| 313-034-2604 | Method failure[b] | 139 | |
| 313-044-3610 | Method failure[b] | 364 | |
| 313-047-3931 | Method failure[b] | 259 | |
| 313-051-4313 | Method failure[b] | 148 | |
| 313-052-4416 | Method failure[b] | 133 | |
| 313-057-4924 | Method failure[b] | 136 | |
| 313-064-5612 | Method failure[b] | 196 | |
| 313-064-5627 | Method failure[b] | 79 | |
| 313-064-5643 | Method failure[b] | 247 | |
| 313-084-7604 | Method failure[b] | 308 | |
| 313-091-8312 | Method failure[b] | 364 | |
| 313-098-9714 | Method failure[b] | 84 | |
| 313-070-6224 | Not classified[d] | 56 | Post-stop date of test article – |
| 313-079-7109 | Not classified[d] | 334 | Post-stop date of test article – |
| 313-074-6614 | Not classified[d] | 186 | Post-stop date of test article – |
| 313-024-1603 | User failure[c] | 185 | |
| 313-029-2127 | User failure[c] | 72 | |
| 313-074-6611 | User failure[c] | 51 | |
| 313-086-7817 | User failure[c] | 334 | |
| 313-072-6440 | Not classified[e] | 84 | Post stop date of test article- |

b(4)

[a]From Sponsor table 9.4.2.1-1

[b]Method Failure – the subject took 100% of her assigned dose within the 30 days before the estimated date of conception and did not take any prohibited medication

[c]User Failure – the subject was compliant with the protocol (could have missed up to 2 consecutive days of pills or up to 4 total pills during the 30days before the estimated date of conception) and did not take prohibited medication.

[d]Unclassified as Method or User Failure for the Pearl Index, but classified as a Method Failure for the life table analysis. Subject was 100% compliant with respect to taking study drug within 30 days before the EDC. EDC post stop of the test article.

[e]Not classified as Method or User Failure for the Pearl Index, but classified as a User failure for the Life Table analysis. Subject was compliant per the protocol missed up to 2 consecutive days of pills or up to 4 total pills in the 30 days before conception.

All of the 23 pregnancies identified by the Sponsor for consideration of efficacy as occurring "on therapy" (i.e. those occurring between the start of the test article to stop of test article +14 days) were in subjects 35 years of age or less. Based on the above noted pregnancies and eligible cycles, the Sponsor determined a total population (women age 18 -49) Pearl Index and Life Table analysis of 1.93 (95% CI 1.23, 2.90) and 0.0297, respectively. In the total population, the Pearl Index attributed solely to method failure was 1.26 (95% Confidence Interval 0.71, 2.08) and the Life Table analysis of failure rate was 0.0240. In the population of subjects 35 years of age or younger (the population considered for effectiveness), the Sponsor determined Pearl Index and Life Table analysis of 2.38 (95% CI 1.51, 3.57) and 0.0348, respectively. In the population of subjects 35 years of age or younger, the Pearl Index attributed solely to method failure was 1.55

(95% Confidence Interval 0.87, 2.56) and the Life Table analysis of failure rate was 0.0278. Of note, three of the four pregnancies who were unclassified with respect to Pearl Index occurred in women who had been 100% compliant with test drug and conceive 1, 8 and 12 days, respectively after discontinuing the drug.

The Medical Officer's review identified 9 additional pregnancies (not considered by the Sponsor as occurring on therapy) that he investigated to determine whether or not they occurred during the "on-therapy" time period or outside of this period. The adjudication process for these 9 pregnancies is summarized below in Table 2.

Table 2 - Additional Pregnancies Reviewed by the Medical Officer To Determine Whether They Occurred "On-Therapy" For Consideration of Effectiveness

| Study Subject | LMP (before study start) | Start OCP | Stop OCP | Clinic Visits | Pregnancy Evaluation | | | Calculated Date of Conception | On Treatme Period |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | S/U hCG date | Ultrasound 1st Tri | Ultrasound 2nd Tri | | |
| 313-067-5924 | | ?-start enrolled - 4-09-03 | Unused test article not returned 3 cycles (84 days) | | | | | | |
| 313-091-8347 | | ?-start enrolled 7-18-03 | Unused test article not returned 3 cycles (84 days) | | | | | | |
| 313-074-6604 | | 6/1/03 – NM 6/29/03- 2M NC 7/27/03 – NM 8/24/03 1M 9/21/03 – 1M 10/19/03 – NM 11/16/03 - !M 12/14/03 – 1M 1/11/04 – 1M 2/8/04 – NM | ??3/6/04 5/31/04 | | | | | | b(4) |
| 313-039-3159 | | 8-24-03 | 2/26/04 | | | | | | |
| 313-034-2607 | | 5/23/03(1) -NM 6/20/03 NM 7/18/03 – NM 8-15-03 - NM 9/12/03 - NM 10/10/03 – NM 11/7/03 – NM 12/5/03 – NM 1/2/04 – | 5/20/04 | | | | | | |

| Study Subject | LMP (before study start) | Start OCP | Stop OCP | Clinic Visits | Pregnancy Evaluation | | | Calculated Date of Conception | On Treatme Period |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | S/U hCG date | Ultrasound 1st Tri | Ultrasound 2nd Tri | | |
| | | NM 1/30/04 - NM 2/27/04 – NM 3/26/04 – NM 4/23/04 - Nm | | | | | | | |
| 313-001-8578 | | 9/7/03(1) 10/5/03(2) 11/2/03(3) | 11/18/03 incompl. pack day-17 – | | | | | | |
| 313-011-0323 | | 8/9/03(1) – Nm 9/6/03(2) - NM P3-NR 11/01/03( 4) - 4M | 11/26/03 | | | | | | |
| 313-052-4421 | | 6/29/03 – NM 7/27/03 - NM 8/25/03 - NM 9/17/03 - NM 10/14/03 - NM 11/11/03 – NM 12/10/03 – NM 1/9/04 – NM 2/6/04 – NM 3/5/04 – NM 3/19/04 – NM 4/17/04 – NM 5/15/04 – | 6/11/04 | | | | | | b(4) |
| 313-052-4421 Cont. | | | | | | | | | |

| Study Subject | LMP (before study start) | Start OCP | Stop OCP | Clinic Visits | Pregnancy Evaluation | | | Calculated Date of Conception | On Treatme Period |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | S/U hCG date | Ultrasound | | | |
| | | | | | | 1st Tri | 2nd Tri | | |
| | | NM | | | | | | | |
| 313-029-2118 | | ? | Poor study documentation received. Terminate - day 87 because missed 3 days of pills | ? | Reported pregnant and then stated as a mistake | | | ? | ? |

b(4)

CH - changed
M – missed
NC – not consecutive
NM – none missed
NR – not returned
S – serum
U – urine
US - ultrasound

Appears This Way
On Original

Of the 9 pregnancies considered, 7 were judged by the Clinical reviewing team as most likely occurring during the "on-therapy" time period. Based on these 7 additional pregnancies, the statistical reviewer has determined the following Pearl Index values and Failure rates (Life Table analysis). See Table 3 and 4 below.

Table 3
Reviewer-Determine Pearl Index (95% Confidence Interval) for Total Subjects and Subjects Aged ≤35 years old:
Study 313-NA.

| Pregnancies classification | Analysis Population | Number of | | Pearl Index[a] (95% CI) |
|---|---|---|---|---|
| | | Pregnancies | Pill Packs | |
| "on-therapy" (stop of study drug to 14 days post) | All Ages (18-49): Modified ITT (FDA)** | 30 | 15463 | 2.52 (1.70, 3.59) |
| | Aged ≤35: Modified ITT (FDA2)** | 30 | 12574 | 3.10 (2.09, 4.41) |

[a] Pearl Index = # of Pregnancy x 1300/# Pill packs.
[b] Modified FDA2 ITT- Includes 7 additional pregnancies (2 without test article documentation, 5 occurring during the period of time from stop of medicine to 14 days).

Table 4

Reviewer-Determined Life Table Analysis*: Accidental Pregnancies Cumulative Termination Rate: Study 313-NA
(Taking into consideration 5 additional "on-treatment" pregnancies

| Pill Pack | Cumulative Termination Rates (95% confidence Interval) | |
|---|---|---|
| | Total Population | 35 years or Younger |
| 1 | 0.0025 (0.0010, 0.0068) | 0.0031 (0.0012, 0.0082) |
| 2 | 0.0046 (0.0022, 0.0097) | 0.0056 (0,0027, 0.0117) |
| 3 | 0.0071 (0.0038, 0.0131) | 0.0085 (0.0046, 0.0158) |
| 4 | 0.0080 (0.0044, 0.0145) | 0.0097 (0.0053, 0.0175) |
| 4 | 0.0122 (0.0073, 0.0204) | 0.0148 (0.0089, 0.0248) |
| 6 | 0.0134 (0.0081, 0.0220) | 0.0162 (0.0099, 0.0267) |
| 7 | 0.0159 (0.0099, 0.0255) | 0.0194 (0.0121, 0.0311) |
| 8 | 0.0159 (0.0099, 0.0255) | 0.0194 (0.0121, 0.0311) |
| 9 | 0.0189 (0.0120, 0.0298) | 0.0232 (0.0147, 0.0365) |
| 10 | 0.0206 (0.0132, 0.0321) | 0.0253 (0.0162, 0.0394) |
| 11 | 0.0242 (0.0157, 0.0372) | 0.0298 (0.0194, 0.0458) |
| 12 | 0.0300 (0.0199, 0.0451) | 0.0371 (0.0246, 0.0557) |
| 13 | 0.0342 (0.0230, 0.0506) | 0.0423 (0.0284, 0.0626) |
| 14 | 0.0342 (0.0230, 0.0506) | 0.0423 (0.0284, 0.0626) |

* Source: Sponsor's submission dated, 2/16/06. Results reflect Modified FDA1 ITT - which includes 5 additional pregnancies occurring during the period of time from stop of medicine to 14 days. The two pregnancies that are questioned as to whether or not they occurred before the start of drug therapy have not been included in this analysis because the analysis was including these subjects was not received from the Sponso.

*Late* in the review cycle, the Sponsor provided additional information on all 9 of the adjudicated pregnancies. The additional information was provided during a "face-to-face" meeting with the Division on March 8, 2006 and in a submission to the EDR on March 14, 2006. This information was reviewed in this current review cycle. Based on this newly provided information as outlined in Table 5, the Clinical team determined that only the original 23 pregnancies as identified by the Sponsor as occurring on treatment should be considered for Efficacy in Study 0858A2-313-NA.

Table 5 – Adjudication of the Nine Additional Pregnancies Based on New Information Provided By The Sponsor Late in the Review Cycles

| Study Subject | On Treatment Period | Calculated date of conception-from original information | Pregnancy Examination – New Information | | | Date of Conception based on new information | Final Decision On Treatment<br><br>Yes or No |
|---|---|---|---|---|---|---|---|
| | | | S/U hCG date | Ultrasound 1st Tri | Ultrasound 2nd Tri | | |
| 067-5924 | Certified receipts documenting attempt to have subject return test product | | | | | | No |
| 091-8347 | Certified receipts documenting attempt to have subject return test product | | | | | | No |
| 074-6604 | 6/14/04 | | | | | | No |
| 039-3159 | 3/12/04 | | | | | | No |
| 034-2607 | 6/3/04 | | | | | | Borderline/No |
| 001-8578 | 12/02/03 | | | | | | No |
| 011-0323 | 12/10/03 | | | | | | No |
| 313-052-4421 | 6/25/04 | | | | | | No |
| 313-029-2118 | a | | | | | Notarized documentation subject was never pregnant | |

b(4)

Cycle Control (analysis of patterns of intermenstrual bleeding, breakthrough bleeding and spotting and the absence of withdrawal bleeding)

Cycle control was considered in the secondary efficacy variable analysis. The applicant analyzed cycle control as:

- The incidence of amenorrhea (no bleeding or spotting) with 95% confidence intervals for each of the 13 pill packs(28-day intervals) and 4 reference periods (90-day intervals) beginning on day 1 of the study.

- The incidence of no bleeding (with or without spotting) with 95% confidence intervals for each of the 13 pill packs (28-day intervals) and 4 reference periods (90-day intervals) beginning on day 1 of the study.

At pill pack 1 the incidence of Amenorrhea was 2.3% (i.e. 97.7% of subjects had bleeding and/or spotting). By cycle 6, the incidence of bleeding and/or spotting was 60.4 % subjects. By cycle 13, the percentage of subject with bleeding and or spotting had improved but it still represented a significant percentage of subjects at 41.3%. Recall that only 43.2% of the subjects were still in the study at cycle 13.

