CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-225

PHARMACOLOGY REVIEW

Review and Evaluation of Pharmacology/Toxicology Data

HFD-580/Karen Davis-Bruno; Ph.D.

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NDA 21-225
Berlex Laboratories, Inc.

Submission Date: 2/2/00

LNG-Releasing Intrauterine device (Mirena)

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Cc: HFD-580/Davis-Bruno/Jordan/Best

NDA 21-225
Berlex Laboratories, Inc.

Review and Evaluation of Pharmacology/Toxicology Data
Key Words: levonorgestrel, progestin, IUD, contraception
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Review completion date: 5/2/00

NDA 21-225
Information to Sponsor: Yes (X), No ( )
Sponsor: Berlex Laboratories, Montville, NJ
Manufacturer: Schering Aktiengesellschaft, Berlin, Germany

Drug:

Code Name: LNG IUS

Generic Name: levonorgestrel releasing intrauterine system

Trade Name: Mirena

Drug Product: Levonorgestrel releasing intrauterine device (IUD) comprised of a T-shaped polyethylene frame with a cylindrical hormone-elastomer reservoir and membrane mounted on the vertical stem. The polyethylene in the T-body is compounded with barium sulfate for radiopacity. The steroid core is composed of 52 mg levonorgestrel and polydimethylsiloxane (PDMS). The core is covered by a polydimethylsiloxane membrane which regulates the release of levonorgestrel to achieve a nominal initial release rate of 20 µg/day. A monofilament brown polyethylene (PE) removal thread is attached to a loop at the end of the vertical stem of the T-body.

Phase 3 clinical trials tested drug product formulations B and C. Formulation C is currently marketed by Leiras Oy in Europe which will eventually be replaced by formulation D, the planned marketed formulation. All three formulations are comparable and generally reflect discontinuation of component supply by the respective manufacturer

Relevant IND/NDAs: IND ——
Drug Class: progestin releasing IUD
Indication: contraception
Clinical Dose: IUD releasing levonorgestrel (15-30 µg/day) for up to 5 yrs.
Route: intrauterine

Drug History: LNG IUS is a medicated IUD, related to ParaGard T 380 A (copper medicated IUD) and Progestasert (progesterone medicated IUD). LNG IUS has improved contraceptive efficacy for 5 years compared to Progestasert (effective for 1 yr.) and ParaGard T 380A (effective for 10 yr.). The addition of LNG is designed to improve contraceptive efficacy with less blood loss compared to copper medicated IUDs. Disadvantages include systemic side effects, amenorrhea and other changes in menstrual patterns. High local concentrations of levonorgestrel may potentially affect the fetus if pregnancy occurs. No evidence of human teratogenicity exists.

Three large controlled clinical trials (AY99, B078, AV97) have been performed with formulations other than D (to be marketed).

The systemic effects and safety of levonorgestrel (LNG) in animals and humans have been well characterized. The nonclinical development of formulation D LNG IUS is primarily based on biocompatibility, genetic toxicology and local tolerance (9 Month Cynomolgus monkey) studies of the drug product and extractions of its PDMS and PE components. Reprotoxicity was evaluated in formulation B.

Pharmacology: Levonorgestrel (LNG) is a potent progestin of the 19-nortestosterone class, which produces secretory endometrial transformation and possesses anti-gonadotropic and anti-estrogenic activity (via induction of estrogen sulphotransferase, decreased cytosolic estrogen receptors). Levonorgestrel has partial androgenic activity, which correlates with the virilizing effects of levonorgestrel in female fetuses.

Human studies indicate that the mechanism of contraceptive action is based on thickening of the cervical mucus, which inhibits sperm passage, suppresses of ovulation in some women and prevents endometrial transformation. LNG is a potent inhibitor of ovulation in the rat and rabbit and prevents implantation in monkeys by inducing changes in endometrial morphology.

Interpretation of interspecies effects of endogenous hormones such as LNG is difficult due in part to the differences required to elicit an optimal response. Estrogens and progesterone are both required for proper endometrial cycling in mammals. The ratio of estrogen to progesterone varies widely among species (rat<dog<Rhesus monkey=human). Rats and dogs require low doses of estrogen and relatively higher doses of progesterone to elicit characteristic responses such as decidual transformation of the endometrium. This indicates that the target organs of these species are more sensitive to the effects of exogenous estrogen than homologous organs in humans. In monkeys the level of estrogen is higher while the level of progesterone is much lower than in rat or dog. The monkey is suggested as the species most sensitive to progesterone. A considerably wider estrogen:progesterone ratio is observed in rats and dogs compared to primates and humans These findings need to be considered in evaluating human safety based on animal data.

