CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-225

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NOV 16 2000

NDA:	21-225
Product Trade Name:	Mirena® (levonorgestrel releasing intrauterine system)
Active Ingredient/s:	Levonorgestrel
Indication:	Contraception
Submission Dates:	1/31/00 (original NDA), 4/10/00 & 8/25/00
Sponsor:	Berlex Laboratories, Inc.
Type of Submission/Priority:	Original/3S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Synopsis

Mirena® (levonorgestrel releasing intrauterine system, LNG-IUS) is an intrauterine device/system (IUD or IUS) intended to release the progestin drug levonorgestrel (LNG) at an approximately nominal rate of 20 µg/day for 5 years. Each device contains a total of 52 mg of levonorgestrel. The sponsor believes that the device achieves contraception in women primarily due to high local concentrations of levonorgestrel (in the uterus) rather than the serum concentration.

A total of 6 studies were submitted in the Human Pharmacokinetic and Bioavailability section of this NDA involving pharmacokinetics in women. The formulation of the IUD was changed a few times (formulations A, B, C and D) and D is the intended "to-be-marketed" formulation. Although formulation C was used in the pivotal clinical trials, there is limited *in vivo* data available for D. Upon review, it was found that there was negligible difference between C and D, and a difference in performance between C and D is not expected clinically. Nevertheless, in support of equivalence between C and D, the sponsor has submitted substantial information on the *in vitro* and *in vivo (ex-vivo)* dissolution profiles of the drug from formulations B, C and D, and an IVIVC analysis. In addition, at OCPB's request, the sponsor has provided limited (3-month) clinical data with the to-be-marketed formulation more recently in their submission dated 8/25/00.

Recommendation

Based on the review, NDA 21-225 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. The suggested labeling changes are included in the section "Labeling Comments" and have been finalized.

Phase IV Commitment: The sponsor is urged a) to collect data on 5-year comparative dissolution profiles for compositions C and D, and (b) continue the ongoing 1-year long clinical study with final formulation (composition D) and present *in vivo* and *ex vivo* data following its completion.

/S/ Dated 11/16/2000

Dhruba J. Chatterjee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D. /S/ Dated- 11/16/00

CC: NDA 21-225, HFD 870 (H. Malinowski, A. Parekh, DJ. Chatterjee), HFD-580 (L. Furlong, J. Best), CDR (B. Murphy). [A Briefing for NDA 21-225, held on 11/13 /2000, was attended by J. Hunt, R. Agarwal, L. Furlong, A. Parekh and DJ. Chatterjee]

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BACKGROUND

Questions addressed in this section:

- What is the pharmacologic rationale for use of this drug?
- What is the main goal of therapy?
- What are other available alternatives?
- What CPB studies have been submitted in support of this NDA?

Progestin-only contraceptives primarily work by blocking ovulation, although less consistently than combinations of estrogen and progestin. Another IUD (PROGESTASERT) that releases low amounts of progesterone locally is believed to be effective due to local effects on the endometrium. According to the Medical Officer's review of this application, "The mechanisms of action of IUDs are still largely unknown. The levonorgestrel IUS has progestational effects on cervical mucus, tubal motility and endometrial histology, which all may contribute to contraceptive efficacy. There is some evidence that IUDs inactivate sperm. At least one study suggests that the levonorgestrel IUS prevents implantation. However, which (if any) of these mechanisms is most important is simply not known."

In the development of LNG IUS, four compositions, named Compositions A, B, C, and D have been used. Composition A was the first system developed although limited work was done with it. Compositions B and C are the systems that have been utilized for the majority of clinical studies, and Composition C is also the product marketed in Europe and Asia. At a request from OCPB, minimal clinical data following use of formulation D was submitted recently (August 25, 2000). For details, see section under "BIOPHARM" within this review.

This IUD is designed to deliver approximately 20 µg of LNG daily for 5 years from the implant. The main intended goal of this product is contraception. Currently, several other progestin-containing products are available for use as contraceptives. These include progestins from oral, intramuscular, subdermal implant and IUD dosage forms or in combination with estrogens in oral 'pills'.

Six full study reports have been submitted that summarize clinical pharmacology and biopharmaceutics related information in support of this NDA. A significant amount of *in vitro – in vivo* correlation (IVIVC) information has been submitted supporting waiver of a bioequivalence study that should have otherwise been conducted to 'link' the clinical and to-be-marketed formulations.

This review follows a 'Question-Based' approach.

OVERALL SUMMARY OF FINDINGS

BIOPHARMACEUTICS

- From the *in vitro* and *in vivo* evidence submitted, formulation D is not expected to perform any different *in vivo* as compared to formulation C. Hence, a waiver for a linking bioequivalence study may be granted.
- The IVIVC has been established using as the medium. The same method should be used in future to determine long term release rate and dissolution profiles.
- For short-term release methods (specifically to release lots) the sponsor has proposed a dissolution method using . Sponsor reports release rates 12% higher with as compared to (approximately) with a strong correlation between the two. From a review of the submitted data, the release rates with may be as high as (with Composition C). This was also considered while setting release specifications.
- In one pregnancy reported after 12 months of use of this IUS, the *ex vivo* release rate was determined to be only (Composition A, dissolution method not mentioned clearly) from a system designed to deliver 20 µg/24hr. Hence, the release rate specification for release of the to-be-marketed batches should not be too wide.
- Sponsor is proposing a , specification for release of lots based on their long experience with the C formulation marketed in Europe. Based on the information submitted, discussions with the CMC reviewer, a **specification** of for initial release of the lots (in was finalized on 11/16/00, and communicated to the sponsor via teleconference.
- From a review of a huge volume of dissolution data from clinical and marketed batches of formulations B and C, it was observed that although release rates were around 20 µg/24hrs (in to begin with, there was at least a 30 - 40 % drop in the release rates in 5 years. In many occasions, the release rates at the end of 5 years were in the range of This is also reflected in the drop in serum LNG concentration with time (years).
- Sponsor mentions 'weight change' and 'chemical extraction' methods while describing long-term dissolution and release rate determination procedures. It has been this reviewers assumption (verified with sponsor via T-CON dated 10/20/2000) that for all 'residual LNG' data presented in the IVIVC analysis, a chemical extraction method was used. The 'weight change' method is a crude and inaccurate procedure to determine the amount of LNG remaining, especially after clinical use. In fact, in Study Report 1211 involving formulations B and C, a release rate determination comparison between the 'weight change' and 'chemical extraction' methods lead to determination of a 30% lower rate with the latter.

PHARMACOKINETICS

- There is a significant drop in the LNG serum concentrations over the time period (5 years) for which the product is intended to be used. At the end of 4-5 years of use, the serum levels of LNG reduce to almost half the initial (0-1 year) levels. However, this reduction of LNG serum levels may not strictly correlate with efficacy (occurrence of pregnancy), as evidenced by sustained efficacy of this product for 5 years.

- *The systemic exposure of LNG from this device (based on LNG serum levels)* is significantly lower when compared to Norplant (LNG implant) or oral LNG. However, the local concentration of LNG (especially in the endometrium) may be appreciably high (≈100 fold) from this device as compared to oral LNG administration (based on data presented in Table 5 in this review, Medical Officer's review and Norplant label).
- With prolonged concomitant use of this IUS with estradiol, there might be an increase of LNG serum concentrations over time due to increased binding of estradiol to SHBG. However, this increase in LNG concentrations is not significantly large, and exposure of LNG even in such cases will be much below levels seen following Norplant or other oral LNG administration (based on data in Table 3, Medical Officer's review and Norplant label).
- Marginally higher blood levels of LNG were achieved with Formulation C as compared to Formulation B (refer to Table 2 and Figure 3).
- There is a potential for secretion of LNG in breast milk.

PHARMACODYNAMICS

- Results of clinical studies indicate that the mechanism of contraceptive effect of the LNG IUS is multi-modal. Inhibition of ovulation is not observed consistently in LNG IUS users. Although the dose of LNG release from the IUS is very low, it has an effect on gonadotropin secretion, which disturbs follicular development, and in addition to the local effect on the endometrium, contributes to contraceptive efficacy.

- A distinct relation between low serum levels of LNG from this device to failure of efficacy (pregnancy) could not be established. Although serum LNG concentrations are relatively much lower following LNG IUS use compared with that after oral and implant products of LNG, the concentrations of LNG in the endometrium are much higher following LNG IUS use compared with that following the administration of an oral. Thus, the bioavailability assessed from serum LNG concentrations may necessarily not be relevant for the contraceptive effects of LNG IUS (based on data presented in Tables 5, 6 and Medical Officer's review).

ANALYTICAL

The analytical methods used in the studies supporting the NDA are acceptable.

LABELING

The Clinical Pharmacology section of the Physican's Package Insert has been modified and these changes have been incorporated on the "N: Drive".