The baseline mean and mean change over time in hemoglobin and hematocrit levels were calculated. During pill pack 7 a significant ($p < 0.001$) decrease from baseline in hemoglobin was reported. There was a mean difference of -0.75(±7.14g/L). By the post-treatment evaluation, mean hemoglobin -0.36(±7.93g/L) was *lower* (although *not significantly*) than baseline supporting the view that subjects were bleeding.

Safety

Study 0858A2-313-NA had 2, 457 subjects exposed to the LNG 90 µg/EE 20µg continuous use regimen (Lybrel™). One death occurred in the study secondary to an ovarian germ cell teratoma. This death was unrelated to study drug administration. Twenty seven additional subjects experienced one or more serious adverse events. Seven events occurring in 6 subjects were considered as possibly or definitely related to study drug use. The clinical team agrees with this assessment for these subjects. These adverse events included 1 case of ectopic pregnancy, 1 case of deep venous thrombosis + pulmonary emboli, 2 cases of cholecystitis (1 with cholelithiasis) and 1 case of uterine fibroids. Twenty one additional subjects had serious adverse events which were considered by the sponsor as probably not or definitely not due to the study drug. Of these twenty one subjects, the Clinical team is reclassifying 4 of these subjects as having serious adverse events that are probably secondary to study drugs. The serious adverse events reclassified as probably related to the study drug in these 4subjects included uterine fibroids (2), biliary pain/gallbladder attack/ cholecystitis (2). Two additional subjects with depression (one severe with suicidal ideation) were reclassified as possibly related to study drug. Thirty percent (30%) of subjects were noted to have headaches and 12 % of subjects were noted to have nausea. None of the adverse events were unexpected for a combined OC product. The common adverse events of headache and

nausea were felt to be slightly higher than in other studies with LNG as the progestin product.
Among the changes in laboratory findings, it was noted that by cycle 7 there was a significant ($p<0.001$) drop in hemoglobin, with a mean difference of -0.75(±7.14g/L) relative to baseline.

Study 0858A2-315-EU

Study 0858A2-315-EU was an open label comparative trial of the LNG 90 µg/EE 20µg continuous use regimen (Lybrel™) vs. a cyclic regimen of LNG 100 µg/EE 20µg for 21 days and placebo, D22-28. The comparator is marketed in EU as Loette® (Alesse® in the US). Healthy women aged 18-49 who were sexually active, at risk of becoming pregnant and willing to rely upon the study drug as their only method of contraception for the duration of the 13–cycle study were eligible for enrollment in Study 0858A2-315-EU, if all other qualifying criteria were met. Subjects were enrolled from 44 sites in Europe (40 sites were used for the basic study and 4 sites conducted a metabolic substudy). The study was conducted from March 2003 to October 2004.

Study 0858A2-315-EU involved the randomization of 651 subjects. Per the Sponsor 10 subjects did not take study drug (some of these subjects are disputed) and 641 subjects took at least 1 dose of study drug (323 in the LNG 90 µg/EE 20µg continuous use regimen and 318 in LNG 100 µg/EE 20µg cyclic regimen) and constitute the Intent-to-Treat population. Only the less than or equal to age 35 years of age population was reviewed for a determination of Pearl Index and Life Table analysis of efficacy in this study.

Of the 641 subjects 1.4% (9) were Black, 0.8% (5) were Asian and 1.4% (9) of subjects were identified as other. The degree of racial diversity in this trial was markedly different than in Study 0858A2-313-NA. The mean age was 27.35 years. This was not substantially different than in Study 0858A2-313-NA. There were 544 subjects in the study population who were 35 years or younger at the time of enrollment. The mean weight and mean body mass index were 63.8 kg and 22.74 $kg/m^2$, respectively. The population studied in the European trial was substantially leaner than the population in the US trial. Sixty-one and one tenth percent (61.1%) had no prior pregnancies. Seventy and five tenths percent (70.5%) reported that they were non-smokers.

Of the 641 subjects who took at least 1 dose of study drug, 176 subjects (27%) discontinued the study drug prematurely. The discontinuation rate in the continuous use regimen arm was 33% (107 subjects) while the discontinuation rate in the cyclic regimen was 21.7% (69 subjects.). In the continuous regimen arm 22.3% of the total discontinuations were for adverse events (72 of 107) and 5.3% were due subject request (17 of 107). These were the most frequent reasons for discontinuations. The corresponding figures for the cyclic regimen were 9.7% for adverse events and 5.3% for subject request. Of the 72 subject who discontinued for adverse events, 47 (65 % of the discontinuations for adverse events) of these were for bleeding-related adverse events (menorrhagia 1.2%, metrorrhagia 8.7%, uterine hemorrhage 0.9% and vaginal hemorrhage 3.7%). Thirty-Eight and seven tenths percent [38.7% (12 out of 31)] of the

subjects who discontinued for adverse events on the cyclic regimen did so because of bleeding-related adverse events.

A total of 3,461 cycles were reported for the 323 subjects in the total study population for the continuous use regimen. Of the total number of cycles reported, 3,072 (89%) were included in the Sponsor's analysis of the Pearl Index and 2,360 (68%) were included in the Life Table analysis of effectiveness. Data from 389 cycles (11% of total) were excluded from the calculation of the Pearl Index and data from 1,101 cycles (32% of total) were excluded from the calculation of the Life Table method because the cycle met one or more of the pre-specified exclusion criteria (see preceding paragraph). A total of 3,698 cycles were reported for the 318 subjects who took the cyclic regimen. Of the total number of cycles reported, 3,270 cycles (88%) were included in the Sponsor's analysis of the Pearl Index and 2,627 cycles (71%) were included in the Life Table analysis of effectiveness. Data from 428 cycles (12%) were excluded from the calculation of the Pearl Index and data from 1,071 cycles (29%) were excluded from the calculation of the Life Table method because the cycle met one or more of the pre-specified exclusion criteria. Only the cycles to which the reason applied were excluded from the analyses of the Pearl Index, and that cycle plus any subsequent cycles were excluded from the life table analyses. The most common reasons for exclusion of a cycle were use of backup contraception (13% vs. 17%) and not sexually active or sexual activity unknown (17% vs. 10%) in both the continuous use regimen and cyclical regimen, respectively.

In the subgroup 35 years of age or younger, a total of 2,881 cycles were reported in the continuous use regimen and 3,116 cycles in cyclic regimen. In the continuous use regimen, 2,564 (89%) were included in the Sponsor's analysis of the Pearl Index and 1,977 (68%) were included in the Life Table analysis of effectiveness. Data from 317 cycles (11% of total) were excluded from the calculation of the Pearl Index and data from 904 cycles (31% of total) were excluded from the calculation of the Life Table. Of the total 3,116 cycles reported for the less than or equal to age 35 on the cyclic regimen, 2,733 cycles (88%) were included in the Sponsor's analysis of the Pearl Index and 2,180 cycles (69%) were included in the Life Table analysis of effectiveness. Data from 383 cycles (12%) were excluded from the calculation of the Pearl Index and data from 936 cycles (30%) were excluded from the calculation of the Life Table method. The most common reasons for exclusion of a cycle were use of backup contraception (13% vs. 18%) and not sexually active or sexual activity unknown (16% vs. 11%) in both the continuous use regimen and cyclic regimen, respectively.

The Sponsor's determined that there were 4 accidental pregnancies occurring during the "on therapy" time period (stop of study drug + 14 days) of the study. Of these 4 accidental pregnancies, 1 was on the continuous use regimen and the remaining three were on the cyclic regimen. One (1) was classified as a Method failures, 2 were classified as User failures and 1 was unclassified (the single continuous use pregnancy) and happened (post-treatment day 6) within the 14 days post discontinuation of study drug. Table 6 presents the Sponsor identified pregnancies and their classification

Table 6 – Sponsor-identified Pregnancies during "on-therapy" time period[a] – Study 315 EU.

| Subject | Pregnancy Classification | Study Drug | Total Duration of Study Drug | Estimated Date of Conception – relative to study drug duration |
|---|---|---|---|---|
| 315-001-0013 | Not classified[b] | LNG 90µg/EE 20µg Continuous | 364 | Post stop date of test article |
| 315-026-11475 | Method failure[c] | LNG 100µg/EE 20µg Cyclic | 245 | |
| 315-034-2252 | User failure[d] | LNG 100µg/EE 20µg Cyclic | 189 | |
| 313-034-2604 | User failure[d] | LNG 100µg/EE 20µg Cyclic | 294 | |

b(4)

[a]From Sponsor table 9.4.2.1-1

[b]Unclassified as Method or User Failure for the Pearl Index, but classified as a Method Failure for the life table analysis. Subject was 100% compliant with respect to taking study drug within 30 days before the EDC. EDC post stop of the test article.

[c]Method Failure – the subject took 100% of her assigned dose within the 30 days before the estimated date of conception and did not take any prohibited medication

[d]User Failure – the subject was compliant with the protocol (could have missed up to 2 consecutive days of pills or up to 4 total pills during the 30days before the estimated date of conception) and did not take prohibited medication.

Based on the above noted pregnancies and eligible cycles, the Sponsor determined a total population (women age 18 -49) Pearl Index and Life Table analysis of 0.42 (95% CI 0.01, 2.36) and 0.0095, respectively for the continuous use regimen. The corresponding values for the cyclic regimen were Pearl Index 1.19 (95% CI 0.00, 1.56) and Life Table analysis 0.148. In the total population, the Sponsor calculated Pearl Index attributed to solely to method failure was 0.00 (95% Confidence Interval 0.71, 2.08). Of note, the single noted pregnancy occurred 6 days post-stopping of the test drug in a woman who was determined to have been 100% compliant (i.e. used the drug perfectly) on the test drug. . In the population of subjects 35 years of age or younger (the population considered for effectiveness), the Sponsor determined Pearl Index and Life Table analysis of 0.51 (95% CI 0.01, 2.82) and 0.0110, respectively for those subjects on the continuous regimen. The corresponding values for the cyclic regimen were Pearl Index 1.43 (95% CI 0.29, 4.17) and Life Table analysis 0.0180. In the population of subjects 35 years of age or younger, the Pearl Index attributed solely to method failure was 0.00 (95% Confidence Interval 0.00, 1.87).

This trial was not intended to support effectiveness in the US. It is markedly underpowered in terms of a US study to support contraception which requires 10,000 cycles and at least 200 subjects completing 13 cycles. While 216 subjects completed 13 cycles on the continuous use regimen, only 2,564 and 1,977 cycles were available to assess the Pearl Index and Life Table method of analysis of failure rates, respectively.

Cycle Control (analysis of patterns of intermenstrual bleeding, breakthrough bleeding and spotting and the absence of withdrawal bleeding)

Cycle control was considered in the secondary efficacy variable analysis. The applicant analyzed cycle control as:

- The incidence of amenorrhea (no bleeding or spotting) with 95% confidence intervals for each of the 13 pill packs (28-day intervals).
- The incidence of no bleeding (with or without spotting) with 95% confidence intervals for each of the 13 pill packs (28-day intervals).

At pill pack 1 the incidence of Amenorrhea was 4.4% (i.e. 95.6% of subjects were bleeding). By cycle 6, the incidence of bleeding and/or spotting was 63.3 % subjects. By cycle 13, the percentage of subject with bleeding and or spotting had improved but it still represented a significant percentage of subjects at 47.1%. The comparator product was a cyclic regimen product with *expected* withdrawal bleeding during the hormone free interval. Therefore, a high percentage of subjects demonstrated bleeding at each cycle. The Sponsor did not provide a rate of *unexpected* bleeding for the comparator.

Safety

Study 0858A2-315-EU had 313 subjects exposed to the LNG 90 µg/EE 20µg continuous use regimen (Lybrel™). No deaths occurred in the study. There were 6 subjects with serious adverse events in the Lybrel™ continuous use group. Only one of these subjects was determined by the Sponsor to have had a serious adverse probably or possibly related to the drug. The clinical team concurs with this.

Integrate Clinical Safety

The safety database for subjects exposed to the LNG 90µg/EE 20µg continuous-use regimen in this NDA is comprised of 2,528 subjects, including 18 subjects in a Phase 1 study (106-US), 58 subjects in a Phase 2 study (208-US), 2,134 subjects in Phase 3 Study 0858A2-313-NA, and 318 subjects in a Phase 3 Study 0858A2-315-EU. In the pooled Phase 3 studies, there were 22, 171 cycles of exposure and 1,137 subjects who completed 13 cycles of use among those subjects who received continuous-use LNG 90µg/EE 20µg. These parameters of drug exposure exceed the Agency's requirement specified in the Guidance for oral contraceptive development. The following points (from the Primary Clinical Review) summarize the major safety findings from the review of the integrated summary of safety:

- There were 13 serious adverse events that the Clinical review team considered to be a least possibly related to the LNG 90µg/EE 20µg continuous –use regimen. These serious adverse events were consistent with those observed with other low dose oral contraceptives.
- Adverse events related to vaginal bleeding, including dysmenorrhea, metrorrhagia, and vaginal hemorrhage, were the most common treatment

emergent adverse events (TEAEs). Other frequently occurring TEAEs included headache (migraine and not otherwise specified), nausea and abdominal pain.