	Estrogen & Progesterone (µg/kg) SC For Decidual Reaction or Transformation of Endometrium			
	Rat	Dog	Rhesus Monkey	Human
17β Estradiol	0.5	0.3	4-8	ND
Progesterone	10,000	300-1000	200-400	ND
17β Estradiol: Progesterone	1:20,000	1:1000-3000	1:50	1:50-100

Based on body weights of 200 g for rat, 10 kg for dog and 5 kg for monkey, ND= not determined

Pharmacokinetics: Plasma levels of LNG in humans are much higher than other species, which correlates with a lower first pass effect in humans. Generally there is little similarity in plasma levels among laboratory species for endogenous steroids and different target tissue sensitivities. This indicates that testing multiples of the human therapeutic dose in animals may not be a reliable procedure.

The rat has a particularly high metabolic clearance rate (MCR) for LNG and non primates have a higher MCR relative to hepatic blood flow suggesting that there may be extraheptic metabolism.

Levonorgestrel is excreted primarily in urine (45%) and feces (32%) in women. Rats have pronounced biliary excretion whereas excretion in rabbits and monkeys is renal. The primary human urinary metabolite is the glucuronide whereas the sulfate conjugate is the predominant circulating metabolite. LNG undergoes extensive metabolism prior to excretion. Humans excrete similar levels of glucuronide conjugates compared to Rhesus monkeys, but >10% of the urinary metabolites in humans were sulfate conjugates that were not found in the primate. Metabolism leading to covalent binding to plasma protein occurred in the Rhesus monkey while little or no covalent binding was found in human plasma. When normalized to %dose/L plasma, the concentration of radioactivity in Rhesus monkey plasma was 5X greater than that in human plasma, whereas the plasma concentration of unaltered LNG among the two species was similar.

Protein binding of LNG occurs in all species, although the degree of binding and the specific carrier protein differ depending on species. Rhesus monkeys, baboon and humans have similarly high specific binding of LNG in plasma. The high affinity binding in primates is 17-20X greater than that in dogs and rabbits. Interestingly the concentration of sex hormone binding globulin (SHBG) in rabbits was 3-4X nigher than primates however SHBG functions primarily as an androgen binding protein with little affinity for estrogen in this species. Guinea pigs and rats do not have appreciable plasma levels of SHBG. In these species binding is restricted to albumin.

A 9 Month PK study in Cynomolgus Monkey using Formulation D (Study DE00364-99616) evaluates uterine and serum concentrations of LNG. Monkeys were divided into four groups of eight animals: Group 1 is sham operated, Group 2 placebo IUD, Group 3 IUS containing LNG (release rate 2.6 µg/day), Group 4 IUS containing LNG (release rate 10.6 µg/day) observation s continued to Week 40. The mean LNG serum concentrations ranged from 1.9-3.3 ng/ml and from 0.6-0.9 ng/ml in the high and low dose groups respectively. Uterine concentrations were 123±63 ng/g and 16±4 ng/g in wet tissue in the high and low dose groups respectively.

A one year Rhesus monkey study using formulation C reports a release rate of 12 3 µg/day with plasma levels of [redacted]. Uterine concentrations were not reported. Authentic bioequivalence data is not available for each of the formulations of LNG-IUS, but suggests that formulation "D" has similar systemic exposure to formulation C. However the local uterine exposures are important with this product and the PK parameters for these formulations have not been determined.