BIOPHARMACEUTICS

Q. Are the clinically tested (CT) and the 'to-be-marketed (TBM)' formulations same?

No. As mentioned in a previous section, the sponsor made several changes to the formulation during the product's almost 25 years of development history. Among the 4 (A, B, C and D) formulations, majority of the clinical safety and efficacy data generated to support this NDA was with the C formulation (which is also currently marketed in Europe and Asia), while D is the formulation 'to-be-marketed' in US. Following a request from OCPB, limited clinical data with formulation D was submitted recently (August 25, 2000). The following table lists the details of the formulations:

Table : LNG IUS formulations used in clinical trials

Component/Description	Composition A	Composition B	Composition C	Composition D
T-Body				
Composition (w/w):				
Removal Thread				
Composition (w/w):				
Membrane				
Composition: - Filler				
Elastomer				
Unfilled elastomer				
Polymer for elastomer				
Composition				
Hormone-Elastomer Core				
Composition - LNG Content (mg)			52	52
- LNG:elastomer (w/w)				

N/Av = Not available

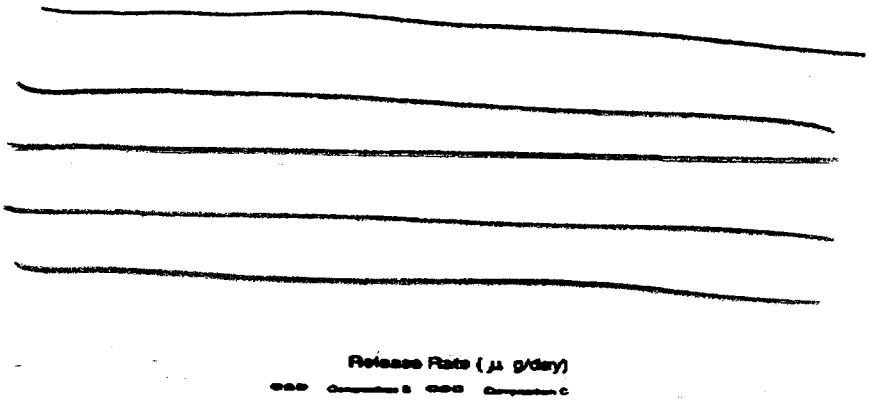
Q. How different are compositions C and D?

Based on the above table and discussions with the CMC reviewer, composition D has essentially the same polymer as C, but from a different manufacturer. Moreover, there is also a minor difference in the manufacturing process for the polymers in C and D.

This difference in the two compositions can be considered minor in relevance to the ultimate clinical performance. *In vitro* release comparing formulations B, C and D and limited *in vivo* data from formulation D has also been provided.

Q. What information is necessary to ensure equivalence of the CT and TBM formulations?

The absolute ideal information would be ensuring bioequivalence of the two formulations for the total length of intended use of the product, i.e., 5 years. However, it is almost impossible to expect availability of such data. Serum levels of LNG did not correlate with different release rates of LNG from the devices (Figure A below). Moreover, since serum levels of LNG from the device may not correlate with either efficacy or side effects of the product, a traditional bioequivalence study would not be appropriate in this case.



Release Rate (μ g/day)

In lieu of the above, an IVIVC (*in vivo – in vitro* correlation may be evaluated to obtain a sense of equivalence. However, because of the nature of the product, a conventional IVIVC analysis (as described in the guidance document involving oral extended release products) is not possible (since serum levels may neither correlate with safety/efficacy, nor release rate).

In the absence of a traditional IVIVC model (as in this case), this reviewer believes that the following (in the order of priority) is essential to prove pharmaceutical equivalence of the two formulations:

1) *In vitro* – Employing an exact similar dissolution method for the two, formulation C (CT) and D (TBM), should show a similar *in vitro* dissolution profile throughout the intended period of product use (5 years).
2) *In utero* – The two formulations should deliver similar absolute amounts of drug at similar time intervals while implanted in the uterus.
3) *In vivo* – Serum levels of LNG from the two formulations should be similar at comparable time points following insertion of the device. [This *in vivo* serum data will be supportive provided (1) and (2) have already been established].

Q. What information has the sponsor provided to ensure equivalence of the CT and TBM formulations?

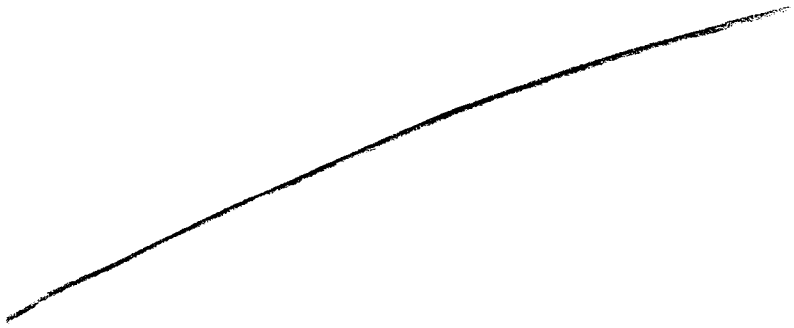
The sponsor has provided the following in considerable detail:

- A level A IVIVC analysis for formulations B and C
- *In vitro* dissolution profiles of formulation C and D and a comparison of the two
- *In vivo* serum levels of LNG following use of the TBM formulation (D) at 1, 2 and 3 months only
- *Ex-vivo* release rate comparisons between C and D

IVIVC Development

The sponsor has developed an IVIVC model with the B and C formulations. Since serum levels of LNG might really not correlate with clinical outcome, the absolute amount of drug delivered from the device (while implanted in the uterus) is a more important determinant of *in vivo* performance. The following has been established in the IVIVC analysis:

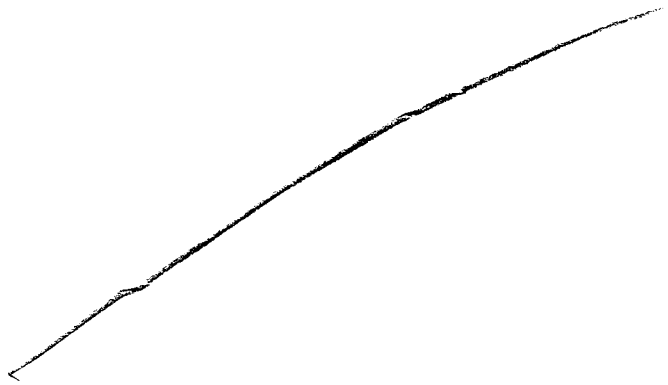
- *Ex vivo* (following use and removal of device) release rates of LNG was expressed as a first order equation, and were comparable between formulations B and C using — as the dissolution medium. When the rates for B were compared between — and —, there was a slight difference (see figures and table below) - the rate of change in release rate was lower in —



Ex-vivo Release Rate Constants for Composition B and C [R. Rate = $A.e^{-k.t}$]

Composition / Protocol	No of IUSs Analyzed	Dissolution Medium	k (SE) day^{-1}	A (SE) µg/day	Reference	
					IND amendment	Data Set
B / 89532	37	—	4.1×10^{-2} (2.2×10^{-3})	18.0 (0.59)	[Serial 003]	1
C / 89532	280		4.5×10^{-2} (6.1×10^{-4})	19.8 (0.17)		
B / 8216	124	—	2.0×10^{-2} (9.0×10^{-4})	19.6 (0.25)	[Serial 006]	Appendix 1

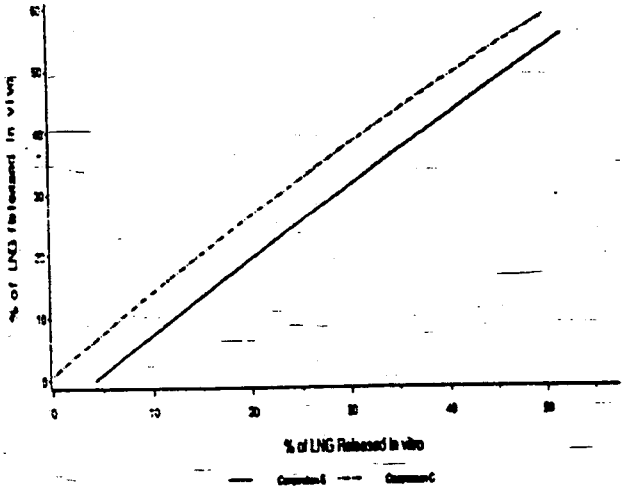
- Using a similar first order equation to construct % LNG released with time showed comparability between B and C (as below).