- Metrorrhagia and vaginal hemorrhage were the most common reasons for safety related discontinuations from the studies.
- In the Phase 3 clinical Study 0858A2-313-NA there were changes of -0.75g of hemoglobin at pill pack 7 that decreased to -.36g at post-treatment evaluation.
- In the comparative study (Study 0858A2-315-EU) with the cyclic regimen, the overall incidence of adverse events related to vaginal bleeding was higher with the continuous-use regimen in the first 6 pill packs, but not in the last 6 pill packs.
- Laboratory changes observed included increases in fasting blood glucose and lipids and are consistent with those observed with other low dose oral contraceptives.
- Body weight increases in these studies are not different between continuous use and cyclic regimen groups and are consistent with a population of women aged 18 to 49 years who use low dose oral contraceptives.
- Histologic changes in the endometrium in a subpopulation (n=146) showed no hyperplasia or malignancy; this is consistent with a decrease in endometrial growth and decidualization without atrophic endometrial changes.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

Initially, no DSI inspections were requested. The usual policy is not to obtain routine DSI inspection when the drug product is essentially similar to a previously approved product. Late in the review cycle upon learning from the Sponsor about mix-ups in subject source document and problems with test-dose accountability, the Division contacted DSI about possible site audits. A request for inspections of three sites James Simon, MD-Laurel, MD, Donald Edger, MD-Lexington, KY and James Maly, MD-Lincoln, NE was made on April 26, 2006. The results of the inspections are outstanding.

Chemistry/ Manufacturing

Lybrel (levonorgestrel/ethinyl estradiol tables and ethinyl estradiol tablets) consists of a combination tablet containing levonorgestrel (90µg) and ethinyl estradiol (20µg) administered in a continuous use regimen. There is no placebo tablet used in Lybrel™.

The drug product is manufactured by Wyeth Laboratories.

The following issues/deficiencies were considered during the review:

- Wyeth changed manufacturing from a ——— method to a ——— method. The ——— method was not utilized in the trial for effectiveness, Study 0858A2-313-NA. While the ——— method was utilized in Study 0858A2-315-EU, this study did not provide data used to determine the effectiveness of this product. b(4)
- On March 01, 2006 a discipline review letter was sent to Wyeth from the Agency. The letter stated, " We have determined that the manufacturing change for Lybrel™ that is covered in your NDA (i.e. from ——— to the ——— ) has

been determined to be a Level 3 change in accordance with the Agency's guidance entitled, *"Guidance for Industry – Immediate Release Solid Oral Dosage Forms – Scale Up and Postapproval Changes; Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing and Documentation,"*[see Section VI (MANUFACTURING) Part B (Process), Item 3 (Level 3 Changes)]. As such, appropriate Test Documentation (Item 3.b.iii.) related to bioequivalence needs to be addressed.

- On March 08, 2006 at a face-to-face meeting with Wyeth, the above was reiterated. Wyeth committed to providing to the Agency additional information to address the BCS classification.
- On March 24, 2006, Wyeth submitted an amendment to support their contention that the product should fall under BCS1 classification and to support their request for a waiver from the requirement for a bioequivalence study.
- An internal CDER BCS working group was consulted to consider Wyeth's proposal that the drug product was under BCS1 classification. The committee determined that Lybrel™ did not meet the criteria for BCS1 classification, and, therefore, did not qualify for a waiver. Wyeth was informed of this decision on April, 28, 2006.
- On May 2, 2006 Wyeth met with the Agency and made the following proposal:
    1) Wyeth will revert to slightly modified [redacted] method and USP dissolution testing. b(4)
    2) Wyeth will submit the following information to the NDA on 22-May-2006:
        a. COAs for three batches manufactured by modified [redacted]
        b. 36 month supporting stability data on [redacted] tablets used in Phase 3 trials packaged in conventional blisters
        c. Updated CTD section to reflect change in manufacturing process and equipment, as appropriate, including updated composition, specifications, and stability sections
    - Wyeth will submit following information on 22-Jun-2006:
        a. One month stability data on three batches
- The Office of New Drug Quality Assessment (ONDQA) had the following response to Wyeth's proposal
    1) The proposal to revert to the [redacted] method is acceptable, but not reversion to the USP method. b(4)
       *Wyeth did not agree,* and was told to submit justification and the decision would be revisited.
    2) The information could be submitted on 22-May-2006, but ONDQA would not agree that the information would be reviewed during this review cycle (as per discussions with the Clinical Division Director)
    3) One month stability data could be submitted on 22-Jun-2006, with the same caveat as point 2, but that three months of accelerated stability data is normally required for a Level 3 change.

As of the date of this memorandum, Wyeth has not submitted the updated CMC information and no further review has occurred,

Product Name

The proprietary name "Librel™" was initially submitted to IND 65,693 on March 6, 2004. The name was found to be unacceptable by the Division of Medication Errors and Technical Supports (DMETS) due to the potential for auditory ("sound-alike") or written

("look-alike") confusion with other established proprietary names. The Division of Drug Marketing, Advertising, and Communication (DDMAC) also objected to 'Librel™" from a promotional perspective for the following reasons: "Librel™ is overly fanciful". "Librel™" could be taken to mean liberal or liberated. The tradename "Lybrel™" was submitted to the Agency on March 10, 2005. This tradename was initially accepted in September 29, 2005, upon the first review by DMETS and DDMAC. Upon re-review, January 12, 2006, the tradename "Lybrel™" was rejected by DDMAC for the same reasons as previously stated for "Librel™", that the name was promotional. I agreed with DDMAC's determination and recommended that "Lybrel™" not be accepted. DDMAC had the same comments for a third tradename ——— . I disagreed with the comments on ——— and recommended that this name go forth. On February 9, 2006, the Sponsor sent a communication to the Division appealing the objection to the tradenames "Lybrel™" and ——— Subsequent to this, DDMAC withdrew their objection. After hearing the company pronounce "Lybrel™" with a short i sound, this reviewer still recommends that this name not be accepted. The pronunciation and the carton illustration with a (humming) bird to me represent an unsubstantiated claim (i.e. free from worries regarding pregnancy) with this product. However, the decision to accept or reject the proprietary Lybrel™ will rest with the Division Director.

b(4)

Preclinical Pharmacology and Toxicology

There are no new non-clinical issues for the proposed lower dosages of levonorgestrel (90 μg) and ethinyl estradiol (20 μg). Based on the previously submitted pharmacology/toxicology data for levonorgestrel and ethinyl estradiol, approval is recommended from a preclinical pharmacology and toxicology viewpoint.

Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

The formulation of Lybrel™ is similar to the currently marketed product Alesse® (100μgLNG/20μg EE) with a slight adjustment to the LNG and lactose content. Two Lybrel™ products were used in the 4 clinical studies submitted and differed only in their manufacturing process. The final to-be-marketed product is a yellow biconvex, debossed film coated tablet manufactured by ——— . Dissolution data was provided to compare the clinical trial batches and the registration/validation batches and showed similar dissolution results using the USP method and the method developed by the Sponsor with no surfactant.

b(4)

Only one human study was submitted that pertained to Clinical Pharmacology. The study was a pharmacokinetic study which looked at the single and multiple dose pharmacokinetics of Lybrel™ after 28 days of continuous administration using the non-to-be-marketed manufacturing process product.

The Chemistry review for NDA 21-864 is ongoing and preliminary review indicates a Level 3 manufacturing change between the Lybrel™ products used in Study 313 and Study 315. Per the clinical reviewing team, only Study 0858A2-313-NA will be used to support the efficacy of NDA 21-864. If only Study 0858A2-313-NA is considered evaluable by the Clinical Division, then the manufacturing equipment and process change

between the Study 0858A2-313-NA product and that to-be-marketed (used in Study 315) could require in vivo bioequivalence documentation.

The Sponsor was notified on March 2, 2006 of Chemistry's perspective regarding the Level 3 change and what is required to support this manufacturing change according to the SUPAC Guidance. The Sponsor replied with an amendment on March 6, 2006 which included in its conclusion that LNG and EE met BCS Class 1 classification. Additional multipoint dissolution data in different pH media was also submitted (will be reviewed at a later date).

A meeting was held with the Sponsor on March 8, 2006 to discuss clinical Study 0858A2-313-NA and the chemistry issues. At the conclusion of this meeting the sponsor agreed to provide additional information to address the BCS classification.
See CMC section for further discussion of the BCS classification issue.

Conclusions and Recommendations

Per the Sponsor, the continuous use regimen was expected to provide sustained ovulation suppression (i.e. efficacy in pregnancy prevention) and sustained amenorrhea. In this reviewer's opinion, the LNG 90 µg/EE 20 µg continuous use oral contraceptive clearly did not deliver the intended results in the "proof-of-efficacy" clinical trial.

I will first discuss the issues with efficacy for this drug product. The measures of efficacy used to determine effectiveness of a contraceptive drug product are the Pearl Index and Life Table analysis of failure rate. During the earlier days of combined oral contraceptives when the drug products consisted of high doses of the estrogen and progestin components, the Division (HFD-510) determined that because there were so few method failure pregnancies in order to have reasonably sized clinical trials, effectiveness would be determined by a failure rate (i.e. pregnancy rate) that considered both method and user failures. User failure rates were limited to patients who followed the protocol with minor violations (as in this protocol subjects who missed greater or equal to three consecutive pills or five in a single pill pack were discontinued and their cycles not counted). As the determination was made that oral contraceptives were safe to use into the perimenopausal years (up to age 50), it was decided that effectiveness should be determined not in all women (i.e. up to age 50), but in the sub-group of women who have higher fecundity and are thus at greater risk. Therefore, evaluation of effectiveness was limited to the population of women less than or equal to age 35.

Historically it was accepted that effectiveness for combination oral contraceptive drug product would be established with demonstration of a Pearl Index (method +user failure) of less than 1. In 1975, the Division (HFD-510) took the issue of approval for Ovcon35 to the Reproductive Health Advisory Committee (AC). At issue was the ***high*** Pearl Index (**1.36**) of this combination oral contraceptive containing lower amounts of norethindrone (400 µg) and ethinyl estradiol (35 µg) compared to other conventional combination oral contraceptive products of that time. Following discussions which

occurred at this AC, the Division adapted a "cut-off" of 1.5 as the Pearl Index value to establish effectiveness.

Over the years as the dose of progestin and estrogen anticipated to suppress ovulation have been lowered the Division-accepted "cut-off" value for the Pearl Index was allowed to rise to 2.

As determined in the primary "proof of efficacy" study, Study 0858A2-313-NA, in women less than or equal to age 35, Lybrel™ has a Pearl Index (method plus user failure pregnancies) of 2.38 (95% CI 1.51, 3.57). The upper bounds of the 95% CI of that Pearl Index estimates that the true Pearl Index could be as high as 3.57. When judged against the "cut-off" value for Pearl Index less than or equal to 2.0, the point estimate and 95% upper bound limit are clearly outside of the limit contemporarily used by the Division to determine effectiveness. The life table analysis of failure rate is 0.0348, which is consistent with the 95% upper bound of the point estimate for the Pearl Index.

There are individuals within the Division who feel that 2.0 should not be the upper limit placed to establish efficacy and that drug products with higher Pearl Indices and Life Table analyses, that is higher pregnancy rates, should be approved and the failure rate indicated in the label. It is argued that the consumer can then make the choice. Indeed, there are two drug products which have been approved despite exceeding a Pearl Index of 2.0.

NDA 20, 130 for Estrostep® was approved on October 9, 1996. The "proof-of-efficacy" study was a double blind, comparative study of Estrostep® to Loestrin® 1.5/30. The primary efficacy variable was not the prevention of pregnancy, but incidence of breakthrough bleeding and spotting through six cycles. A total of 593 women completed the six cycles and 3735 cycles were evaluable. The calculated Pearl Index (method + user failures) for Estrostep® was 2.4 in the population of women less than or equal to age 35. The reviewing Medical Officer's initial conclusion was that the trial did not support with confidence that Estrostep® is a safe and efficacious contraceptive. Her comment was that the Pearl Index of 2.4 is substantially higher than the Pearl Index for other marketed products. Even though the comparator Loestrin 1.5/30 also showed a relatively higher Pearl Index (1.5) in the study, the reviewer concluded that the products used in this study may not be substantially equivalent to the marketed products. NDA 20,130 received a *not approvable* recommendation on August 27, 1992. The *not approvable* letter mentioned only CMC deficiencies and labeling deficiencies. The summary basis of approval (unsigned) suggested that the primary endpoint of breakthrough bleeding and spotting was acceptable. It appears that efficacy findings on the Pearl Index of Estrostep® obtained in the comparative clinical trial was not factored into the final decision to not approve. The estrogen/progestin doses in Estrostep® were previously considered in two approved products. The CMC issues for Estrostep® were subsequently resolved and the product received an approval action on October 9, 1996.