Toxicology: Repeated administration of high doses of exogenous progestins to laboratory animals results in the extension of the pharmacologic activity. Following LNG administration for one year, clotting times are decreased in female rats, while increased prothrombin times and transiently increased fibrinogen levels are observed in female cynomolgus monkeys. Decreases in total serum cholesterol levels are observed in female rats, male dogs and female cynomolgus monkeys after one year administration of LNG. Hyperplasia of the clitoris and decreases in the vaginal cornified and superficial cells occurs in the dog. An increase in cervical glandular secretion accompanied by a decreased vaginal mucosal keratinization occurs in monkey. Corpora lutea are absent in the ovaries of dogs and Cynomolgus monkeys given repeated, high doses of LNG and follicle persistence (dog) or follicular atresia (monkey) are observed. LNG causes a decrease in the relative uterus weight in dogs, while in cynomolgus monkeys an increase in the incidence of thickening of the uterine wall, accompanied by decidual

transformation of the uterine endometrium is observed. LNG induces hyperplasia of prolactin secreting cells in the anterior pituitary of male and female dogs although no increase in the relative pituitary weight is observed. Slight hyperplasia and lactation of the mammary glands of male dogs is observed after 6 month administration and an increased incidence of mammary gland hyperplasia and benign mammary tumors is observed following administration of LNG to dogs for 7 years. An observed increased in hepatic glycogen and fat deposition is attributed to the increase in absolute and relative liver weights observed in rats after administration of LNG for one year.

9 Month Cynomolgus Monkey Formulation D: Study number DE00364-99616 evaluates uterine and serum concentrations of LNG. Monkeys were divided into four groups of eight animals: Group 1 is sham operated, Group 2 placebo IUD, Group 3 IUS containing LNG (release rate 2-3 µg/day), Group 4 IUS containing LNG (release rate 10-11 µg/day) for a 40 week observation. The mean LNG serum concentrations varied from 1.9-3.3 ng/ml and from 0.6-0.9 ng/ml in the high and low dose groups respectively. Uterine concentrations were 123±63 ng/g and 16±4 ng/g in wet tissue in the high and low dose groups respectively.

Slight to moderate superficial endometrial necrosis and slight endometrial inflammatory cell infiltration was noted (incidence not provided) which was attributed to the mechanical effects of the implant as these findings were present in the placebo control. All LNG treated monkeys had secretory gland activity and pre-decidual stromal changes in the endometrium. In endometrium not in contact with LNG IUS moderate to marked stromal decidualization and moderate suppression of the endometrial glands was present in tissues adjacent to the LNG IUS. Group 3 (4/8) experienced a longer duration of the first menses and prolongation of cycle length followed by cessation of menses in 2/8 monkeys. Group 4 experienced prolongation of cycle length (1/8) followed by cessation of menses and complete cessation of menses from implantation until study termination in 7/8 monkeys. Moderate epithelial suppression in the oviducts of 6/8 high dose monkeys and increased mucus in the cervical lumen in 4/8 high dose monkeys occurred.

1 Year Rhesus Monkey Formulation C: This device released 12.3-13.5 µg LNG/day of which 5.7 µg LNG/day was bioavailable. LNG plasma levels from Day 7 after LNG IUS installation through the end of the treatment period were [redacted] ng/ml. This represents a human equivalent dose of 4 µg LNG/day. The only systemic effect was a decrease in partial thromboplastin time compared to the sham operated controls. Uterine effects included decreased relative weight, reduced recent corpora lutea and marked decidual reaction with marked glandular atrophy as well as some necrosis of superficial layers of the endometrium compared to placebo or sham controls. Cervical morphology was normal with 1/8 animal exhibiting palisading of the endocervical gland nuclei. There was no evidence of hyperplasia of endo-or exocervical epithelium.

Toxicology of IUD components:
Polydimethylsiloxane (unfilled elastomer, membrane tubing) widely used in medical implant materials, drug delivery devices, prostheses, reconstructive surgery and drug product components (dimethicone, simethicone). The different siloxane compounds are quite similar chemically and are considered biologically inert. Longterm studies in mice

and rabbits have shown no clear evidence of carcinogenicity (including preneoplasia) of PDMS.

PDMS components of LNG-IUS have been evaluated for genotoxicity, immunotoxicity and reprotoxicity. Systemic tolerance of PDMS was evaluated in rat. Segments of [redacted] is a component of the membrane tubing) were implanted SC (10 X 1 mm). Rats received 1, 3, 9 rods in the low, mid and high dose groups respectively. An interim study group of 6/sex/group were necropsied on Week 4. The main study group (20/sex/group) continued to 26 weeks post implantation. Findings were limited local changes at the implantation site. Local irritations, focal fibrosis, hemorrhage and inflammation at the implantation site was present in all including controls. Clinical chemistry changes were inconsistent across dose groups and sex suggesting a lack of systemic effect. The females necropsied at Week 4 had significantly lower serum aspartate aminotransferase, serum urea and platelet counts. In the LD group, males had significantly lower monocytes, females had lower β globulin. In the MD females, significantly higher neutrophils and lymphocytes with lower albumin:globulin ratios. In the HD group significantly higher neutrophils and lymphocytes continued in females with significantly higher albumin and albumin:globulin ratios in males.