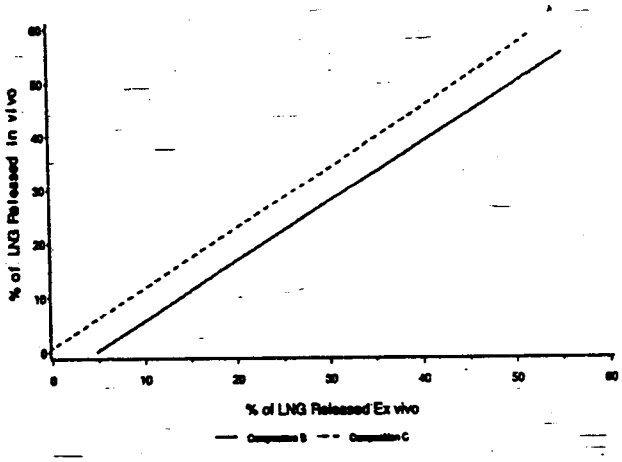
Ex-vivo release rate constants based on residual LNG for Compositions B and C in two clinical studies.

Composition / Protocol	No of IUSs Analyzed	k (SE) day^{-1}	A (SE) µg	Reference	
				IND amendment	Data Set
B / 89532	46	4.1×10^{-4} (7.3×10^{-5})	48.5 (0.42)	[Serial 003]	1
C / 89532	317	4.2×10^{-4} (3.4×10^{-5})	51.6 (0.22)		
B / 8216	63	4.3×10^{-4} (1.2×10^{-5})	41.0 (0.70)	[Serial 006]	Appendix 1

- To demonstrate the IVIVC, the *in vitro* dissolution data were divided into 50-day intervals, and the mean of the dissolution rates during each interval was assigned to the 50-day interval. In a similar fashion, the times for LNG IUS removal were divided into 50-day intervals, and the amount of LNG released *in vivo* at those time points determined. Plots were constructed for % LNG released *in vivo* (based on amount remaining) versus either % released *in vitro* or *ex vivo* (following figures and table). Note: Initial loading amount is different for B and C.



Level A correlation for Composition B and C utilizing long-term dissolution as the *in vitro* measurement



Level A correlation for Composition B and C utilizing *ex-vivo* release as the in vitro measurement

Relationship between *in utero* release and long term dissolution or *ex vivo* dissolution (Equation: Y = m*X + b)

***In Utero* Release and *In Vitro* Dissolution**

Composition	m	b
B	1.18	-4.60
C	1.15	2.23

In Utero Release and Ex Vivo Dissolution

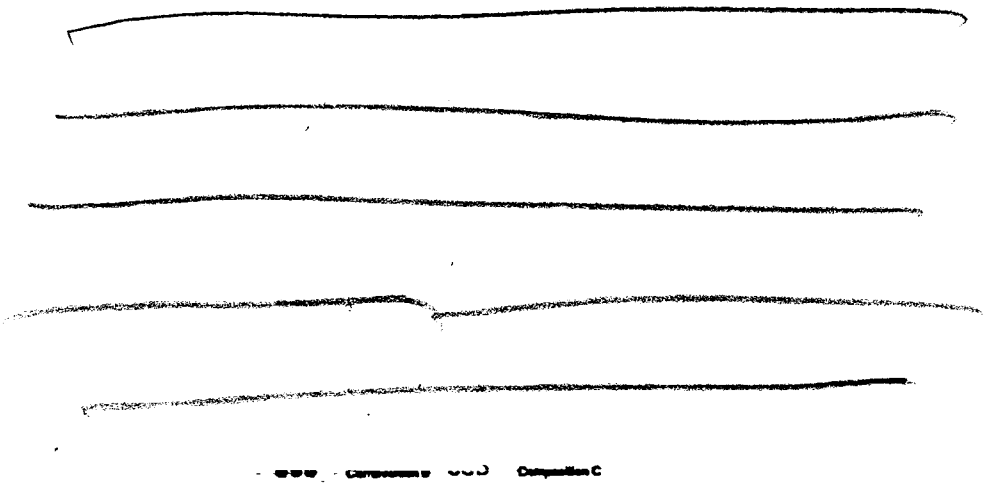
Composition	m	b
B	1.10	-5.34
C	1.15	0.44

- Following the establishment of this IVIVC, there was a change in the dissolution method (, and the above relationship was re-constructed for formulation C plotting % released *in vivo* against the new *in vitro* release rate. The m and b values for C were 1.35 and 2.13, respectively. This showed that approximately, a similar IVIVC relationship existed with the new dissolution method.

IVIVC Validation

According to the agency's guidance on IVIVC, the model needs to be internally and externally validated. That generally involves development of systems with different release rates and checking whether the % released *in vivo* can be predicted from the model and the value of % released *in vitro*. For this product such a model was not developed. However, the sponsor also presents the following that might substitute for internal validation:

Figure 1



IVIVC for *in utero* release and long term *in vitro* dissolution rate for Compositions B and C (Y = m*X + b)

Composition	m (SE), mg*day/µg	b (SE), mg
B		
C		

Statistical analysis indicated the equivalence of the two slopes ($p = 0.33$), and an overall correlation ($r^2 = 0.83$) of the long-term dissolution rate and the LNG amount remaining in the IUS. The values of b are slightly different numerically, and the difference is due to variability or a lag in the initial dissolution. As in the case of the *ex vivo* release rate, the long-term dissolution rate data also correlate linearly with the *in utero* release. In addition, because *in vivo* release correlates with both the *ex vivo* release rate and the long-term dissolution rate individually, the latter two measures of *in vitro* release rate correlate with each other.

Sponsor submitted limited clinical data from formulation D following a discussion at a pre-NDA meeting. This data is only till 3 months of use (and will continue till 1 year). Although no true external validation is possible with this limited data, this data provides assurance that formulation D releases the drug in comparable amounts as compared to composition C in the first 3 months.

Reviewer's Comments on IVIVC

Figure 1 should be interpreted as, higher the amount remaining in the device (or the shorter is the duration of its use), the higher is the release rate that may be achieved from it (conversely, if the release rate is higher, it indicates that the device has been in use shorter). The IVIVC presented is not exactly similar to traditional models for IVIVC that are generally developed for oral extended release formulations designed for QD or more frequent administration. The nature of the current product and minimal correlation of efficacy/safety with serum drug levels makes development and validation of such a model almost impossible. This reviewer believes that sufficient evidence has been presented in this analysis to assume that an IVIVC relationship exists.

This device is designed to sit in the uterus and deliver locally the desired amount of LNG. So, theoretically, just if the *in vitro* dissolution profile and rates match between the CTF and the TBM prototypes, there is no reason to believe that the *in vivo* performance of the two formulations will differ significantly. Such evidence has also been provided (see below).

Comparison of *In vitro* Dissolution between Formulations C and D

Using the 'modified long-tern dissolution method' (— as medium) the sponsor shows comparability of formulation C with pilot and production batches of D for a 1–year period. Please refer to Tables 1-2 (F2 comparison) and Figures 1-5 within **Attachment 1** for details of the comparative dissolution between formulations C and D.

Reviewer's Comments on Release Rate Comparison

The *in vitro* release rate profiles appear to be identical (for all practical purposes) when compared between the production C and D batches. However, this comparison is only for one year, and needs to be followed for the total period of intended use (i.e., 5 years). The sponsor should be encouraged to do such analysis, and submit the results when they are available.

***In Vivo* Use of TBM Formulation D**

During a teleconference between the sponsor and OCPB (pre-NDA period), it was decided that for a planned safety study with formulation D, sponsor should collect serum samples and determine *ex vivo* release of the devices. The sponsor recently (8/25/2000) submitted a study report with data following 3 months of clinical use of the IUS in 16 patients. Serum levels were determined at months 1, 2, 3, and *ex vivo* release was compared to the initial amounts of LNG in the devices (please refer tables 2 –4 and figure within **Attachment 2** for a details of the results).

Reviewer's Comments on in vivo study with formulation D

- Formulations C and D show comparable serum LNG levels at 3 months (approx. 230 pg/mL).
- Although no long-term (over 3 months) information on *ex vivo* release profile was available, data provided in this study indicates that a) the device does deliver the drug (since LNG levels were detectable in serum), b) that the serum level of LNG at 3 months is in the similar range as observed with formulations B and C (both of which were safe and effective) and c) that there is no evidence of an initial burst effect.

- In order to determine the amount of LNG delivered the residual amounts in the devices after three months were compared with a *mean* value of initial LNG amount from all the devices used. In 3 months only a negligible amount (1.8 mg, based on a 20 µg/24 hr release, ≈ 3.5% of initial load) of LNG was expected to be released. Hence, there were some negative values for the amount released in 3 months, which made this *ex vivo* analysis less meaningful for this short period of time.

Dissolution Specifications

Method: The release rate test is conducted on [redacted] IUS for a period of two weeks. In this release rate test, each IUS is placed in a bottle filled with [redacted] of dissolution medium [redacted]. The IUSs are allowed to stabilize in the dissolution medium at [redacted] for [redacted] After stabilization, the bottles are placed in a [redacted]. The medium is [redacted]. The concentration of LNG in the dissolution medium is determined by [redacted] The mean release rate of the last four days is calculated for each IUS, and the mean release rate of the [redacted] IUSs tested is reported as the short-term *in vitro* release rate.