NDA 21-241 for Ortho Tri-Cyclen® Lo [189 µg norgestimate(NGM)/25 µg EE day 1-7, 215 µg NGM/ 25 µg EE day 8-14 and 250 µg NGM/ 25 µg EE days 15-21) was approved

on August 22, 2002. The Pearl Index (method + user failures) was 2.67 in the population of women less than or equal to age 35. Despite reservations on the clinical benefit for this product (i.e. the high Pearl Index), the primary Medical Officer recommended approval. In making his decision to recommend approval, the reviewer comments that the rate for this product was lower than the "typical use" rate provided in class labeling and taken from the book *Contraceptive Technology*[1]. The reviewer also comments that historically other oral contraceptives had been approved with Pearl Indices greater than that of Ortho Tri-Cyclen® Lo. These products were noted in the review as Estrostep®, Pearl Index = 2.4 (see discussion above), Tri-Norinyl® Pearl Index = 2.6, Brevicon® Pearl Index = 5.18 and Norinyl®, Pearl Index = 2.51. The information on the Pearl Indices was provided by the Sponsor for Ortho Tri-Cyclen® Lo. Lastly the reviewer comments that Ortho Tri-Cyclen® Lo had a lower pregnancy rate than the approved product Loestrin in the comparative Phase 3 trial. I disagree with these points used by the reviewer as the basis of his recommendation. Relative to the first point, I believe that a Pearl Index obtained in a "proof of efficacy" clinical trial should not be considered as "typical use". "Typical use" failures are defined in table 9-2 from Hatcher's *Contraceptive Technology*[1] as the percentage of accidental pregnancies among typical couples who initiate use of a method (not necessarily for the first time). Per this reference, "pregnancy rates during typical use reflect how effective methods are for the average person who does not always use methods correctly or consistently. Typical use does not imply that a contraceptive method was always used". Subjects in a clinical trial, by the very nature of their clinical trial participation, are not the "average person". "Proof of efficacy" clinical trial requirements for self-kept diaries, frequent clinical visits and telephone follow-up with providers, constitute built in reminders for compliance which are not in place for real world use. Further, in the clinical trial(s) to support efficacy, individuals with more than a few missed pills would not be included to determine pregnancy rates. These individuals would be discontinued from the study (in this trial individuals were discontinued from the study if they missed ≥3 consecutive pills or ≥5 pills on any given cycle) and their contribution to total pregnancies and total cycles not counted. A clinical trial designed to support effectiveness of a drug product, provides the best rates that will be achieved with a particular drug product. The rates obtained in such clinical trial should not be accepted because they are lower than those rates obtained using a lesser standard. Under real world conditions (i.e. away from the clinical trial prompts), the pregnancy rates attributed to user failure are like to be significantly greater than the rates seen in "proof-of-efficacy" clinical trials. Per Trussel and Vaugham 1999, "the risks of pregnancy during typical use of reversible methods of contraception are considerably higher than risks of failure during clinical trials"[2].

With respect to the second point made to support the recommendation for approval of Ortho Tri-Cyclen® Lo, I am unable to corroborate the rates provided above for Tri-Norinyl®, Brevicon® and Norinyl®. The Pearl Index noted in the summary basis of approval (SBA) for the three drugs are as follows

- NDA 17-566/17-743 for Brevicon® (500 µg norethindrone/ 35 µg EE) was approved on December 26, 1974 – based on 4 user-failure pregnancies in 1103 subjects for 12, 943 cycles. The Pearl Index was calculated to be 0.37. This Pearl Index was in women who were less than or equal to 35 at the time of the trial.

- NDA 17-565 for Norinyl® (1mg norethindrone/35 μg EE) was approved on December 27, 1974 – based on 3 pregnancies in 1010 subjects for 12,195 cycles. The Pearl Index was calculated to be 0.3.
- NDA 18-977 for Trinorinyl® (500 μg/1000 μg/ 500 μg/35 μg EE) was approved on April 11, 1984. The approval was based on the previous approval of the higher phase (Norinyl®) and the lower phase (Brevicon®) in other products. Only cycle control data was evaluated. No new efficacy trial data was obtained.

It would appear from this brief review of the SBA for these products that the Ortho Tri-Cyclen® Lo reviewer was misled by the Sponsor's discussion of the historical rates for these products.

The third point made by the Ortho Tri-Cyclen® Lo reviewer is probably one of the most controversial issues regarding trials for oral contraceptives currently being considered by the Division. In more recent years some Sponsors (like that of Ortho Tri-Cyclen® Lo) have come in with comparison studies, which are often small (thought not always), to support approval of their products. Frequently approval of the drug product is sought based on comparison to the approved product with the highest Pearl Index or the worst cycle control if that is the variable of interest. The Ortho Tri-Cyclen® Lo reviewer commented *"the pivotal study was not powered a priori for efficacy equivalency or superiority with regard to cycle control." He further commented, "Though comparative studies were advocated by the World Health Organization at one time for contraceptive products, I believe that a comparator is not necessary for contraceptive efficacy studies and can be handled entirely by Pearl Index and life table analysis. Comparators would serve a better role comparing side effects or cycle control"* I echo the sentiments of the Ortho Tri-Cyclen® Lo reviewer and would add that an open-label designed-trial is not suitable for comparative trials. The incentive is too great to be less than honest in providing results or not forthcoming with information that impact upon those results.

Based on the considerations for approval of Estrostep® and Ortho Tri-Cyclen® Lo, this reviewer considers Estrostep® and Ortho Tri-Cyclen® Lo to be aberrancies from the Division's long-standing policy to accept a Pearl Index of 2.0 or less as establishing efficacy. *A decision on the approvability of **Lybrel™** should not be made based on comparisons to these outliers.* The following Table provides some other examples of Pearl Indices obtained from the summary basis of approval of other (mostly contemporary) "low dose" (20 – 35 μg of EE) oral contraceptives.

Table 7 - Cross Study Comparisons of Pearl Indices for Selected Approved Oral Contraceptive Products (20 mcg EE and an extended regimen 30 mcg EE product) and Lybrel™ – population less than or equal to age 35

| Product | Estrogen/ Progestin Components | | Proof-of-Efficacy 6 or 13-Cycle | Approval Date | PI (95% CI) | Pregnancy Rate - Life Table (95% CI) |
|---|---|---|---|---|---|---|
| | E | P | | | | |
| Estrostep® **NDA 20-130** | 20 µg EE<br>20 µg EE<br>20 µg EE | 1000 µg NE,1-5<br>1000 µg NE,6-12<br>1000 µg NE,13-21 | 6-cycle **primary efficacy – incidence of breakthrough bleeding** | October 9, 1996 | **2.4** (ND) | ND |
| Loestrin® **NDA 17-876** | 20 µg EE | 1000 µg NEA | 12-cycle | October 1, 1976 | **0.98** (ND) | ND |
| | | | | | | |
| Alesse® **NDA 20-368** | 20 µg EE | 100 µg levonorgestrel | 6-cycle | March 27, 1997 | **0.84** (ND) | 0.0041 |
| Mircette® **NDA 20-3713** | 20 µg EE x 21d<br>10 µg EE x 5d | 150 µg desogestrel | 13-cycles (for efficacy)<br>18-cycles total | April 02, 1998 | **1.11** | 0.011 (0.003,0.018) |
| Cyclessa® **NDA 21-090** | 25 µg EE<br>25 µg EE<br>25 µg EE | 100 µg desogestrel<br>125 µg desogestrel<br>150 µg desogestrel | 6-cycle | December 20, 2000 | **1.23** | 0.0051 |
| Yasmin® **NDA 21-098** | 30 µg EE | 3,000 µg drosperinone | 13-cycles | May 11, 2000 | **0.41** (ND) | ND |
| OrthoTriCyclen® Lo(25) **NDA 21-241** | 25 µg EE<br>25 µg EE<br>25 µg EE | 180 µg norgestimate<br>215 µg norgestimate<br>250 µg norgestimate | 13-cycles | June 25, 2001 | **2.67** (ND) | ND |
| Seasonale® **NDA 21-544** | 30 µg EE | 150 µg levonorgestrel | 13-cycles | September 5, 2003 | **1.98 (0.54, 5.03)** | 0.0126 (0.002,0.025) |
| Loestrin® 24 **NDA 21-871** | | | 6-cycle | February 17, 2006 | **1.79 (0.49, 4.57)** | ND |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yaz™ **NDA 21-676** | 20 µg EE | 3,000 µg drosperinone | 13-cycles | March 16, 2006 | **1.42 (0.73, 2.47)** | 0.006 (0.000 0.012) |
| Lybrel® **NDA 21-864** | 20 µg EE | 90 µg levonorgestrel | 13-cycles | NA | **2.38 (1.51, 3.57)** | 0.03481 |

NA – not applicable

ND – not presented in the review or not done

With the exception of the previously noted products, Estrostep® and Ortho Tri-Cyclen® Lo, all of the above "low-dose" oral contraceptives (and indeed all previously approved oral contraceptives) have demonstrated Pearl Indices below 2.0. The FDA has informed it's consumer customer (the U.S. public) that the expected failure rate of combined oral contraceptive products is *1* to *2* %[3] (*not* greater than 2%), consistent with the Division's policy of establishing effectiveness for drug products based on a cut-off value of 2.0 for the Pearl Index.

The preceding paragraph notwithstanding, because of the noted differences of current opinion regarding the "cut–off" value of 2.0 for the combined user plus method failure Pearl Index, I believe that it is instructive (for the consideration of approvability of Lybrel™) to look beyond the overall (method + user failure) Pearl Index and evaluate how the drug product performs in women who have use it perfectly. "Perfect use" failures are defined in *Contraceptive Technology*[1] as the percentage of accidental pregnancies among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly). Even though a "perfect use" Pearl Index (method failure) obtained in a "proof-of-efficacy" clinical trial is supported by the same built in prompts as discussed above, it is this reviewer's opinion that an individual who uses a method perfectly is so highly self-motivated that the clinical trial prompts may be less influential and important to this individual. The "perfect use" Pearl Index for Lybrel™ is 1.55 (95% Confidence Interval 0.87, 2.56) and the Life Table analysis of the method failure rate is 0.0278. According to Hatcher's *Contraceptive Technology*[1], the percent of women experiencing an unintended pregnancy with "perfect use" of combined oral contraceptive pill should be less than 1% (0.3% in the table comparing various forms of contraception). This is the information in the oral contraceptive class labeling and is the information that is being disseminated to the public. The following table that depicts the method failure rates for low estrogen dose combined oral contraceptive drug products clearly demonstrates Pearl Index values that are less than one with one exception.

Table 8 - Cross Study Comparisons of "Perfect Use" Pearl Index for Selected Approved Oral Contraceptive Products (20 mcg EE contraceptive products and an extended regimen 30 mcg EE product)

| Product | Estrostep | Alesse | Loestrin | Ortho Tri-Cyclen Lo | Mircette | Cyclessa | Yasmin | Seasonale | Yaz |
|---|---|---|---|---|---|---|---|---|---|
| method failure rate | ND | 0.84 | 0.29 | **1.65** | 0.7 | 0.268 | 0 | 0.99 | ND |

NA – Not applicable
ND – not done or not illustrated in the review

The "perfect use" Pearl Index of each of these products with the exception of Ortho Tri-Cylen® Lo (Estrostep® unknown) was less than 1.

In fact, if one were to compare the "perfect use" (method) failures of Ortho Tri-Cylen® Lo and Lybrel™ with that of other forms of contraception as provided in the Class

labeling and provided in the effectiveness table in Hatcher's *Contraceptive Technology*[1], it would appear that the couple who used these drug products (Ortho Tri-Cylen® Lo and Lybrel™) "perfectly" would potentially be at greater risk for unintended pregnancy than the couple who perfectly practiced periodic abstinence post ovulation (1% unintended pregnancy rate) and only slightly better than the couple who used the male condom perfectly (2% unintended pregnancy rate). Even though combined oral contraceptives are relatively safe products for most women, I find it hard to justify any risk associated with ethinyl estradiol and levonorgestrel given the effectiveness rate relative to these non-pharmaceutical forms of contraception. For those women who are either unable or do not want to use these non-pharmaceutical methods in a perfect manner, Table 7 shows that there are effective approved oral contraceptive options.