Polyethylene (T body, removal threads, insertion tube): The toxicology of PE has been well characterized and is generally considered inert. As with other medical grade polymers, tumors have been reported following SC, IM or IP, PE implants which have been attributed to the physical presence of foreign material rather than its chemical composition. Longterm implantation of medical devices containing polyethylene presents no appreciable risk to humans.

Carcinogenicity: An 18 month rabbit study evaluated local uterine effects of sustained intrauterine release of LNG. The rabbit was chosen by the sponsor because this species develops spontaneous endometrial cancer as a function of age which is similar to human. The rabbit has chronic estrogenic stimulation of the endometrium unopposed by significant amounts of progesterone.

Intrauterine PDMS implants were placed in the right horn were expected to release 25 µg LNG/day (actual [redacted] ng/ml at month 20). The mortality was 47% for the LNG IUD treated rabbits and 40% in the placebo IUD group. The incidence of lesions diagnosed as endometrial carcinoma was highest among animals with LNG IUD but the difference was not statistically significant. Uterine cysts occurred with significantly greater frequency in animals with LNG IUD but in both the untreated left and the right uterine horn. Animals with necropsy reports had endometrial morphology indicative of papillary hyperplasia. The result suggested that continuous release of LNG from the IUD did not increase endometrial cancer or cause progression of preneoplastic morphological changes. Placebo silastic devices did not increase the incidence of endometrial cancer. Exposure in the rabbit, based on release rates, is equivalent to 3X the predicted human exposure.

Reproductive Toxicology: Embryo/fetal toxicity and teratogenicity were examined by administration of LNG via a [redacted] intrauterine device (modified formulation B) to pregnant New Zealand White rabbits Gestation Day 9-29 with a delivery rate of 7µg

LNG/day. Three experimental groups were utilized 1) rabbits with placebo devices placed between two embryos in each horn 2) LNG UID placed between two embryos in each horn and 3) sham operated controls. There were no treatment related effects on any maternal parameters such as corpora lutea, length of gestation, implantations, litter size or resorptions. A higher incidence of red exudate in the cage pan was noted compared to placebo or sham controls. There were no treatment related fetal malformations or developmental changes as revealed by gross external, soft tissue or skeletal exams. Fetuses examined adjacent to the intrauterine device were similar to those distal. No evidence of virilization of female fetuses was observed.

Literature reports that d,l norgestrel given 10 mg/kg SC to pregnant rats (organogenesis) resulted in a significant shift of the sex ratio to males with a corresponding increase in the anogenital distance. Levonorgestrel is the active form of d-norgestrel and is 2X as potent as the racemate.

Genetic Toxicology: Extractions of formulation D [redacted] were evaluated in a test battery which included a bacterial mutagenicity assay, mouse lymphoma, human lymphocyte chromosome aberration assay (culture media [redacted] and mouse micronucleus assay [redacted] using the maximum feasible volumes. Additional studies were performed with earlier developmental formulations which were not reviewed. Polyethylene containing components of formulation D consist of the T body, removal threads and insertion tub. The unfilled elastomer and membrane tubing [redacted] consist of [redacted] Extracts of formulation D components (PE, PDMS) were also negative in vitro/vivo using a similar test battery (except CHO cytogenetics replaced human lymphocytes).

Biocompatibility: The biocompatibility of [redacted] components (unfilled elastomer and membrane tubing) of formulations C and D were evaluated using extracts prepared to the highest feasible concentration. [redacted] rods (essentially membrane tubing with a solid core) were evaluated in rats following SC implantation for 6 months.