Sponsor Recommends: [redacted] for initial release of lots
Reviewer recommends: [redacted] for initial release of lots

Upon review of the release rate data submitted with [redacted], it was observed that release rates in [redacted] might be 30 – 40 % lower when compared with the [redacted] medium. Moreover, there might be as much as a 40% drop in release rate in the final year of device use compared to the initial rate. Hence, the lower limit of the release specification need to be raised in order to maintain *in vivo* release of LNG within the safe and effective range over 5 years. The above specification was (based on information provided on clinical lots) finalized upon discussions with the CMC team, and was communicated to the sponsor via teleconference on 11/16/2000.

PHARMACOKINETICS

Q. What is the PK profile of levonorgestrel?

The PK of LNG has been described in many studies before, and many of its PK parameters are described in the respective labels of approved products, either from a combination with estradiol, or by itself. According to "The Pharmacologic Basis of Therapeutics" (Goodman and Gilman, 9th edition), LNG is almost completely absorbed orally (BA 94%, or 100 % when administered in combination with estradiol) with V_d of 1.7 L/kg, half life ≈ 15 hours, Cl of 1.5 ml.min/kg and ≈

52% of the dose is excreted in the urine. About 37% of the drug is bound to albumin. When coadministered with estradiol, clearance and albumin binding decrease and half-life increases from an increased drug binding to SHBG.

According to the sponsor, the most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylations at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α, 5β-tetrahydro-LNG, while excretion occurs predominantly in the form of glucuronides. Some of the parent LNG also circulates as the 17β-sulfate.

Due to the availability of sufficient knowledge on the PK of LNG (as above), an attempt has not been made in the current submission, to delineate the ADME characteristics of LNG. The sponsor has monitored the serum levels of LNG during prolonged use of several formulation of the IUD.

Q. What is the PK profile of levonorgestrel from this IUD?

This section lists a summary of all PK studies conducted with different formulations of the IUS.

(i) ***Report B073/1207: Serum levonorgestrel concentration during 78 month use of LNG IUD***

The objective of this open-label study was to compare the clinical performance and contraceptive efficacy of the Nova T (a copper IUD) and the LNG IUS (Mirena) over 78 months. The pharmacokinetic objective was to investigate serum concentrations of levonorgestrel (LNG) in subjects using the LNG IUS for a minimum of 5 years (60 months) and a maximum of 6.5 years (78 months). Fifteen subjects received 20 µg/24 h of LNG from an IUS (Composition B) containing approximately 46 mg of LNG.

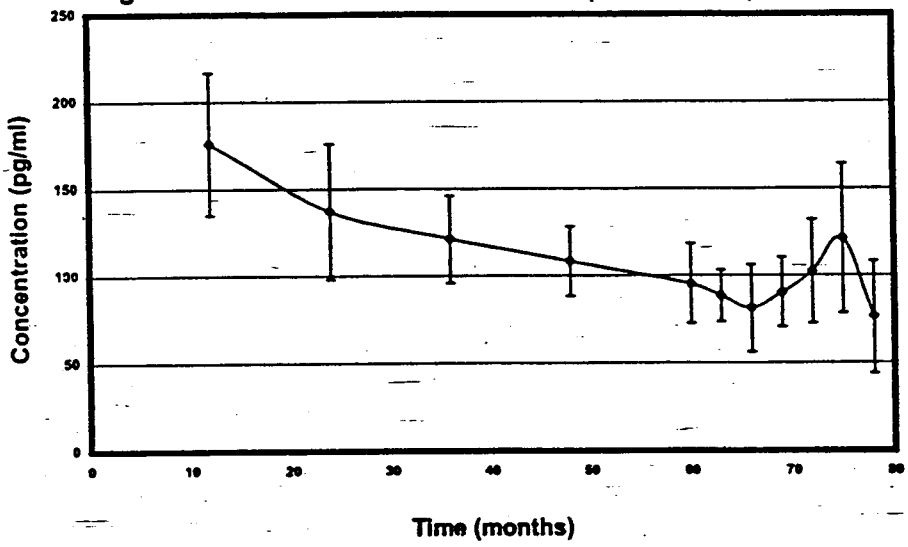
The clinical plan was to enroll 3000 subjects between the ages of 18 and 38 years, who were regularly exposed to the risk of pregnancy, and were willing to rely solely on the Nova T IUD or LNG IUS for contraception. Serum LNG concentrations were analyzed after *in utero* administration of LNG as part of the LNG-IUS. Blood samples for the determination of LNG in serum were drawn at 3, 12, 24, 36, 48, and 60 months after insertion of the IUS, and at 63, 66, 69, 72, 75, and 78 months after insertion. Serum LNG concentrations were determined by using a specific validated RIA.

Fifteen subjects were enrolled in the pharmacokinetic arm of the study. The mean age of the group was 32.4 years (range 23 to 38 years) and the mean weight was 55.5 kg (median 58 kg; range 50 to 84 kg). Twelve subjects completed the 5 years of the original protocol and three subjects remained upto 6.5 years. Serum analyses revealed that LNG concentrations were detectable until 6.5 years (78 months) after initial insertion of the IUS. Mean serum LNG concentrations were 176 ± 41 pg/mL at 12 months (N= 8), 95 ± 23 pg/mL at 60 months (N = 12), and 76 ± 32 pg/mL at 78 months (N = 3). Table 1 (and Figure 1) shows mean serum LNG concentrations from 12 to 78 months. Results indicate that the IUD may maintain sustained levels of LNG beyond the intended 5 year period.

Table 1: Serum LNG concentrations (Mean ±SD) after insertion of LNG IUS

Time (Months)	N	Serum LNG Concentration Mean ± SD (pg/mL)
12	8	176 ± 41
24	14	137 ± 39
36	13	121 ± 25
48	4	108 ± 20
60	12	95 ± 23
63	6	88 ± 15
66	11	91 ± 25
69	10	90 ± 20
72	14	102 ± 30
75	5	121 ± 43
78	3	76 ± 32

Figure 2 - Serum LNG Concentration (mean ± s.d.) vs. Time



(ii) Report B078/102-89532-07: Five-year clinical performance of the two formulations of LNG IUS - Serum LNG concentration with the new formulation (Composition C) compared to the original one (Composition B)

The objectives of this randomized, double blind, Phase 3 study were to evaluate the 5-year clinical performance and safety of the LNG IUS with the reformulated IUS. The pharmacokinetic objectives of the study were to determine and compare the serum concentrations and release rates of LNG in subjects using 1 of 2 compositions of the LNG IUS for 1 year. This study was designed to compare the clinical performance and contraceptive efficacy of 2 different compositions of the LNG IUS over 5 years.

The clinical plan was to enroll 400 subjects (350 Composition C and 50 Composition B) between the ages of 18 and 38 years, who had at least 1 pregnancy, were regularly exposed to the risk of

pregnancy, and were willing to rely solely on the LNG IUS for contraception. The first 99 subjects enrolled in the study at a single predetermined center were randomized to either the Composition B or the Composition C IUS. Composition B was the clinical LNG IUS, which contained ho..mone-releasing sleeve of the elastomer ———— , and Composition C contained a hormone-releasing sleeve of elastomer ———— The remaining subjects in the study were given the Composition C IUS. Blood samples for the determination of LNG in serum were drawn at 3, 6, 12, 24, 36, 48 and 60 months after insertion of LNG IUS. Serum LNG concentrations were determined by using a specific validated RIA. Ninety-nine subjects (49 Composition C, 50 Composition B) were enrolled into the pharmacokinetic arm of the study. The median and mean serum LNG concentrations from 3 to 60 months at each time point are shown in Table 2. Figure 2 shows the mean serum concentration – time profile.