In the Integrated Summary of Efficacy submitted in the application, the Sponsor presents a Pearl Index (method + user failure) for Lybrel™ of 1.33 , obtained by combining the cycles from Study 0858A2-313-NA and Study 0858A2-315-EU. The clinical and statistical reviewers are rejecting this analysis based on the following discussion. The Sponsor did not prospectively (any time from the initial submission of the original protocol in the IND to completion of either study) indicate to the Division, its intention to present a combined analysis of the two studies for registration purposes in the US. The Division never asked the Sponsor to submit a combined analysis. In fact, even though the Division was aware of the study (0858A2-315-EU) to be conducted in Europe, the Division did not receive a copy of this protocol for review. The Division's understanding was that Study 0858A2-313-NA would be the only study supporting effectiveness of Lybrel™. The Division has not traditionally sought "proof of efficacy" data from more than one clinical trial for an oral contraceptive drug product when the estrogen and progestin components of that drug product were well known entities (i.e. not new molecular entities), as is the case for the ethinyl estradiol and levonorgestrel components of Lybrel™.

Further, the Sponsor prospectively powered the trial for US registration, Study 0858A2-313-NA, to more than meet the Division's requirements for 10,000 cycles and 200 women exposed to and completing 13 cycles of use. The efficacy data submitted for Study 0858A2-313-NA demonstrates that even after accounting for the very high drop-out rate (57%), 12,572 cycles were available for evaluation of efficacy in the subgroup of women age less than or equal to 35 and 15, 461 cycles in the total population of 18-49.

Even if there had been agreement "in principle" between the Division and the Sponsor to combine the two studies, there are certain statistical requirements to present combined efficacy data that would have to be proposed and agreed upon prospectively. There were no such proposals made. From a statistical perspective combined analysis could be used as supportive only when the efficacy is adequately demonstrated in the individual studies. In this application Study 0858A2-313-NA has a Pearl Index of 2.38 while Study 0858A2-315-EU has a Pearl Index of 0.51 and was clearly under-powered in terms of a US contraceptive trial.

I will make one final point with respect to a post-hoc combining of the efficacy results for Study 0858A2-313-NA and Study 0858A2-315-EU. The populations of these two studies, as seen in the demographics, are different. The US/Canadian study is a more ethnically diverse study (77% Caucasian and 23% total for Black, Hispanic, Asian and other minorities) than was the European study (96% Caucasian and 4% Black, Asian and other minorities). The degree of racial diversity in the US/Canadian trial, while not absolutely representative, is more reflective of the US population. Secondly, the US/Canadian study populations was substantially heavier that the European study population (BMI of 26.04 vs. 22.7 and mean weight of 70.3 kg vs. 63.8 kg). For all the reasons stated in the preceding 4 paragraphs (inclusive), *efficacy results from the combined analyses of Study 0858A2-313-NA and Study 0858A2-313-NA should not be considered as the primary evidence to support approvability of Lybrel™.*

During the March 8, 2006 pre-decisional meeting, the Sponsor continued to maintain that it had intended all along to combine Studies 0858A2-313-NA and 0858A2-315-EU. The Sponsor was asked to provide the specific citation(s) that states explicitly their intent to support registration in the US with a combined efficacy analysis. The Sponsor provided on March 13, 2006, a list of three documents. Two of these documents ( ) were dated after the completion of both Studies 0858A2-313-NA and 0858A2-315-EU and, even if they had previously been sent to the FDA (not the case) could not be considered as a prospective indication of the intent to combine the studies. The third was a protocol for Study 0858A2-315-EU that was not sent to the Division. After an extensive search through the archival files for IND 65, 693, no confirmation of the Sponsor's contention could be made. Therefore, there is no evidence that the Sponsor prospectively (before completion of the two trials and before they looked at the completed trial data) informed the Division that they would combine the two studies for purposes of registration in the US.

Next, I will address the cycle control issues with Lybrel™. This reviewer has serious concerns regarding the lack of cycle control in the form of irregular bleeding and spotting (unanticipated bleeding) demonstrated in subjects treated with this drug product. It is difficult to assess the bleeding associated with one drug product relative to that demonstrated in a separate trial for another product. Various Sponsors have utilized different measures to discuss bleeding. However, the extended and continuous cycle regimens would appear to have more unanticipated bleeding than the cyclic regimens which are designed to have an approximately 28-day withdrawal bleed. As stated at the outset of this **Discussion** section, in addition to providing effective contraception, this product was intended to provide sustained amenorrhea. In the study report for Study 0858A2-313-NA, the Sponsor states "*In addition to inhibition of menses, the LNG 90 µg/EE 20 µg continuous use regimen is intended to reduce all types of bleeding and spotting*". The question is should a Sponsor who purports that their product provides sustained amenorrhea and reduces all types of bleeding and spotting be required to provide the evidence that demonstrate this? My response to this question is yes. The clinical trial data did not demonstrate sustained amenorrhea. At cycle 1, 98% of subjects had bleeding and/or spotting. By cycle 13, 40% of subjects had bleeding and/or spotting. While one can say that the percentage of subjects with bleeding and/or spotting improved

from cycle 1 to cycle 13, a product that demonstrates 40% of women to have bleeding and/or spotting at one year certainly does not represent sustained amenorrhea or reduced bleeding and spotting.. Another concern to think about is whether with "real world" use, the poor cycle control might lead women to discontinue this drug product thereby increasing the exposure of these women to unintended pregnancies. One additional note on the cycle control with Lybrel™, the hemoglobin was significantly decreased, with a mean difference of -0.75(±7.14g/L), from baseline by cycle 7. By the post-treatment evaluation, the mean hemoglobin was lower (though not significantly), -0.36(±7.93g/L), compared to baseline. Even though this degree of change in the hemoglobin certainly does not represent a "clinically' significant change in terms of need for medical intervention (i.e. blood transfusion), it certainly is not consistent with "class labeling" for which one of the noted "non-contraceptive health benefits" is "decreased blood loss".

In this reviewer's opinion, the enormous public health impact of unintended pregnancies linked to discontinuations of oral contraceptives because of poor cycle control argues heavily against approval of a product with questionable cycle control.

In summary, I agree with the primary Medical Officer's review for Lybrel™ and recommend that this product **not** be approved because of a demonstrated lack of efficacy and poor cycle control. Short of providing new clinical trial data, in a population comparable to the US population, which demonstrates an acceptable overall (user failure + method failure) Pearl Index and method failure Pearl Index, I do not believe that the Sponsor can satisfy the doubts regarding the efficacy of this product. Also the chemistry issues with respect to a Level 3 manufacturing change needs to be completely and satisfactorily addressed.

**Label**

The recommendation is for a Not Approvable decision. Should this recommendation not be followed and Approval be granted to market this product, the label should reflect not only the Pear Index and Life Table analysis of failure rate for the population of women 18-35 and 18-49, but the failures due to method alone (i.e. "perfect use" Pearl Indices) should also be reflected for both the 18-35 and 18-48 age populations.

References:


1. Hatcher, RA, Trussell J, Stewart F, Nelson, A, Cates W: Contraceptive Technology, 18th Revised Edition, New York, Ardent Media, 2003

2. Trussel, J and Vaugham, B.: Contraceptive Failure, Method-Related Discontinuation and Resumption of Use: Results from the 1995 National Survey of Family Growth, Family Planning Perspectives, 1999, 31 (2) 64-72 and 93.

3. FDA Office of Public Affairs: Birth Control Guide, FDA Consumer magazine, original 1003, revised 12.2003.


Shelley R. Slaughter, M.D, Ph.D.
Reproductive Medical OfficerTeam Leader

cc: NDA 21-864,
HFD-580/D. Shames/S. Slaughter/P. Prices/J. Kim,

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/s/
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Shelley Slaughter
5/22/2006 04:03:15 PM
MEDICAL OFFICER

**CLINICAL REVIEW/COMPLETE RESPONSE**

| | |
|---|---|
| Application Type | NDA 21-864 |
| Submission Number | 000 |
| Submission Code | N |
| Original PDUFA Date | March 27, 2006 |
| Original Review Completion Date: | March 30, 2006 |
| Complete Response Stamp Date: | August 22, 2006 |
| Reviewer Name: | Phill H. Price, M.D. |
| Review Completion Date: | May 16, 2007 |
| Established Name: | Levonorgestrel (LNG) (90μg)/Ethinyl Estradiol (EE) (20μg) Continuous Use |
| **(Proposed) Trade Name:** | **Lybrel™** |
| Therapeutic Class: | Estrogen/Progestin |
| Applicant: | Wyeth Pharmaceuticals, Inc. |
| Priority Designation | S |
| Formulation: | Levonorgestrel; 18,19-Dinorpregn-4-en-20-yn-3-one,12-ethyl-17-hydroxy-,(17α)-,(-)- Ethinyl Estradiol 9-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)- |
| Dosing Regimen: | Levonorgestrel 90μg and Ethinyl Estradiol 20μg daily---for continuous use |
| Indication: | Prevention of Pregnancy in women who elect to use this product as a method of contraception |
| Intended Population: | Woman at risk for pregnancy |

## Table of Contents

# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

Non-Approval of levonorgestrel 0.090mg ethinyl estradiol 0.020mg (LN/EE) for prevention of pregnancy is recommended based on an unacceptable Pearl index. In addition there is an unacceptable discontinuation rate and poor cycle control. The safety profile is acceptable (See **Medical Officer's original cycle review dated March 30, 2006.)**

From a clinical viewpoint, the evidence provided **does not support the conclusion that Lybrel™** provides an effective method of contraception. Efficacy data for this product demonstrated a high Pearl index 2.38 (CI 1.51, 3.37) for a de-novo oral contraceptive being sought for approval. The method failure Pearl index is (1.55 (CI 0.87, 2.56) which is unacceptable for a hormonal **contraceptive in this reviewer's opinion. In** addition, this product has an unacceptable rate of discontinuation which appears to be driven by unexpected bleeding. This reviewer concludes this product does not provide an acceptable the level of contraceptive effectiveness. With one exception, the methods for identifying failure rate (i.e., Pearl index and Life Table Method for pregnancy rates) are higher with this drug product than these same methods for other lower dose combined oral contraceptives that have received approval from this Agency. The higher unexpected bleeding profile puts patients at risk for discontinuation of the product and, thus, unintended pregnancy. The high study discontinuation rate in the US trial is consistent with the **possibility of high product discontinuations. It is this reviewer's belief that this drug product** should not be approved based on its efficacy profile. The safety profile is not considered to be more concerning than with other approved cyclic and extended regimen oral hormonal combination contraceptives. Although 2 cases of pulmonary emboli were identified in the total of 2,811 (Study 313NA, 315EU, 320CA, 322US, 316NA and 318WW) subjects studied, the rate of VTE with this product does not appear greater (per 1,000) than other approved 28-day regimens and extended cycle regimens. As with all hormonal contraceptive, the risk of DVT/PE and stroke should be identified in labeling and discussed with the patient.

## 1.3 Summary of Clinical Findings

Wyeth, Inc. has proposed an extended use regimen of at least one year duration of a combined oral contraception (COC). Wyeth is proposing use of a slightly lower dosage than their approved product Alesse® to be used continuously. This product utilizes 0.090 mg of levonorgestrel (LN) and 0.02 mg of ethinyl estradiol (EE) continuously compared to Alesse® which utilizes 0.10 mg of levonorgestrel and 0.02 mg of ethinyl estradiol over a 21- day treatment period. Historically, oral contraceptives have been given for 21days of active drug with a 7-day withdrawal period. A more recently approved product, Seasonale®, is given for 84 days continuously of active drug followed by 7 days of withdrawal on placebo pills. The stated benefit of prolonged contraception is a reduction in the number of withdrawal bleeding periods that woman undergo while taking oral contraceptives.

Oral contraceptives were introduced in the 1960s, and the standard 21-day regimen (21days with active pills and a 7-day hormone free interval) was established to mimic the length of the natural menstrual cycle to make it acceptable to women. This regimen remained unaltered for over 30 years. There were a number of small studies that evaluated OCs (previously approved in cyclic 21 or 28 day regimens) taken for longer the standard than 21-day regimens, typically for 42 or 84 days. While overall the acceptability of these extended cycle regimens was good, the breakthrough bleeding rate was higher than that observed with the standard 21-day regimen and this discouraged development. The first OCs that were introduced without the 7-day hormonal free interval were intended to either improve the contraceptive efficacy by reducing the hormone-free interval from 7 to 4 days or to improve the bleeding profile by adding 0.10mg of ethinyl estradiol (EE) to 5 of the remaining 7 days, which are usually hormone free. The first OC to alter the 21-day regimen with the intention to prolong the interval to a hormone withdrawal **bleed was Seasonale™ which has 84 days of** active drug (LNG 0.150 mg/EE 0.030 mg) followed by 7 days of placebo.