Biocompatibility of LNG-IUS Formulation D & Component Extracts

Study Type	Species #/s.../group	Extraction ratio/dose	Findings
Systemic injection test (IV, IP)	Mouse 5 or 10 F	0.2 g/ml	None
Pyrogen test	Rabbit, 3 F	0.2 g/ml,	None
Intracutaneous Test	Rabbit, 3F	0.2 g/ml,	None
Muscle implantation test	Rabbit, 2 F @ 5 day exposure 3F @ 90 day exposure	4 pieces of LNG release cylinder & 4 control article per paravertebral muscle	Negative Day 5: very thin encapsulation of 4/8 LNG IUS & thin 4/8 control Day 90: thin encapsulation of 1/12 control 0/12 LNG-IUS
	Rabbit , 2-3M	Unfilled elastomer	Day 5: thin encapsulation of 4/8 sites, focal hemorrhage 5/8 sites Day 90: very thin-thin encapsulation 6/11 sites min-mod encapsulation 5/11, slight fibrosis all sites, min necrosis observed 3/11 sites
	Rabbit, 2-3 M	Membrane tubing	Day 5: slight hemorrhage at implant site and slight- min @ adjacent muscle tissue Day 90: Thin encapsulation 5/11 sites, min. inflammation and/or min-slight fibrosis 9/11 sites, focal min. muscular degeneration at 3/11 sites
	Rabbit • 2-3 M • 2-3 F	T body (polyethylene)	• Day 5: focal hemorrhage 1/8 sites, thin encapsulation 5/8 sites. Day 90: thin encapsulation + min hemorrhage 1/12, min-slight fibrosis all sites, min ncecrosis 4/12 sites • Day 90: Minimal-slight hemorrhage 6/7 sites & thin encapsulation 4/7 sites; Day 90: thin encapsulation 3/12 sites, moderate encpuslation 1/12, min-slight fibrosis all sites, min-mod inflamm. 8/12 sites, min to slight necrosis 4/12 sites
	Rabbit 2-3 M	Removal threads (polyethylene)	Day 5: 3/8 slight hemorrhage, 8/8 thin encapsulation Day 90: 8/12 thin encapsulation, 5/12 small pale focus at site, 8/12 min-slight fibrosis

Study Type	Species #/sex/group	Extraction ratio/dose	Findings
Maximization (contact sensit-ization) test	Guinea pig, 5-10F	• Induction Phase 1: LNG IUS D extract ± [illegible] (1:1) 0.1 ml intra-dermal X2 on Day 1 • Induction Phase: LNG IUS topical site [illegible] on D7, occluded 48h • Challenge Phase: LNG IUS D topical extract 0.3 ml D28, occluded 24h	• No appreciable local reaction • No contact sensitization
	Guinea pig, 10 M	Unfilled elastomer [illegible] extraction	[illegible] extract induction phase slight irritation intradermal, challenge & [illegible] induction, challenge) Negative, No contact sensitization
	Guinea pig, 10M	Membrane tubing [illegible] extraction	[illegible] extract induction phase slight irritation intradermal, challenge & [illegible] induction, challenge) Negative, No contact sensitization
Hemolysis test	Rabbit blood, 1F	0.2 g/ml [illegible] extract	Negative
Systemic Tolerance	Rat, 6/sex/group interim necropsy and 20/sex/group main	[illegible] membrane tubing component) [illegible] rod 1, 3, 9 rod/rat	• All doses: local irritation, focal fibrosis, hemorrhage and inflammation at implant site • Interim/Main unremarkable
In vitro cytotoxicity test	Mouse fibroblasts	0.2 g/ml [illegible] µg/ml	Negative
	Mouse fibroblasts	Unfilled elastomer [illegible] extracted [illegible] µg/ml	Undiluted extract & 1:5 dilution: slight cytotoxicity (Grade 1) all wells
	Mouse fibroblasts	Membrane tubing [illegible] extracted [illegible] µg/ml	Undiluted extract: slight cytotoxicity all wells

Study Type	Species #/sex/group	Extraction ratio/dose	Findings
	Mouse fibroblasts	T body (PE) extracted [redacted] µg/ml	Undiluted: slight-mild cytotoxicity all wells 1:3 dilution: slight cytotox in 1/3 wells and mild in 1/3 wells 1:5 dilution: slight cytotox in 2/3 wells
	Mouse fibroblasts	Removal threads (PE) extracted [redacted]	Undiluted extract: slight cytotox in 1/3 wells mild in 2/3 wells Dilution 1:5: slight cytotox all wells
	Mouse fibroblasts	Insertion tube extracted [redacted] µg/ml	Undiluted extract: slight cytotox. 1/3 wells (repeated 2X) Dilution 1:5: no cytotox to slight cytotox in 2/3 well (assay repeated 2X)

