# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-225**

## STATISTICAL REVIEW(S)

# Statistical Review and Evaluation
**Clinical Studies**[1]

Date: DEC 4 2000

NDA #: 21-225

Applicant: BERLEX Laboratories, Inc.

Name of Drug: Mirena LNG-IUS (levonorgestrel-releasing intrauterine system)

Indication: intrauterine contraception for up to 5 years

Documents Reviewed: Vol. 2.1, 2.2, 2.246, 2.326, 2.351,
IR Response dated 3/17/00

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Lesley Furlong, M.D. (HFD-580)

Summary of Studies

Results from two large clinical studies were submitted to support this application (see Table 1). Study B078 is an open-label study conducted in 2 centers in Finland which enrolled 340 subjects to use the LNG-IUS product for up to 5 years. Study AY99 is the re-evaluation of a subset of centers and subjects from an open-label study (#8216) conducted in Europe from 1982 through 1989. The re-evaluation included only data which was verifiable from the original study, and included 1110 subjects in qualified centers using the LNG-IUS product. All subjects were healthy women, aged 18-38, desiring contraception. For the contraception indication, the efficacy endpoint of interest is the Pearl Index (unintended pregnancies per 100 women-years of use).

The original protocols allowed for enrollment of women 18-38 years of age. The Medical Officer requested a subset analysis of women ≤ 35 years old at enrollment. This subset analysis will be the focus of the efficacy assessment for this application. This included 285 subjects from study B078 and 884 subjects from study AY99, for a total of 1169 qualified subjects ≤ 35 years old.



[1] Clinical studies

Table 1: Summary of Clinical Studies

| Study Number (Dates Conducted) | # of Centers (Locations) | Treatment Arms (# Randomized) | Indication | Duration of Treatment |
|---|---|---|---|---|
| B078 | 2<br>Finland | LNG-IUS (present formulation) n=340<br><br>LNG-IUS (old formulation) n=50 | Prevention of pregnancy | 5 years |
| AY99<br><br>(1/82 – 1989) | 15 (Europe)<br><br>7 centers were qualified for the re-evaluation | LNG-IUS n=1856 total<br><br>n=1110 at qualified centers | Prevention of pregnancy | 5 years |

## Review Issues

There were only 3 issues which the Medical Officer requested I address in this efficacy review. The first two regarded the recalculation of pregnancy rates for all pregnancies and for ectopic pregnancies. The third issue was the inclusion of bleeding/spotting results in the label.

In response to an information request (dated 3/17/2000), the applicant provided the pregnancy and exposure data necessary to calculate the Pearl Index (and 95% confidence intervals) for each of the 5 years. The Pearl Index is the number of unintended pregnancies per 100 women-years of use. The Medical Officer also wanted the pregnancy rates for ectopic pregnancies. These are presented in Tables 2 and 3. According to the Medical Officer, these rates are sufficiently low enough to support efficacy.

Table 2: Pearl Index for All Pregnancies (subjects ≤ 35 years old at qualified centers)

| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| Total # of subjects | 1169 | 1169 | 1169 | 1169 | 1169 |
| Total # of months on treatment | 12389 | 22444.2 | 30908.6 | 38481.1 | 45099.5 |
| In-treatment pregnancies | 2 | 2 | 2 | 3 | 3 |
| Pearl Index 95% CI | 0.19 (0.02, 0.70) | 0.11 (0.01, 0.39) | 0.08 (0.01, 0.28) | 0.09 (0.02, 0.27) | 0.08 (0.02, 0.23) |

Source: March 17, 2000 Response to Information Request

Table 3: Pearl Index for Ectopic Pregnancies (subjects ≤ 35 years old at qualified centers)

| | 1 year | 2 years | 3 years | 4 years | 5 years |
|---|---|---|---|---|---|
| Total # of subjects | 1169 | 1169 | 1169 | 1169 | 1169 |
| Total # of months on treatment | 12389 | 22444.2 | 30908.6 | 38481.1 | 45099.5 |
| In-treatment pregnancies | 1 | 1 | 1 | 2 | 2 |
| Pearl Index 95% CI | 0.10 (0.00, 0.54) | 0.05 (0.00, 0.30) | 0.04 (0.00, 0.22) | 0.06 (0.01, 0.23) | 0.05 (0.01, 0.19) |

Source: March 17, 2000 Response to Information Request

The third review issue is the inclusion of menstrual pattern change results in the label. In the proposed label, the applicant included results from a 1-year study (AV97) which collected diary data on menstrual flow (incidence of bleeding and spotting). That study included women 18-25 years old who were randomized to Mirena or placebo for 1 year, in an open-label, parallel design. The proposed label presented the results.

The subjects enrolled in Study AV97 were nulliparous women and were not the intended patient population for the contraception indication. The subjects enrolled in the two efficacy studies were older, and had had at least one child. The recommended patient profile in the label specifically states "for women who have had at least one child". The results from study AV97 cannot be assumed to adequately represent the expected menstrual pattern changes in the intended patient population. Therefore, I feel that the bleeding and spotting data from AV97 should not be presented in the section of the label. In addition, the label describes potential menstrual pattern changes in other sections (Warnings, Precautions – Patient Counseling), so the information is available to clinicians.

## Summary

The Pearl Index rates (and CI) for all pregnancies and for ectopic pregnancies are presented in Tables 2 and 3 for each of the 5 years in the efficacy studies. These rates were calculated based on the desired subset of patients: women ≤35 years of age in qualified centers. If the Pearl Rate(s) is reported in the label, it should be based on this subgroup analysis.

It is not appropriate to include the menstrual pattern change (bleeding and spotting from study AV97 in the section of the label. This study is not in the intended patient population. The usefulness of this type of information to clinicians would be in counseling patients, and it is presented in the Warnings and the Precautions sections of the label for that purpose.

Katherine B Meaker, M.S.
Mathematical Statistician

Concur: Dr. Nevius

Dr. Kammerman

cc:
Archival NDA 21-225
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