**The NDA for Lybrel™ is supported by a single** Phase 1 study (106-US) to determine the pharmacokinetic properties of LNG and EE, a Phase 2 study (208-US) to demonstrate the inhibition of ovulation, and 2 pivotal Phase 3 safety and efficacy studies 313-NA and 315-EU. The sponsor believed that the 0.090 mg of levonorgestrel and 0.02 mg of ethinyl estradiol continuous regimen represented the optimal regimen to provide contraception with inhibition of ovulation and menses. Studies were designed to evaluate the return to menses and the safety and efficacy of continuous-use LNG 0.090mg/EE 0.02mg during a second year of treatment were on-going at the time of filing of this NDA. (This review will comment later on study 0858A2-230-CA in this Safety Update.)

| | |
|---|---|
| **Name of Drug:** | **Lybrel™ (0.090 mg of** levonorgestrel and 0.02 mg of ethinyl estradiol) |
| Class: | Oral Contraceptive |
| Route of Administration: | Oral |
| Indication: | Prevention of Pregnancy |
| Pivotal Efficacy and Safety Trial | One pivotal US trial (313-NA) and one supportive European trial (315EU) |
| Number of Subjects Enrolled in Trials | Study 313-NA 2134 subjects; study 315EU 641 subjects (323 test drug--318 active drug) |
| Number of Subjects In safety database | 2,851 in safety database; 22,171 cycles of exposure for up to 1 year (13 cycles of use) |

### 1.3.2 Efficacy

**Efficacy was based on the study drug's ability to prevent pregnancy in the Phase 3 clinical trials. This was calculated by utilizing the Pearl index (PI) and using all "on-treatment" pregnancies** defined as pregnancies occurring between the start of the study drug through 14 days following the last dose of study drug. This is consistent with the definition utilized by the Division .Two other Pearl indices were also utilized, those occurring between the start of the study drug through 7 days after treatment and those occurring between the start and stop of the study drug. Primary emphasis for the purpose of determining effectiveness is placed in subject population age 35 years or less.

According to the sponsor the total number of on treatment pregnancies in Study 313-NA was 23. Utilizing a denominator of 15,461 cycles and 13 **pill packs per year, the sponsor's Pearl's index of "Study Drug is 1.93** (95% CI 1.93 [1.23, 2.90]) for all subjects. The primary comparator drug is Seasonale® (Pearl index 1.98). According to the sponsor if the Pearl index is restricted to women age 35 years or younger the Pearl index increases to **2.38** (CI 1.51, 3.57) for a total of 12,572 cycles. *The population of women age 35 years or younger is the population considered for effectiveness of the study drug.* The Life table analysis for the total population was based on 11,295 pill packs. The Life table analysis gives a cumulative termination rate for accidental pregnancies of 0.0297 with 13 pill packs. The pill pack cumulative termination rate of the LNG 0.090 mg/EE 0.02 mg continuous use regimen per woman was 0.4541. For subjects age 35 years or younger at study start the Life table analysis for this population was based on 9,180 pill packs. The Life table analysis gives a cumulative termination rate for accidental pregnancy of 0.0348 with 13 pill packs. The pill pack cumulative termination rate of the LNG 0.090 mg/EE 0.020 mg continuous use regimen per woman was 0.4750.

Efficacy conclusion: (See original Medical **Officer's review dated March 27, 2006)**
The Pearl index and life table analyses are *not supportive* of approval of this product. The final Pearl index is **2.38** (CI 1.51, 3.57) for the age group 35 years or less and the Life table analyses is 0.0350 (CI 0.0227, 0.0539). The Pearl index for method failure is **1.55** (0.87, 2.56) The Pearl index for the total population is **1.93** (CI 1.23, 2.90) with a Life table of 0.0297 (CI 0.0230, 0.0506).

### 1.3.3 Safety

The safety database for Study Drug comprised a total of 2,533 subjects, including 18 subjects in a Phase 1 study (106-US), 58 subjects in a Phase 2 study (208-US), 2457 subjects in Phase 3 studies (313-NA and 315-EU) who received the continuous use regimen, and 318 subjects in a Phase 3 study (315-EU) who received LNG 100μg/EE 20μg in a 21-day cyclic regimen as a comparator. The total number of subjects is 2,851. In the pooled phase 3 studies, there were 22,751 cycles of exposure, and among those subjects who received continuous use LNG 0.090 mg/EE 0.020 mg, 1,137 subjects completed 13 cycles of use.

# 7 INTEGRATED REVIEW OF SAFETY

This ***Safety Update*** contains safety information up to August 21, 2006. Follow-up safety data is contained in 5 studies that are either a pharmacokinetic study (Protocol 0858A2-108-US), a continuing-use study conducted in Canada (Protocol 0858A2-320-CA) or studies being conducted to supported an indication for Cycle Related Symptoms (Protocols 0858A2-322-US, 0858A4-316-NA, 0858A4-318-WW).

## 7.2.9 Additional Submissions, Including Safety Update

The safety update was presented by the sponsor on September 27, 2005. The 4-month safety update contains information that was not available at the time of filing the NDA. The following safety information was supplied:

- **Poststudy pregnancy and return to spontaneous menses follow-up information for subjects who participated in study 313-NA.**
- **Results of study 0858A2-314-NA (314-NA), an observational rollover study from study 313-NA, that captured the time to return to spontaneous menses or pregnancy in subjects with 6 to 13 pill packs of exposure to continuous-use LNG 90 µg/ EE 20 µg in study 313-NA.**
- **Preliminary information from study 0858A2-320-CA (320-CA), an ongoing 1-year extension to study 313-NA.**
- **Any serious adverse drug experiences not previously reported (if any) for this IND from the official internal database (described in section 5) through 14 Jun 2005.**

Study 0858A2-230-CA

As part of the Complete Response to the Approval Letter for Lybrel™, the sponsor submitted a final safety update on August 21, 2006. The safety update includes data from all on-clinical studies of Lybrel™, regardless of the indication, dosage form or dose level.

Safety data is provided from study 0858A2-230-CA that was ongoing at the time of the original NDA. This was a Phase 3, single-treatment, multicenter, open-label, one year extension study of a continuous use regimen of Lybrel™. This study was conducted at 7 sites in Canada with 79 subjects who had completed one year of treatment in study 0858A2-313-NA.

This submission provides safety data for 79 subjects who chose to participate for up to 1 additional year of treatment with continuous use LNG 0.090 mg/EE 0.02 mg.

One or more treatment emergent adverse events (TEAEs) were reported by 61(77.2%) of subjects. Overall, TEAEs were categorized by Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) term. Infection (21.5%), headache and pharynigitis (12.7% each) were the most frequently reported events by subjects.

Of the seventeen subjects (21.5%) who discontinued from the study, no subject reported adverse events as the primary reason for discontinuation; the most common reason (n=10) was subject request. Eight (8) of the subjects request were medical reasons and 1 each because of bleeding/spotting that were not considered clinically important.

A total of 11 (13.9%) subjects had TEAEs that were considered to be possibly or definitely related to study drug. Nine (9) of these events were mild to moderate in severity. Two subjects reported severe TEAEs that were considered to be related to test article but they did not result in withdrawal from the study and were not considered serious adverse events. Subject 320-003-000079 had headache/migraine that resolved following treatment with Fiorinol™; subject 320-004-000126 experienced menstrual pain that resolved following treatment with ibuprofen. One subject experienced moderate cholelithiasis that was considered to be possibly related to test article. An ultrasound confirmed the diagnosis of cholelithiasis. The condition resolved following surgery performed on day 694 of treatment. In addition, one subject discontinued test article, desiring to become pregnant and reported a successful pregnancy after approximately 2 months.

There were two serious events considered to be unrelated to study medication. Two subjects were hospitalized during the study for events not considered to be related to study medication. One subject discontinued because of anxiety and asthenia and 1 subject discontinued because of attempted suicide. The investigator stated that the subjects' suicide attempt was in response to a relationship- breakup with her boyfriend. The subject who experienced the serious advents of panic attack and fatigue had a history of both before enrolling into the study. However, she did not state these conditions in the original screening medical history.

There were no deaths in this study.

Laboratory Evaluations
There were increases from pretreatment baseline to post-treatment in systolic and diastolic blood pressure (about 2mm Hg each). There was an increase in body weight from pretreatment baseline to post-treatment that was not significantly different from baseline values. Both of these results are not considered clinically significant and have been observed with other low dose oral contraceptives.

Significant increases were observed in the hemoglobin and hematocrit from pretreatment baseline to post-treatment evaluation. Glucose concentrations were unchanged.

Five subjects had clinically important elevations in LDL values and one subject had a clinically important elevation in total cholesterol. There was also a significant decrease ($p<0.05$) mean decrease in HDL cholesterol from baseline to pill pack 20 and at the post-treatment evaluation; there were no significant mean changes in other lipid parameters. Both of these observations have also been seen in low dose oral contraceptives.

A cervical cytology smear was taken before beginning the second year of treatment, during pill pack 20 and post-treatment. The results of cervical cytology smears show no clinically important changes.

Endometrial Histology Substudy
Nine subjects were enrolled in the endometrial biopsy substudy at 1 investigative site. Subjects in the endometrial histology substudy were scheduled to have an endometrial biopsy before treatment in year 2 and during pill pack 26. Two biopsies were performed on subjects while they were still receiving test article. Therefore, results are reported on 7 subjects at pill pack 26. Results show that one subject had a secretory endometrium, one subject showed a weakly/proliferative endometrium (under no tissue/diagnosis), and 5 subjects had final reports as **"other" (Other includes diagnosis such as "tissue insufficient for diagnosis", "no endometrium identified" and "no tissue identified."**

In conclusion, second year safety data from study (0858A2-230-CA) demonstrates no new adverse events or increase in frequency of adverse events from the first year of study.

Studies 322-US

Study 322-US is a phase 3, randomized, double-blind placebo-controlled study being conducted at approximately 40 sites in the US with approximately 5 to 10 subjects per site. Study 322-US started in July 2005 and is expected to be completed in July 2006. The primary objective is to evaluate the efficacy of continuous LNG 0.090 mg/EE 0.020 mg in preventing moderate to severe cycle related symptoms compared to placebo.

Adverse events were reported in 148 (74.0%) subjects. Back pain, dysmenorrhea, headache, infection, nausea and pain were reported by > 10% of subjects according to classification by COSTART.

A total of 16 (8.0%) subjects were withdrawn from the study because of adverse events. Under Body as a Whole 2 subjects withdrew because of headache, Under Cardiovascular system, 2 subjects withdrew because of migraine headache, and under Urogenital system, 1 subject withdrew due to metrorrhagia and 2 withdrew due to vaginal hemorrhage.

Six serious events were reported by 4 (2%) subjects. One subject reported abdominal pain, nausea, and a ruptured ovarian cyst; 2 subjects reported events (acute appendicitis and cholelithiasis) during the single-blind washout interval; one subject reported an automobile accident that resulted in fractures of the femur and ankle during the post treatment observation interval.

There were no deaths in study 322-US.

*Study 316-NA*

Protocol 0858A4-316-NA is a phase 3, multicenter, randomized double-blind, placebo-controlled study that is being conducted at approximately 75 sites in North America with approximately 5 subjects per study site. Study 316-NA started in June 2005 and is expected to be completed in August 2007.

The primary objective of study 316-US is to evaluate the effect of LNG 0.090 mg/EE 0.020 mg administered in a continuous daily regiment versus the effect of placebo on the mean change in average Daily Record of Severity Problems (DRSP) 21-item total daily score from baseline to the cycle 1 efficacy period and from baseline to the last on-therapy efficacy period.

Ninety-nine (99) subjects were enrolled in study 316-NA and have data in the database as of the July 14, 2006 cut-off. Adverse events were reported in 77 (77.8%) of subjects. Abdominal pain, back pain, dysmenorrhea, headache, infection, nausea, pain, and upper respiratory infection were reported by $\geq$ 10% of subjects. AEs were recorded using classification by COSTART.

A total of 5 (5.1%) were withdrawn from the study because of adverse events. Four (4) subjects were withdrawn because of worsening PMDD symptoms and 1 subject was withdrawn because of a *pulmonary embolus* which occurred during the post-treatment period (at 86 days). This subject was a 42 year old white female who weighed 123.8 kg (BMI = 46.3 kg/m$^2$) who was on Celebrex , Glucosamine, Clobetasol™ Cream and Novo-Difenac™. **She had no history of DVT.** A lung scan revealed a massive saddle block embolus and a large venous thrombus was found in her leg with a Doppler ultrasound. She survived and was treated with appropriate anticoagulants.

There were no deaths in study 316-NA.