Table 2: Serum LNG concentrations by time and composition

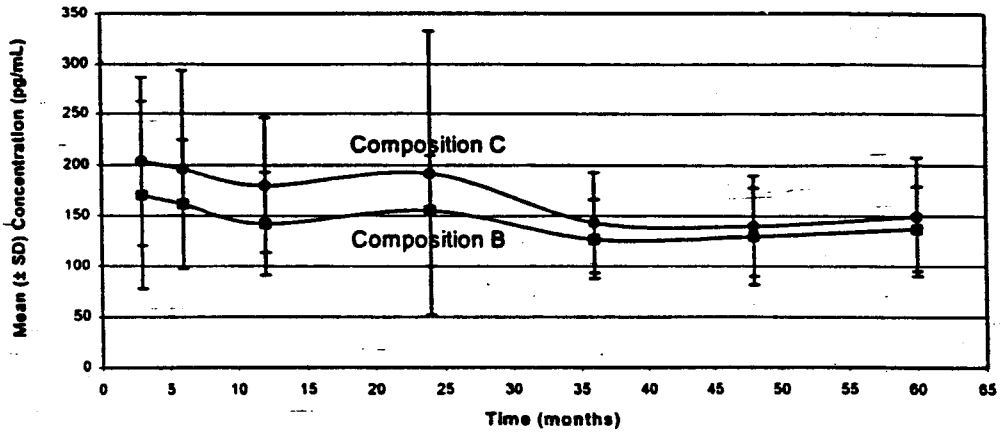
	Elastomer ———— Composition C					Elastomer ———— Composition B				
Time (months)	N	Median Conc. (pg/mL)	Mean Conc. (pg/mL	SD	Range	N	Median Conc. (pg/mL)	Mean Conc. (pg/mL	SD	Range
3	41	195	204	83	—	41	144	170	92	—
6	40	185	196	98	—	45	153	161	64	—
12	38	177	180	66	—	37	133	142	51	—
24	32	158	192	140	—	29	141	155	55	—
36	28	139	143	50	—	25	114	127	39	—
48	27	126	140	50	—	26	132	130	48	—
60	19	142	159	59	—	26	129	137	42	—

Statistical analyses revealed 3-month median serum LNG concentrations of 195.00 pg/mL and 144.00 pg/mL for Compositions B and C, respectively. The median concentration at 60 months decreased to 142.00 pg/mL for Composition C. Median serum LNG concentrations were higher in the Composition C treatment group for the first 3 years, when compared with the Composition B treatment group. Thereafter, they were similar. Analysis of variance (ANOVA) revealed a significant difference ($p = 0.02$) in serum LNG concentrations between the two compositions. Serum LNG concentration changed statistically significantly ($p < 0.0001$) over time when the concentrations at 12 months and after were compared with those at 3 months.
The serum LNG $AUC_{3\text{-}60\ months}$, was calculated for subjects with serum samples collected at the 3 and 60-month time points, and who had not missed more than one of the other time point ($N = 38$). There was no significant difference between the 2 compositions for $AUC_{3\text{-}60\ months}$. ($p = 0.17$) The log transformed ratio (Comp. C/Comp. B) was 116.5 % (90% CI, 96.9 - 140.1).

Statistical analyses revealed 3-month median serum LNG concentrations of 195.00 pg/mL and 144.00 pg/mL for Compositions B and C, respectively. The median concentration at 60 months decreased to 142.00 pg/mL for Composition C. Median serum LNG concentrations were higher in the Composition C treatment group for the first 3 years, when compared with the Composition B treatment group. Thereafter, they were similar. Analysis of variance (ANOVA) revealed a

significant difference (p = 0.02) in serum LNG concentrations between the two compositions.

Figure 3 - Serum LNG Concentration vs. Time (Composition B vs. C)



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The serum LNG $AUC_{3\text{-}60\ months}$, was calculated for subjects with serum samples collected at the 3 and 60-month time points, and who had not missed more than one of the other time point (N = 38). There was no significant difference between the 2 compositions for $AUC_{3\text{-}60\ months}$. (p = 0.17) The log transformed ratio (Comp. C/Comp. B) was 116.5 % (90% CI, 96.9 - 140.1).

(iii) Report B336/1274: Levonorgestrel plasma concentrations during 6 Months of use with 10 µg/24 h releasing intrauterine device

The objective of this open-label study was to compare the clinical performance of the LNG IUS with the Nova T copper releasing IUD. The pharmacokinetic objectives were to evaluate the stability of serum LNG concentration upto 6 months. Ten female subjects received 10 µg/24 h of LNG delivered via an IUS.

The clinical plan was to enroll 60 women who, immediately after a first trimester abortion, had agreed to the insertion of an IUD or IUS. A subgroup of 10 subjects gave informed consent allowing blood sampling for serum LNG concentrations to be carried out in association with scheduled blood sampling for E2, progesterone, luteinizing hormone (LH), and FSH concentrations according to the protocol. Blood samples for the determination of LNG in serum were drawn at 1, 2, 3, and 6 months of use of the IUS. Serum LNG concentrations were determined by using a specific validated RIA. All serum samples collected were analyzed in a single assay session.

Mean serum LNG concentrations at the 1-, 2-, and 3-month time points, 98.9 ± 35.5 pg/mL, 86.6 ± 25.1 pg/mL, and 90.0 ± 41.8 pg/mL, respectively (N = 10). At the 6-month time point, a 29% reduction in mean serum concentration, (70.0 ± 7.9 pg/mL) was seen with a large variation in serum LNG concentrations.

Results of the study indicate decreasing LNG concentrations at 6 months of use, which would suggest a limited period of IUS use with the 10 µg/24 h release.

(iv) Report B089/1243: Report on Levonova (Composition C) in menopausal use: Combined hormone replacement therapy with LNG IUD and subcutaneous estradiol implants

The purpose of this open-label study was to test the efficacy of the LNG IUS to oppose estrogen stimulus on the endometrium, and to assess safety and acceptability as part of hormone replacement therapy (HRT). The pharmacokinetic objective was to evaluate the pharmacokinetics of LNG and sex hormone binding globulin (SHBG) in menopausal women after 1 year of treatment with the LNG IUS and concurrent estrogen replacement therapy. Subjects received 20 µg/24 h LNG (Composition C) from the LNG IUS and 50 µg/24 h estradiol (E2) transdermally for the first 4 weeks. From 4 weeks until termination, each subject continued to receive 20 µg/24 h LNG from the IUS, in addition to 20 µg/24 h or 60 µg/24 h estradiol subcutaneously, from the implant. The clinical plan was to enroll 46 postmenopausal females with natural menopause confirmed by a follicle stimulating hormone (FSH) level greater than 30 IU/L, who had not used HRT for 2 weeks before entering the study. Physical and gynecological examinations, and vital signs were used to evaluate the good health of the subjects.

Subjects were randomized to 1 of 2 treatment groups at the time of study entry. Each subject received the LNG IUS and transdermal E2 patches (50 µg/24 h). After 4 weeks, transdermal E2 treatment was discontinued and subcutaneous therapy begun. Group 1 received one subcutaneous estradiol implant releasing 20 µg/24 h and Group 2 received three subcutaneous estradiol implants releasing a total of 60 µg/24 h.

Forty-six subjects (23 per treatment group) were enrolled in the study and completed both the transdermal and subcutaneous estrogen replacement therapies while using the LNG IUS. The mean ages and weights were 51.7 years (range 44 to 60 years) and 69.9 kg (range 52 to 107 kg) and 52.3 years (range 46 to 66 years) and 63 kg (range 47 to 85 kg) for Group 1 and Group 2 respectively.

Blood samples were drawn for serum LNG concentrations at 4, 8, 12, 30, and 56 weeks post insertion of the LNG IUS. Blood samples for SHBG were drawn at 0, 4, 5, 6, 7, 8, 12, 30, and 56 weeks post insertion of the LNG IUS. Serum samples were assayed separately for LNG and SHBG. LNG concentrations were determined by a specific validated RIA. SHBG concentrations were determined using a _____. Tables 3 and 4 summarize mean serum concentrations of LNG and SHBG, respectively

Table 3: Mean serum concentrations of LNG with concurrent doses of E2

	LNG with 20 µg/24 h E2 (Group 1)		LNG with 60 µg/24 h E2 (Group 2)	
Time (weeks)	N	Mean ± SD (nmol/L)	N	Mean ± SD (nmol/L)
4	20	0.92 ± 0.29	23	1.11 ± 0.42
8	22	0.91 ± 0.26	21	1.09 ± 0.39
12	20	0.88 ± 0.27	21	1.06 ± 0.39
30	20	0.81 ± 0.29	21	1.06 ± 0.45
56	16	0.77 ± 0.22	20	0.96 ± 0.40

312.5 pg/mL = 1 nmol/L

Table 4: Mean Serum SHBG concentrations with 20 µg and 60 µg doses of E2

Time (weeks)	SHBG with 20 ug/24h E2 (Group 1)		SHBG with 60 ug/24h E2 (Group 2)	
	N	Mean ± SD (nmol/L)	N	Mean ± SD (nmol/L)
0	22	66.14 ± 27.36	23	72.96 ± 33.45
4	22	53.09 ± 19.00	23	58.39 ± 29.64
8	22	51.14 ± 17.21	23	55.74 ± 26.23
12	22	54.92 ± 33.53	23	56.13 ± 26.87
30	21	58.00 ± 34.47	22	61.27 ± 28.37
56	17	56.24 ± 28.42	21	65.57 ± 33.06

Mean serum LNG concentrations were highest (Group 1: 0.92 ± 0.29 nmol/L, Group 2: 1.11 ± 0.42 nmol/L) 4 weeks after insertion of the system. Mean LNG concentrations decreased significantly ($p < 0.001$) over time in both groups. Serum concentrations at week 56 were 0.77 ± 0.22 nmol/L for Group 1 and 0.96 ± 0.40 nmol/L for Group 2. Compared with Group 2, LNG concentrations in Group 1 were statistically significantly lower throughout the study ($p = 0.03$).