*Study 318-WW*

Study 318WW is a phase 3 multicenter, randomized, double-blind, placebo controlled study that is being conducted at approximately 80 sites worldwide with approximately 7 subjects per study site. The primary objective of study 318-WW is to evaluate the effect of treatment with LNG 0.090 mg/EE 0.020 mg administered in a continuous daily regimen versus the effect of placebo on the mean change in the average DRSP 21-item total daily score from baseline to the cycle 1 efficacy period and from baseline to the last on-therapy efficacy period.

Twenty eight (28) subjects were enrolled in study 318-WW and have data in the database as of July 14, 2006. Adverse events were reported in 25 (93%) of subjects. Abdominal pain, arthralgia, asthenia, back pain, breast pain, headache, infection, and nausea were reported in $\geq$ 15% of subjects. AEs were recorded using terminology by COSTART.

A total of 3 (5.1%) of subjects were withdrawn from the study because of adverse events. One subject withdrew because of migraine which occurred during the double-blind treatment period; 2 subjects withdrew because of adverse events (abdominal distention and emotional lability) that occurred during the post-treatment period.

There were no deaths in study 318-WW.

In conclusion, information provided by the sponsor in the safety update does not indicate any significant adverse changes in the safety profile of LNG 0.090 mg/EE 0.020 mg. There was one SAE in study 322-US of pulmonary embolism (This subject was a 42 year old white female who weighed 123.8 kg [BMI = 46.3 kg/$m^2$] and was enrolled in the PMDD symptoms study). One pulmonary embolism was also seen in study 313NA. (She was a 22 year old white female, healthy, who weighed 69.55 kg and was 165.1cm in height; a PE was diagnosed after 331 days of treatment). Pulmonary embolism is a rare event (1:10.000) with lower dose OCs. This reviewer believes that two pulmonary embolisms **out of 2,851 subjects treated with Lybrel™ in** all of the studies submitted to the original NDA and complete response do not constitute an untoward safety signal with this drug product. **The safety profile for Alesse™ over a 10 year period (Alesse™ contains the same** amount of ethinyl estradiol and slightly less levonorgestrel [10mcg]) also support the belief that there *is not* **a high index of suspicion that Lybrel™ might** increase the risk of pulmonary emboli.

# 10 APPENDICES/ADDENDUM

## Addendum to Review of Lybrel™-NDA 21-864

As stated in the Executive Summary for this review of the Complete Response and in the original **Medical Officer's review, I recommended that** (levonorgestrel 0.090 mg/ethinyl estradiol 0.02 mg) not be approved for prevention of pregnancy based on an unacceptable demonstration of pregnancy rate (as evidenced by the Pearl index and Life Table methods). In addition, there is an unacceptable discontinuation rate and poor cycle control. The safety profile is acceptable. As **part of the Approvable decision letter on Lybrel™** issued by the Division on June 27, 2006, the Division sought the input of a Reproductive and Urologic Advisory Committee (AC) regarding certain general issues with respect to efficacy cycle control and safety of hormonal contraceptive methods that were germane to the concerns **with Lybrel™. This meeting was convened on** January 23-24 of 2007 with the expectation that an expert committee might provide additional guidance to the Division regarding hormonal con**traceptives in general. The Division's hope was that these discussions might help it with the decision on approvability of Lybrel™, even though** Lybrel was not specifically discussed.

After review of the proceeding (questions and answers posed to the committee) of the Reproductive and Urologic AC on January 23-24, this **reviewer remains convinced that Lybrel™** should *not* be approved unless the high pregnancy rate could be offset by a demonstrable non-contraceptive benefit or an additional safety benefit to the patient. **Lybrel™ demonstrated a high** pregnancy rate (especially method failure) that is accompanied by an unacceptable discontinuation rate and poor cycle control. No demonstrated benefit **to taking Lybrel™ has been** presented. Even the objective of sustained amenorrhea was not demonstrated in the data presented in the NDA.

The following represents *my reading* of the proceeding regarding the 3 issues of pregnancy rate, discontinuation rate and poor cycle control.

**Pregnancy rate**
The Division, prior to 1996, had a fixed Pearl index of 1.5 or less; the Pearl index gradually **increased to 2 and in 2001 increased to 2.38 (actually 2.67). Pregnancy "creep" was an issue** within the Division that staff members felt should be addressed.

The AC did not reach a consensus as to whether there should be a fixed pregnancy rate despite several attempts by the Division to prod the committee to provide a specific number representing an acceptable pregnancy rate. Risk/benefit ratios were discussed and theoretical benefits of lower dose pill (e.g. decrease in ovarian cancer) were discussed. However, after review of the minutes and comments made by various members, I am unable to ascertain how a new contraceptive with a high pregnancy rate, poor cycle control and a demonstrated high discontinuation rate provides a better risk/benefit ratio to the subject. In the end the vast majority of subjects will take this method of contraception for one reason, a desire not to get pregnant. One and one-half percent will become pregnant in the first year when **they taken there method "perfectly" and other**

unknown number will become pregnant because of poor cycle control that leads to discontinuation and possibly pregnancy. In the absence of clear advice from the AC that provides sound reasoning to move forward with a drug product such as Lybrel™, other than proposed theoretical benefits, (no theoretical benefit could be remotely supported by information in the NDA), the existence of other approved 0.020mg ethinyl estradiol products on the market that provide a better pregnancy rate and better cycle control, I am still unable to recommend approval of Lybrel™.

**Cycle Control**
Prior to the AC the Division had the impression that a non-product related AC might provide board information on the importance of cycle control. Previous published data support the concept that subjects with more unscheduled bleeding and spotting were more likely to discontinue a product and were more likely to become pregnant right after discontinuing that product. Since this was not a product-specific meeting the issue of poor cycle control that was observed in the Lybrel™ review was not discussed. In the AC discussion, the committee felt that the FDA should approve products based on their demonstrated safety and efficacy and allow the clinician to determine acceptability. Acceptability might include poor cycle control if there was positive counterbalance in some unspecified benefit. In the Lybrel™ review no specified or unspecified benefit was demonstrated in regards to cycle control.

The description of scheduled vs. unscheduled bleeding was recommended to be placed into the approved label. This reviewer concurs with this recommendation.

**Discontinuation rates**
The AC provided no additional input into discontinuation rates that might have impacted upon a modification in this reviewer's overall conclusion regarding Lybrel™. The high discontinuation rate that is directly related to unscheduled bleeding (approximately 50%) remains a cause for concern with this product. Ultimately as with many products, the consumer will decide that too much unscheduled bleeding is not acceptable and will stop taking this product, however, in that time interval, because of unscheduled bleeding, an unanticipated pregnancy may have occurred that may be directly attributable to method failure.

The AC stated that the patient should be told that the risk of pregnancy increased substantially as soon as the patient stops using hormonal contraception. The Division has provided information on discontinuation rates to the physician in previous labels; the same will occur in the clinical studies section of the Lybrel™ label.

This reviewer believes despite my recommendation that the product not be approved, if Lybrel™ is ultimately approved, then the pregnancy rate (Pearl index and Life table analyses) should be place in the clinical studies section. This pregnancy rate should be in the form of both the Pearl index and the life table analyzes with appropriate confidence intervals. Since this study was meant to support the US approval process alone, study 313-NA pregnancy rates should be the sole pregnancy rate in the clinical studies section. It is also recommended that the pregnancy rates should *not be removed at subsequent printed labels* for this product. Also, monthly

bleeding rates should be stated in the approved label as well as discontinuations because of bleeding.

## 11 REVIEWING TEAM VERSION OF DRAFT LABELING *

***Primary reviewer, medical team leader, statistical team leader—Final sent to sponsor May 16, 2007**

b(4)

36 Page(s) Withheld

_____ Trade Secret / Confidential

6 Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Medical-_____*

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

/s/
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Phill H. Price
5/16/2007 03:12:34 PM
MEDICAL OFFICER

Shelley Slaughter
5/17/2007 02:51:23 PM
MEDICAL OFFICER
I concur with the Dr. Price's (primary medical officer) recommendation that this continuous regimen oral combination contraceptive not be approved. See also the TL memorandum for my rationale for the concurrence with the recommendation.

4/5/06

**CLINICAL REVIEW**

| | |
|---|---|
| Application Type | NDA 21-864 |
| Submission Number | 000 |
| Submission Code | N |
| Letter Date: | May 27, 2005 |
| Stamp Date: | May 27, 2005 |
| PDUFA Goal Date: | March 27, 2006 |
| Reviewer Name: | Phill H. Price, M.D. |
| Review Completion Date: | March 30, 2006 |
| Established Name: | Levonorgestrel (LNG) (90μg)/Ethinyl Estradiol (EE) (20μg) Continuous Use |
| **(Proposed) Trade Name:** | **Lybrel™** |
| Therapeutic Class: | Estrogen/Progestin |
| Applicant: | Wyeth Pharmaceuticals, Inc. |
| Priority Designation | S |
| Formulation: | Levonorgestrel; 18,19-Dinorpregn-4-en-20-yn-3-one,12-ethyl-17-hydroxy-,(17α)-,(-)-<br>Ethinyl Estradiol 9-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)- |
| Dosing Regimen: | Levonorgestrel 90μg and Ethinyl Estradiol 20μg daily---for continuous use |
| Indication: | Prevention of Pregnancy in women who elect to use this product as a method of contraception |
| Intended Population: | Woman at risk for pregnancy |

## Table of Contents

## Table of Tables



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# 1 EXECUTIVE SUMMARY

## 1.1 Recommendation on Regulatory Action

Non-Approval of levonorgestrel 90μg/ethinyl estradiol 20μg (LN/EE) for prevention of pregnancy is recommended based on an unacceptable Pearl index. In addition there is an unacceptable discontinuation rate and poor cycle control. The safety profile is acceptable.

**There is insufficient evidence to conclude from a clinical viewpoint that Lybrel™ provides an** effective method of contraception. Efficacy data for this product demonstrated a high Pearl index 2.38 (CI 1.51, 3.37) for a de-novo oral contraceptive being sought for approval; the method failure Pearl index is (1.55 (CI 0.87, 2.56) the highest method failure rate reviewed in the Division (HFD-580). In addition, this product has the highest rate of discontinuation associated with an oral contraceptive; the discontinuation of use is driven by unexpected bleeding. This reviewer concludes this product does not provide the level of contraceptive effectiveness that has been seen with similar lower dose combined oral contraceptives and should not be approved. Safety is not considered a major concern with this product except for the fact that in demonstrating a high discontinuation rate and unexpected bleeding, the subject is at an increased risk for unintended pregnancy.

## 1.2 Recommendation on Postmarketing Actions

No Postmarketing studies are deemed necessary. The recommendation is for non-approval.

### 1.2.1 Risk Management Activity

No additional risk management is deemed necessary. The recommendation is for non-approval.

### 1.2.2 Required Phase 4 Commitments

In view of the fact that the recommendation is for non-approval, no Phase 4 commitments will be recommended.

### 1.2.3 Other Phase 4 Requests

None

## 1.3 Summary of Clinical Findings

### 1.3.1 Brief Overview of Clinical Program

Wyeth, Inc. has proposed an extended use method of at least one year duration of a combined oral contraception (COC). Wyeth is proposing use of a slightly lower dosage than their approved product Alesse® to be used continuously. This product utilizes 0.090 mg of levonorgestrel (LN) and 0.02 mg of ethinyl estradiol (EE) continuously compared to Alesse® which utilizes 0.10mg of levonorgestrel and 0.02mg of ethinyl estradiol over a 21- day treatment period. Historically, oral contraceptives have been given for 21days of active drug with a 7-day withdrawal period. A more recently approved product, Seasonale®, is given for 84 days continuously of active drug followed by 7 days of withdrawal on placebo pills. The implied benefit of prolonged contraception is a reduction in the number of withdrawal bleeding periods that woman undergo while taking oral contraceptives.

Oral contraceptives were introduced in the 1960s, and the standard 21-day regimen (21days with active pills and a 7-day hormone free interval) was established to mimic the length of the natural menstrual cycle to make it acceptable to women. This regimen remained unaltered for over 30 years. There were a number of small studies that evaluated OCs taken for longer than 21-days, typically for 42 or 84 days. While the acceptability of these extended cycle regimens was good, the breakthrough bleeding rate was higher than that observed with the standard 21-day regimen and this discouraged development. The first OCs that were introduced without the 21-day regimen were intended to either improve the contraceptive efficacy by reducing the hormone-free interval from 7 to 4 days or to improve the bleeding profile by adding 10µg of ethinyl estradiol (EE) to 5 of the remaining 7 days, which are usually hormone free. The first OC to alter the 21-day regimen with the intention of inhibiting menses was Seasonale which has 84 days of active drug (LNG 150µg/EE 30µg) followed by 7 days of placebo.