Mean serum SHBG concentrations decreased significantly ($p < 0.001$) in both groups during the first 4 weeks and then remained consistent through the duration of the study. Baseline, Week 4, and Week 56 concentrations (nmol/L) were 66.14 ± 27.36, 53.09 ± 19.00, and 56.24 ± 28.42 respectively for Group 1 and 72.96 ± 33.45, 58.39 ± 29.64, and 65.57 ± 33.06 respectively for Group 2. Group 2 serum SHBG concentrations were higher than Group 1 throughout the study, however, the difference was not statistically significant ($p = 0.46$).

(v) Literature Reports:

Due the a long (≈ 20 years) product development history of this product, there are some literature references on this product that provides useful PK information

a) Serum and tissue concentrations of LNG during use of the LNG IUS.

[Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentration of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin. Endocrinol.* 1982; 17:529-36]

The objective of the study was to determine the LNG concentrations in endometrial, myometrial, Fallopian tube and fat tissue in women using a LNG IUS compared with women receiving oral LNG.

Thirteen healthy, regularly menstruating women between the ages of 41 and 49 years, who were scheduled for hysterectomy due to uterine fibroids, were enrolled in the study. Thirty-six to 49 days before surgery, 9 subjects were inserted with a LNG IUS containing 63 mg of LNG, designed to release 30 µg/24 h. The remaining 4 women were given Cyclabil® tablets containing 2 mg estradiol valerate and 250 µg LNG, each day for 7 days before surgery. Immediately after the uterus had been removed, tissue samples were obtained. In addition, a blood sample was obtained at the time of the removal of the uterus. Plasma LNG concentrations were determined by using a specific validated RIA. Methods for determining LNG concentrations in endometrial, myometrial, Fallopian tube, and fat tissue were developed and validated for this study.

Results of the study are summarized in Table 5. Mean LNG concentration in plasma and fat was lower in the LNG IUS group than in the oral group; the difference between treatment groups for LNG concentrations in plasma was statistically significant ($p < 0.15$) but not for the fat concentration ($p < 0.05$). There appeared to be a linear relationship between LNG concentration in plasma and fat ($r = 0.82$, $N = 11$). The mean concentrations of LNG in the myometrial and fallopian tissues were similar when comparing the 2 groups. The endometrial LNG concentrations were much higher in the IUS group (808 ng/g wet weight) than in the oral group (3.5 ng/g wet weight).

Table 5: LNG concentrations by tissue type and route of administration

Tissue	IUS Mean ± SD	N	Oral Mean ± SD	N
Plasma (pg/mL)	202 ± 102	7	559 (± 209)	4
Fat (ng/g wet weight)	1.23 ± 0.46	7	4.41. ± 1.06	4
Myometrium				
ng/g wet weight	2.43 ± 1.86	6	1.42 ± 0.46	4
pg/mg protein	34 ± 23	4	25 ± 15	4
Endometrium				2
ng/g wet weight	808 ± 511	4	3.5	2
pg/mg protein	6937 ± 3126	4	44	
Fallopian Tube				
ng/g wet weight	1.8	3	1.7	2
pg/mg protein	17	3	19	2

In conclusion, the LNG concentrations in myometrial, Fallopian tube, and fat tissue were of the same order relative to wet tissue weight in both the IUS and orally treated groups. The only statistically significant difference between the groups was a higher LNG concentration in fat tissue in the oral group when compared with the IUS group. This was correlated with higher plasma concentrations seen 12 hours after oral administration compared with low, steady plasma concentrations via the *in utero* route. Endometrial LNG concentrations were many fold higher in the IUS group than in the orally treated group. This was expected as the LNG is released directly in the

endometrium. If the weight of the different organs in which tissue concentrations were determined is considered, the total amount of the LNG was lowest in the endometrium.

b) Secretion of LNG in milk during use of the LNG IUS

[Heikkilä M, Haukkamaa M, Luukkainen T. Levonorgestrel in milk and plasma of breast-feeding women with a levonorgestrel-releasing IUD. *Contraception* 1982; 25:41-9]

The objective of this study was to investigate plasma and breast milk concentrations of LNG for a 3-month duration in subjects using the LNG IUS beginning 6 weeks after delivery of a full-term healthy baby.

Ten breast-feeding, amenorrheal women were enrolled in the study. Five subjects each received LNG IUSs releasing 10 µg/24 h and 30 µg/24 h at six weeks postpartum. Blood samples for plasma concentrations of LNG were drawn at 0 (time of insertion), 1, 2, 3, 4, 6, 8 and 12 weeks after insertion. Plasma and milk LNG concentrations were determined by using a specific validated RIA.

The mean plasma concentrations were 207 ± 64 pg/mL and 235 ± 87 pg/mL for the 10 and 30 µg/24 h IUSs, respectively. Differences between the 2 groups could be seen in the first 3 to 4 weeks, when plasma LNG concentrations of the 30 µg/24 h IUS were higher than those of the 10 µg/24 h IUS. These higher concentrations dropped rapidly over the first few weeks and both concentrations from both groups were similar thereafter. LNG concentrations in the 10 µg/24 h group were consistent throughout the time studied. Mean breast milk LNG concentrations were similar, 56 ± 35 pg/mL and 57 ± 34 pg/mL for the 10 and 30 µg/24 h IUSs, respectively, throughout the study. The plasma to milk ratio was 100:15 during the first week after insertion and 100:25 at the end of the 3-month period. No correlation between plasma and breast milk concentrations was observed. The amount of LNG excreted per day in 600 mL of breast milk is approximately 0.1% of a daily dose of 30 µg, or 0.03 µg. The daily dose reaching an infant via breast-feeding is 0.1% of a daily 30 µg dose. On a body weight basis, the amount received by the infant is approximately 1.2% of the adult amount.

PHARMACODYNAMICS

Q. What is the pharmacodynamic nature of levonorgestrel from this IUS?

The following are some of the conclusions that can be drawn from some of the pharmacodynamic evaluations that have been made with this IUS and reported in the NDA either as literature references, or as study reports:

- According to progesterone concentrations in one study comparing this LNG-IUD with a copper IUD, 15/17 cycles in women using the LNG-IUDs were ovulatory, whereas only 8/17 cycles showed normal follicular growth and rupture as judged by ultrasound. In ovulatory cycles, the peak progesterone concentrations were lower than in the copper IUD control subjects. The preovulatory estradiol and LH peak concentrations were also lower than in control subjects. SHBG concentrations were lower in LNG-IUD users than in copper IUD users.

- According to the serum concentrations of E2 and progesterone in another study, the hormone profiles were divided into four types of reaction: A) anovulatory, B) anovulatory but with high follicular activity, C) ovulatory but with luteal insufficiency, and D) ovulatory. Among the 29 treatment cycles, there were 10 D-type, 3 C-type, 13 B-type and 3 A-type of ovarian reactions: 44.8% of the cycles were ovulatory (C + D) and 55.2% were anovulatory (A + B). In general, serum concentrations of levonorgestrel were low in ovulatory cycles and were high in anovulatory cycles. The difference was statistically significant. There were marked individual differences. The decline of serum LNG from the 1st (492 pmol/L) to the 6th (320 pmol/L) treatment months was 34.9% on average. The amenorrheic cycles coincided mostly with the hormonal profile of ovulatory types, which indicated that the cause of amenorrhea is due to the local effect of levonorgestrel on the endometrium. The levonorgestrel concentrations were significantly correlated with serum SHBG, $r = 0.8856$, p less than 0.001, and with E2, $r = 0.4661$, $p < 0.05$.
- In one clinical study, an attempt was made to relate efficacy failure (pregnancy) with serum concentration of LNG from the LNG-IUD (as in table 6 below).

Table 6: Pregnancies occurring with currently marketed product (Composition C) in Europe

Leiras Reference No.	Plasma/Serum LNG (pg/mL)	Duration of Treatment (mo)	Comment
(7) SWE		6	
(11) SWE		18	Uterine perforation; IUS detected intra-abdominally
SWE		24	IUS was not detected at time of delivery. Expulsion prior to conception suspected
LEI03348-99		40	
LEI02995-98		45	
LEI02992-98		36	
LEI02556-98	Not detectable	6	Expulsion prior to pregnancy suspected
LEI02532-98		18	

- The sponsor presents some data relating the nominal release rate (dose) to the effect in some "dose-finding" studies. It was observed that 20 and 30 µg/24h systems were comparable in their efficacy and safety profiles and comparable to or better than the Nova T (copper IUD) system. There was one pregnancy (among 30 women) from the 10 µg/24h system after 7 months of usage (serum level of LNG at that time). Moreover, it was determined that the lower-rate systems were not adequate for the 5-year period. Also, the higher rate (50 µg/24h) systems were suppressing ovulation, and it was difficult to maintain the delivery rate at that level for 5 years. All these facts led to the choice of 20 µg/24h as the optimal dose.

Q. Has the selection of dose been appropriate?

- More thorough and better-designed dose finding studies may have been conducted to determine the 'real' minimum effective dose. But, considering the nature of the product, those studies

needed to be long and burdensome. Based on the studies that the sponsor conducted, the 20 µg/24h selected dose seems to be roughly optimal considering efficacy, safety as well as a practically achievable delivery rate that can be maintained (at least theoretically) for 5 years. However, it has not been clearly determined by the sponsor what may be the threshold release rate below which there is a high probability of device failure.

- Based on a discussion with the Medical Officer (Dr. L. Furlong) assigned to the NDA, it was ascertained that the Medical Officer found the dose selection satisfactory.

ANALYTICAL METHODOLOGY

Q. Are the analytical methods used appropriate?

During the 25-year history of development of this product, several analytical methods were used for assay of LNG in serum. With time, better methods were available which reduced the errors for the assay.

Radioimmunoassay (specific for LNG) was most commonly used for the assay of LNG in biological fluids. The assays were highly specific for LNG, sensitive, sufficiently accurate and precise. For most values of LNG between 100 – 500 pg/ml (common levels obtained in the clinical studies), all within and between-run accuracy and precision c.v. values were within —— Concentrations < 50 pg/ml was generally associated with higher % c.v values. However, lower % c.v. values (was obtained with a more recent method. The HPLC method utilized for higher concentrations of LNG (residual LNG in devices etc.) had precision and accuracy c.v. values within ——

Based on the above information, the assay methods used to generate the data within this NDA is acceptable.

LABELING COMMENTS

The relevant section of the label has been edited and that section along with the suggested corrections are included below. Please note that a majority of the changes in this section has already been made by the Medical Officer, and this reviewer is in agreement with those changes. Additional changes are also included herein.

CLINICAL PHARMACOLOGY

2 pages redacted from this section of the approval package consisted of draft labeling

12 Page(s) Withheld

MAR 27 2000

Best

MAR 27

FILING MEMORANDUM

NDA#:	21-225
Product/Active Ingredient/s:	Mirena (52 mg levonorgestrel @ 20 µg/day for 5 years)
Indication:	Contraception
Submission Date:	January 31, 2000
Sponsor:	Berlex Laboratories
Type of Submission:	Original NDA
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Today's Date:	March 20, 2000.

Synopsis

Mirena® (levonorgestrel-releasing intrauterine device) is composed of a T-shaped frame on which a reservoir containing 52 mg levonorgestrel (LNG) is mounted. This reservoir is covered with a membrane that regulates the release of LNG from the system at the rate of 20 µg/day. One application of this system is intended for a 5-year period of use.

The sponsor has listed four formulations (A, B, C and D) in the NDA during the long drug development history for this product (please see attachment). Most of the clinical trials were performed using formulations B and C. These formulations differ mostly in polymer composition. Extensive *in vitro – in vivo* (IVIVC) correlation has also been presented comparing formulations B and C. The 'to-be-marketed' formulation D has a different supplier for the incorporated elastomer as compared to C. No clinical trial/study was performed with this formulation (D). A formal bioequivalence study for a product of this kind (5 – year IUD) may not be feasible. Detailed IVIVC may provide relevant information on relative performance of formulations B, C and D.

According to a teleconference between the sponsor and members of OCPB (please refer to minutes of TCON dated 8/10/99 attached) and the pre-NDA meeting (1/27/98), it was decided that the above formulation difference will NOT be a filing issue. The NDA will be reviewed in light of the IVIVC and the respective *in vitro* performance of the formulations. The sponsor was requested to collect plasma and *ex-vivo* data on LNG (from a clinical trial that has already been planned with formulation D) and submit the information at least 90 days prior to the NDA action date. The protocol for this clinical study (IND ——————— and amendments submitted between Feb 8 and March 21, 2000) with formulation D appears satisfactory from an OCPB perspective.

Recommendation

Based on the above facts and all the other information provided (see attached list of studies) in the NDA, this application is file-able from a Clinical Pharmacology and Biopharmaceutics perspective. The following should be communicated to the sponsor:

1. The review clock may be extended (as previously decided) if the *in vivo* clinical results with Formulation D are not obtained 90 days prior to the NDA action date.

2. The sponsor is expected to submit detailed analytical methods and validation reports as soon as they can.
3. To help the review process, the sponsor is requested to submit electronic summary of reports for all PK and/or Biopharmaceutics related studies (including all IVIVC results).

/S/

Date 3/27/00

Dhruba J. Chatterjee, Ph.D.
Pharmacokinetics Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

FT Signed by Ameeta Parekh, Ph.D. (Team Leader) /S/ Date 3/27/00

- Attachments

- CC: NDA 21-225, HFD-870 (S. Huang, A. Parekh, D.J. Chatterjee), HFD-580 (L. Furlong, J. Best), CDR (B. Murphy).

Attachment I

LIST OF STUDIES

6.5.2 Tabular summary of studies included in Item 6

Table 2: Tabular summary of studies included in Item 6

Report No. (SAG/Leiras) [Protocol No.]	Type of Study	Study Design	Number of Female Subjects (Age Range/Mean)	Dosage Form	Dose	Batch No./Mfg. Site /Date Mfg.	Applicant Conclusion
B073/1207 [8216]	Pharmacokinetics, 6.5 years	Open-label, randomized, comparative study	15 (23-38/32.4)	Test LNG IUS 20µg/24 h Composition B Reference Nova T, 200 mm²	Test One LNG IUS for duration of 78 months	Test 060782, 080782, 090782, 100782, 130782/Leiras, Turku, Finland/1982 Reference HF23/NA/NA	Serum concentration of LNG was detected for 6.5 years after insertion of the LNG IUS.
B078/102-89532-07 [89532]	Pharmacokinetics	Double blind, randomized, comparative study	Test (new) 49 (25-38/32.8)	Test LNG IUS 20µg/24 h Composition C	Test One LNG IUS for duration of 60 months	Test 92543/Leiras, Turku, Finland/1989	Change in elastomer of the IUS did not significantly effect the safety and efficacy over five years use when compared to the IUS with the original elastomer
			Reference (original) 50 (23-38/32.9)	Reference LNG IUS 20µg/24 h Composition B	Test One LNG IUS for duration of 60 months	Reference 73181/Leiras, Turku, Finland/1987	
B336/1274 [Protocol number not available]	Pharmacokinetics	Open-label	10 (NA)	LNG IUS 10µg/24 h Composition A	One LNG IUS for duration of 6 months	140579 Leiras, Turku, Finland/1979	Serum LNG concentration decreased 29% at 6 months, suggesting its limited use.

IUS = Intra uterine system; LNG = Levonorgestrel; Mfg = Manufacture; NA = Not available

Table2: Tabular summary of studies included in Item 6 (Continued)

Report No. (SAG/Leiras) [Protocol No.]	Type of Study	Study Design	Number of Female Subjects (Age Range/Mean)	Dosage Form	Dose	Batch No./Mfg. Site/Date Mfg.	Applicant Conclusion
B089/1243 [90513]	Pharmacokinetic study with estrogen therapy	Open-label, two treatment randomized, parallel	Group 1 23 (44-60/51.7)	Group 1 LNG IUS Composition C 20 µg/24 h	IUS One LNG IUS for duration of 56 months Patch One patch applied transdermally twice a week at 3-and 4-day intervals for four weeks followed by Implant Group 1 One implant subcutaneously implanted and kept for 56 weeks Group 2 Three implants subcutaneously implanted and kept for 56 weeks	IUS 120112, 120102/ Leiras, Turku, Finland/1991 Patch B146400, B1347000, B139700 and B132900/NA/NA Implant 1185200/Leiras Turku, Finland/1991	Subjects with higher estradiol dose had significantly higher serum LNG concentrations (p = 0.03).
			Group 2 23 (46-66/52.3)	Group 2 Estraderm® Transdermal patch 50 µg/24 h and estradiol implant 20 µg/24 h			

IUS = Intra uterine system; LNG = Levonorgestrel; Mfg = Manufacture; NA = Not available.