This NDA is based on a Phase 1 study (106-US) to determine the pharmacokinetic properties of LNG and EE, a Phase 2 study (208-US) to demonstrate the inhibition of ovulation, and 2 pivotal Phase 3 safety and efficacy studies 313-NA and 315-EU. The 0.090 mg of levonrorgestrel and 0.02 mg of ethinyl estradiol continuously was selected as the best approach to provide contraception with inhibition of ovulation and menses. Studies were designed to evaluate the return to menses and the safety and efficacy of continuous-use LNG 90µg/EE 20µg during a second year of treatment are on-going at the time of filing of this NDA.

| | |
|---|---|
| **Name of Drug:** | **Lybrel™ (0.090 mg of** levonorgestrel and 0.02 mg of ethinyl estradiol) |
| Class: | Oral Contraceptive |
| Route of Administration: | Oral |
| Indication: | Prevention of Pregnancy |
| Pivotal Efficacy and Safety Trial | One pivotal US trial (313-NA) and one supportive European trial (315EU) |

| | |
|---|---|
| Number of Subjects Enrolled in Trials | Study 313-NA 2134 subjects; study 315EU 641 subjects (323 test drug -318 active drug |
| Number of Subjects In safety database | 2,851 in safety database; 22,171 cycles of exposure for up to 1 year (13 cycles of use) |

1.3.2 Efficacy

**Efficacy was based on the study drug's ability to prevent pregnancy in the Phase 3 clinical trials. This was calculated by utilizing the Pearl index (PI) and using all "on-treatment" pregnancies** defined as pregnancies occurring between the start of the study drug through 14 days following the last dose of study drug. This is consistent with the definition utilized by the Division .Two other Pearl indices were also utilized, those occurring between the start of the study drug through 7 days after treatment and those occurring between the start and stop of the study drug. Primary emphasis for the purpose of determining effectiveness is placed in subject population age 35 years or less.

According to the sponsor the total number of on treatment pregnancies in Study 313-NA was 23. Utilizing a denominator of 15,461 cycles and 13 **pill packs per year, the sponsor's Pearl's index of "Study Drug is 1.93** (95% CI 1.93 [1.23, 2.90]) for all subjects. The primary comparator drug is Seasonale® (Pearl index 1.98). According to the sponsor if the Pearl index is restricted to women age 35 years or younger the Pearl index increases to **2.38** (CI 1.51, 3.57) for a total of 12,572 cycles. ***The population of women age 35 years or younger is the population considered for effectiveness of the study drug.*** The Life table analysis for the total population was based on 11,295 pill packs. The Life table analysis gives a cumulative termination rate for accidental pregnancies of 0.0297 with 13 pill packs. The pill pack cumulative termination rate of the LNG 90µg/EE 20µg continuous use regimen per woman was 0.4541. For subjects age 35 years or younger at study start the Life table analysis for this population was based on 9,180 pill packs. The Life table analysis gives a cumulative termination rate for accidental pregnancy of 0.0348 with 13 pill packs. The pill pack cumulative termination rate of the LNG 90µg/EE 20µg continuous use regimen per woman was 0.4750.

Efficacy conclusion:
The Pearl index and life table analyses are ***not supportive*** of approval of this product. The final Pearl index is 2.38 (CI 2.09, 4.41) for the age group 35 years or less and the Life table analyses is 0.0350 (CI 0.0227, 0.0539). The Pearl index for method failure is 1.55 (0.87, 2.56) The Pearl index for the total population is 1.93 (CI 1.23, 2.90) with a Life table of 0.0297 (CI 0.0230, 0.0506).

1.3.3 Safety

The safety database for Study Drug comprised a total of 2,533 subjects, including 18 subjects in a Phase 1 study (106-US), 58 subjects in a Phase 2 study (208-US), 2457 subjects in Phase 3

studies (313-NA and 315-EU) who received the continuous use regimen, and 318 subjects in a Phase 3 study (315-EU) who received LNG 100µg/EE 20µg in a 21-day cyclic regimen as a comparator. The total number of subjects is 2,851. In the pooled phase 3 studies, there were 22,751 cycles of exposure, and among those subjects who received continuous use LNG 90µg/EE 20µg, 1,137 subjects completed 13 cycles of use.

No ***new*** safety concerns are noted with this regimen that has not been previously reported with the 21 or 24 day regimens. There were no deaths in this study attributable to study drug. There were one case of DVT and pulmonary embolism that appears to be attributed to the study drug and a second DVT that is complicated by the subject being asthmatic and obese.

Adverse events related to dysmenorrhea, vaginal bleeding, metrorrhagia and vaginal hemorrhage were the most common treatment-emergent adverse events (TEAEs). These TEAEs were higher than those commonly seen with a similar 21-day cyclic regimen that includes a 7-day hormone free interval. Other frequently occurring TEAEs included headache, (migraine and not otherwise specified), nausea and abdominal pain; none of these are unexpected for a low-dose oral contraceptive.

The overall incidence of vaginal bleeding was higher with the continuous use regimen in the first 6 pill packs but not in the last 6 pill packs. There were fewer total days of vaginal bleeding compared to the 21-day regimen; however, more subjects discontinued because of unpredictable bleeding and cycle control. There were decreases in hemoglobin at 7 months (.75grams) and at the end of the study (.36grams), but they were deemed to be not clinically meaningful changes because they would not have required transfusion.

Metrorrhagia and vaginal hemorrhage were the most common reasons for safety-related discontinuations from these studies. It is also noted that in a sub-population of 146 subjects no hyperplasia or malignancy were observed and pathological specimens revealed decrease endometrial growth and decidualization without atrophic endometrial changes.

If there is an approved label it should reflect the bleeding associated with this means of contraception and the higher drop out rate associated with a continuous use of a low dose oral contraceptive.

1.3.4 Dosing Regimen and Administration

This is the first totally continuous use oral contraceptive; there is no withdrawal period of either 3 or 7 days. There is one approved product (Seasonale®) that utilizes 84 days of active pill use and -7 placebo days.

1.3.5 Drug-Drug Interactions

There are a number of drug-drug interactions that have been identified with the use of oral contraceptives. The co-administration of antibiotics, anticonvulsants, and other drugs increase the metabolism of OCs. Several of the anti- protease inhibitors have been studied with co-

administration of OCs and significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some **cases. Herbal products containing Saint John's** Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. CYP 3A4 inhibitors may increase plasma hormone levels. Higher dosages of this formulation are presently in the class label.

1.3.6 Special Populations

Combination oral contraceptives are intended for the population at risk for pregnancy. The pharmacokinetics of levonorgestrel and ethinyl estradiol is described in 18 fasting women. No unexpected findings were noted in these studies. No studies were performed exclusively addressing particular ethnic groups. No additional studies were preformed to evaluate the effect on hepatic or renal function. Class labeling describes the effect of steroid hormone in subjects who have impaired liver function.

The sponsor requested a full waiver of all pediatric studies according to the class label. The safety and efficacy of this product has been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 and older. This product is not indicated before menarche. A waiver is recommended.

# 2 INTRODUCTION AND BACKGROUND

## 2.1 Product Information

**Lybrel ™ (levonorgestrel and ethinyl** estradiol tablets) must be taken ***exactly as directed*** and at intervals not exceeding 24 hours to achieve maximum contraceptive effectiveness. The dosage of **Lybrel™ is one yellow tablet daily** without any tablet-free interval.

## 2.2 Currently Available Treatment for Indications

Over the last 40 years multiple oral contraceptives have been developed. Oral contraceptives may be either monophasic or multiphasic. Two estrogens have been utilized, mestranol and ethinyl estradiol. Ethinyl estradiol is the primary estrogen used in most OCs today. The doses of estrogen in active OCs vary between 20μg to 50 μg per day. Multiple progestins have been utilized including norethindrone, norethindrone acetate, levonorgestrel, ethynodiol diacetate, norethynodrel, desogestrel, norgestimate, gestodene (not approved in US) and drospirenone. Each compound has a different potency and a different balance between estrogen and progesterone activity and any residual androgenicity.

## 2.3 Availability of Proposed Active Ingredient in the United States

The proposed ingredients in this oral contraceptive have been available for over 23 years (levonorgestrel component) compared to norgestrel component (1968). There are multiple

generic products utilizing LN/EE in varying dosages of either the estrogen or progestin. These products are usually taken for 21 active drug days and 7 placebo days. Recently in 2003, Seasonale, which contains LN 150µg/EE30µg was approved for usage over 84 active days of treatment and 7 placebo days.

## 2.4 Important Issues With Pharmacologically Related Products

There are no new or additional pharmacological issues associated with this product.

## 2.5 Presubmission Regulatory Activity

The first discussion between Wyeth and FDA regarding a continuous use regimen of LNG/EE occurred on April 8, 2002. Main agreements included the following:

- Preclinical pharmtox studies performed to support marketed LN/EE products are sufficient to support the proposed continuous use program.
- One 30-day, multiple dose, clinical PK study with the proposed clinical dose will be sufficient to support development of LN/EE continuous use regimen.
- Standard study design for oral contraceptives (10,000 cycles, including 200 women being exposed for at least 13 cycles) would support the indication for continuous use. An extension would be needed for long term safety and bleeding patterns, as would post-treatment follow-up for return to menses and fertility.
- Further discussion between FDA and Wyeth should occur for indication [redacted] b(4)
- Wyeth should address the possibility that unintended pregnancies may be diagnosed at a later gestational age with a continuous regimen.

On August 28, 2002 Wyeth filed their IND. This IND proposed to study LN 90µg/EE 20µg in a continuous use regimen. Contraceptive efficacy and safety, bleeding profile, cyclic symptomatology in women with dysmenorrhea or symptoms of PMS at baseline were to be studied. The IND contained the following 2 studies:

- A single center, open-labeled study to evaluate the effects on ovulation of LN 90µg/EE 20µg in a daily, continuous oral regimen (Study 208-US)
- A Phase 3, multiple center, open-labeled study to evaluate the safety and efficacy of LN 90µg/EE 20µg in a continuous daily regimen for oral contraception (Study 313-NA)

On October 31, 2002 there was a correspondence between Wyeth and FDA. Wyeth submitted changes to a Phase 2 protocol. These include a clarification in the SAP that bleeding data will be collected and reported; androstendione is added to increase the amount of androgen data collected; and an addition to the number (15/day) of cigarettes a subject could smoke was added.

On November 8, 2002 Wyeth received the following comments from FDA:

- A coagulation profile that includes platelets, anti-thrombin-3, factor V Leiden, and Proteins C and S should be incorporated into the baseline, Month 6 and the end of treatment assessments
- Monthly pregnancy test (either at home or in the clinic) between the protocol scheduled clinical assessments should be incorporated into the clinical trial to reduce the possibility that a pregnant subject might be exposed to study drug for more than 100 days
- The CRSS sub-study is ***purely exploratory*** and can not lead to any product claims. If claims are to be obtained, Wyeth should contact the Division of Neuropharmacology for the PMS indication, and the Division of Antiflammatory, Analgesic, and Ophthalmologic Drug Products for the dysmenorrhea indication
- An interim analysis is not acceptable to support an NDA. Data should be not submitted prior to completion and final analysis of the US Phase 3 study
- Because of the extensive number of exclusions, ***it is unlikely that an accurate pregnancy rate will be obtained that is consistent with the general population*** that will be taking OCs (e.g., certain antidepressants/anxiolytic and antibiotic drugs which are used significantly in the general population are excluded). If these subjects are excluded, a disclaimer may need to be placed in the label stating these subjects were not studied.

On December 5, 2002 Wyeth submitted responses **to FDA's comments of November 8, 2002 on** the Phase 3 protocol:

- All subjects in Protocol 313-NA will have their platelets levels evaluated at baseline and at the 6 months and 1 year (end of treatment) assessments. Wyeth will assess anti-thrombin 3, factor V Leiden, ad Proteins C and S in a sub-population
- Wyeth will obtain either at home or in the clinic a pregnancy test during each 28-day pill pack
- Wyeth will consult with the other FDA divisions to discuss the data requirements for product claims
- Data on return to menses will be collected in a separate extension study form subjects who choose to participate and who do not elect to use hormonal contraception when they complete Protocol 313-NA
- Wyeth reduced the number of exclusion from pervious Wyeth clinical trials of oral contraceptives. One exception is the antidepressant/anxiolytic exclusion. This relates to 308 subjects in the CRSS. The antibiotic exclusion is similar to that in the current label for Alesse®. Wyeth proposed to leave the antibiotic exclusion criterion as stated.

On December 30, 2002 Wyeth submitted additional changes to their Phase 3 protocol:

- Return to menses follow-up was removed from the protocol and will analyzed in an extension study
- Subject participation was changed from 16 months to 13 months for basic and endometrial histology sub-study subjects, and from 18 to 15 months for cycle-related symptom sub-study subjects
- Study duration was changed from 22 to 19 months
- Hemostasis measures have been added to the endometrial histology sub-study for all subjects at visits 1B, 3 and 4A