Table2: Tabular summary of studies included in Item 6 (Continued)

Report No. (SAG/Leiras) [Protocol No.]	Type of Study	Study Design	Number of Female Subjects (Age Range/Mean)	Dosage Form	Dose	Batch No./Plant/Date Manufactured	Applicant Conclusion
B074/1211 [8216, 89532]	In vitro	N/A	N/A	Composition B LNG IUS 20 µg/24 h Composition C LNG IUS 20 µg/24 h	N/A	Composition B 060782, 080782, 090782, 100782, 73181/ Leiras, Turku, Finland/1982 Composition C 92543/Leiras, Turku, Finland/1989	Both compositions had similar LNG release patterns during one year in utero
B330/102-89532-08 [89532]	In vitro	N/A	N/A	Composition B LNG IUS 20 µg/24 h Composition C LNG IUS 20 µg/24 h	N/A	Composition B 73181/Leiras, Turku, Finland/1987 Composition C 92543/Leiras, Turku, Finland/1989	Both compositions had similar LNG release patterns during five years in utero

N/A = Not applicable; LNG = Levonorgestrel; IUS = Intra utrerine system

Attachment II
Composition of formulations

agreed that interim data from this study may be submitted while review of this NDA is ongoing. The four compositions are summarized in Table 10.

Table 10: LNG IUS formulations used in clinical trials

Component/Description	Composition A	Composition B	Composition C	Composition D
T-Body				
Composition (w/w):				
Removal Thread				
Composition (w/w):				
Membrane				
Composition:				
- Filler				
Elastomer				
Unfilled elastomer				
Polymer for elastomer	Po			
Composition				
Hormone-Elastomer Core				
Composition				
- LNG Content (mg)			52	52
- LNG:elastomer (w/w)				

N/Av = Not available

Information about batches of LNG IUS used in the key studies in this submission is tabulated in Table 11. A more detailed accounting of the formulation and manufacture changes for Composition B, C and D was submitted to the Agency in an IND amendment [Serial No. 011] on September 23, 1999. This information is also available in Item 4, vol. 1, p. 21

6.8 In vivo performance of the LNG IUS

As discussed previously in Section 6.6, serum LNG concentrations and derived pharmacokinetic parameters are not appropriate to assess in vivo performance of the LNG IUS. More direct and more appropriate evaluation of in utero release performance was based on laboratory test procedures on the used IUSs obtained at various times during the clinical studies. In utero release of LNG from the IUSs removed during and at the end of the two clinical studies (Protocol 8216 and Protocol 89532) was evaluated using three methods, namely: loss of weight of the IUS, ex vivo release rate and determination of remaining (residual) LNG by chemical extraction. Results and discussion of in utero release of IUSs used in two clinical studies can be found in Report B074 (1385 Composition B IUSs available upto 5 years from Protocol 8216, and 6 Composition B and 37 Composition C IUSs available during the first 14 months of Protocol 89532) and Report B330 (50 Composition B IUSs and 340 Composition C IUSs available up to 5 years from Protocol 89532). Report B074 and Report B330 are provided in Item 6, vol. 13, p. 265 and Item 6, vol. 15, p. 1 respectively. Additional data analysis methods

Text Table 7: Comparison Of LNG IUS Compositions Used In the Phase 3 Clinical Trials (B And C) and the Planned Marketed Product (D)

Component/Description	Composition B	Composition C	Composition D	Comments
Membrane				
Material Description (Trade name) [Supplier(s)]: Membrane				
- Elastomer				
- Filler				
Composition: - Filler				
Manufacturing Process:				

Formulation History / Studies

Table: Compositions Used in the Clinical Pharmacology and Contraception Studies Described in the Mirena® NDA 21-225[1]

When Developed (approximate)	Composition A 1978 - 1981	Composition B 1982 - 1987	Composition C 1989 - present	Composition D 1996 - present
Study Type	**Report Numbers for Studies Using the Specified Composition[2]**			
CLINICAL PHARMACOLOGY				
Studies on LNG Release and Plasma Levels		B073/1207		
	B336/1274			
		B074/1211	B074/1211	
		B330/102-89532-08	B330/102-89532-08	
Studies on Endometrial Histology		B071/1203		
	B072/1204			
Studies on Effects of Cervix and Vagina		B077/1206		
Clinical Pharmacology During Hormone Replacement Therapy			B091/1268	
Studies to Evaluate Dosage Form Performance[3]				Protocol No. 303700[3]
CONTRACEPTION				
• Controlled Trials with CRFs		AY99/LE102-98042-01[4] B075/1208 (B071/1203) (B073/1207) (B077/1206) (B076/1044)		
		B078/102-89532-07 (B330/102-89532-08)	B078/102-89532-07 (B330/102-89532-08)	
			AV97/LE102-92533-01	
- Controlled Trials / No CRFs		B079/1231		

[1] The information in this table has been extracted (with one exception – see Footnote 3) from the Table of All Studies that was submitted in the Mirena NDA 21-225 (in Item 8.7 – Integrated Summary of Safety). Please refer to the Table of All Studies for additional information pertaining to the above studies, and for information about the compositions used in all studies for which only publications are available and in other non-contraception studies. A copy of the Table of All Studies (NDA Item 8.7.4) is provided for the convenience of the reviewer.

[2] Interim reports are listed in parenthesis immediately following the corresponding final study report.

[3] This Phase 1 study is ongoing; in accordance with an agreement reached previously with the Division, interim results from this study will be submitted during the NDA review period.

[4] Report No. AY98/LE102-98042-01 is a reevaluation of the study described in Report No. B075/1208.

When Developed (approximate)	Composition A	Composition B	Composition C	Composition D
	1978 - 1981	1982 - 1987	1989 - present	1996 - present
Study Type	**Report Numbers for Studies Using the Specified Composition[2]**			
CONTRACEPTION (cont.)				
- Uncontrolled Trials / with CRFs			B083/LE102-96505-01	
			AX96/102-89548-03	
			B346/LE102-91543-02	
			AY08/LE102-92505-01	
			AZ31/LE102-92528-01	
- Uncontrolled Trials / No CRFs		B081/1230		
		B082/1212		
- Other Studies / No CRFs			B084/1256 B085/LE102-95503-01[5]	

APPEARS THIS WAY
ON ORIGINAL

[5] Partly the same population as in the study described in Report No. B084/1256

Attachment "III"

D/F

Teleconference Minutes

Date: August 10, 1999 **Time:** 11:30-12:20 PM **Location:** Parklawn; 17B-43

IND — **Drug:** Levonorgestrel-Releasing Intrauterine System

Indication: Contraception

Sponsor: Berlex Laboratories, Inc.

Type of Meeting: Guidance

AUG 31 1999

Meeting Chair: Ameeta Parekh, Ph.D.

External Lead: Herman Ellman, M.D.

Meeting Recorder: Jennifer Mercier, B.S.

FDA Attendees:
John Hunt – Deputy Director, Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-860)
Ameeta Parekh, Ph.D. – Team Leader, OCPB @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Moo-Jhong Rhee, Ph.D. – Team Leader, Division of New Drug Chemistry II (DNDCII) @ DRUDP (HFD-580)
Jennifer Mercier, B.S. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Herman Ellman, M.D. – Director, Endocrinology and Fertility Control, Clinical Research and Development
Rolf Krattenmacher, Ph.D. – Associate Director of Project Management, Female Health Care
Brenda Marczi, Ph.D. – Associate Director, Drug Regulatory Affairs
Armen Meilikian, Ph.D. – Associate Director, Clinical Pharmacology
Jo-Ann Ruane – Manager, Drug Regulatory Affairs
Hannu Allonen, M.D., Ph.D. – Director, R&D Project Management
Pasi Merkku, Ph.D. – Product Development Manager, Head of Pharmaceutical Development
Pirjo Saliinen – Project Manager
Heikki Voipio – Director, Regulatory Affairs

Meeting Objective: To discuss the IVIVC submission dated May 24, 1999.

Discussion:

- the sponsor has linked formulation changes from Composition B to Composition C
- the sponsor is now using Composition D as the to-be-marketed formulation because they are no longer able to obtain the polymer from —
- the IVIVC data submitted in the May 24, 1999 submission is attempting to link Composition C to Composition D

- the sponsor plans to begin a clinical study using the to-be-marketed product following submission of the NDA; during that time, the sponsor will collect some dry blood levels as additional data to validate the IVIVC
- blood samples will be monitored, in addition to *ex-vivo* release information from removed IUS; this pattern can be compared to previously submitted data to strengthen the IVIVC
- the new information can be submitted within the review cycle and would not be considered a filing issue
- the sponsor is reminded that information submitted less than 90 days before the action date would result in the extension of the clock

Decisions made:

- the sponsor will submit additional data during the review clock for validation of the IVIVC
- the sponsor will submit the protocol for the study prior to initiation

Unresolved decisions: None

Action Items:

- Fax meeting miutes to sponsor within 30 days

LS1
Minutes Preparer

LS1
Concurrence, Chair

8.8 Overdose and Drug Abuse Information

Not applicable since use of product will always be under strict medical supervision.