Overall Summary/Evaluation:

Safety evaluation of formulation D LNG IUS consisted of 7 biocompatibility tests, 4 genetic toxicology tests and a 9 month local toxicity study in cycling female cynomolgus monkeys. No remarkable in vitro cytotoxicity hemolysis, delayed contact hypersensitivity, intracutaneous injection site irritation or product related systemic toxicity (IV, IP mouse) including pyrogenicity were detected with LNG IUS (D) or component (PE, PDMS) extracts. Muscle implantation demonstrates thin encapsulationof the device by Day 5. The sponsor notes that the fibrosis, inflammatory cells, regenerating or degenerating muscle fibers were similar to those seen in control animals using high density polyethylene rod implants. These local effects are expected with implantation of medical grade PE/PDMS polymers.

No systemic or local intolerance was observed following implantation of a modified (T-body arms removed to fit smaller uteri) composition D LNG IUS in cynomolgus monkeys which released 2 or 8 µg/day LNG for 9 months. The uterine concentrations at Week 40 were 11 ng/g with the low dose releasing product and 78 ng/g with the 8 µg/day-releasing product. These uterine levels were 32 and 15X greater than the plasma of [redacted] provided by these products respectively. Additional PK data provided in the one year Rhesus monkey study (formulation C) demonstrates that a delivery rate of 12-13.5 µg/day provides plasma levels of [redacted] ng/ml. This suggests that formulation C and D provide similar systemic exposures. However uterine exposure is of greater concern with this product. The clinical dose is expected to deliver 20 µg/day for 5 years. Trials were performed using formulation C, although formulation D is to be marketed.

Dose Delivered (µg/day)	Dose Delivered (µg/kg/day)*	HED (µg/kg/day)	Multiple of Human Dose*
8	3	1	2.5

*reference body weight 3 kg for monkey, 50 kg human

The effects of LNG were limited to local endometrial changes of expected progestin effects (secretory gland activity, predecidual stromal changes, prolongation or cessation

of menses). Control animals with placebo IUS implants had observed changes limited to the endometrium (prolongation of the duration of menses, necrosis, inflammatory cell infiltration and focal endometrial hyperplasia with partial mucinous metaplasia) which were attributed to the mechanical effect of the device rather than chemical intolerance of the PDMS or PE components. The presence of LNG did not alter the local tolerance of the PDMS or PE component materials.

Genotoxicity testing of extracts of the LNG IUS or PE and PDMS components were negative.

A modified version of formulation B LNG IUS intended to deliver a total of 7 µg/day to pregnant rabbits Gestation Day 9-29 resulted in no compound related maternal or embryotoxicity, teratogenicity or effects on fetal development.

PDMS containing components of formulation D LNG IUS consisted of unfilled elastomer, membrane tubing/hormone reservoir were subjected to extraction followed by biocompatibility testing. Regardless of the source or method of manufacture, the results indicate acceptable biocompatibility. No remarkable in vitro cytotoxicity, delayed contact hypersensitivity, intracutaneous injection site irritation, pyrogenicity or hemolysis was detected in components. Muscle implantation tests of unfilled elastomer and membrane demonstrate thin to moderate encapsulation by Day 5. The unfilled elastomer was associated with slight fibrosis and minimal necrosis during implantation. However in actual use of the product, this component does not contact the body surface. The encapsulated components were associated with inflammation and/or fibrosis with identical incidence/severity as the control/standard indicating that each PDMS membrane was well tolerated by the local tissue.

Since the membrane of each LNG IUS will be in contact with the uterine mucosal membranes of humans for 5 yrs., PDMS membrane toxicity was assessed following SC implantation (anterior back each side of spine) in rats for 6 months. The SC implnants produced some local irritation which was similar to controls (USP negative control plastic reference standard).

Polyethylene components of the drug product include the inert T-body frame, removal thread and insertion tube. Regardless of the source or method of manufacture, the results indicate acceptable biocompatibility. In the muscle implantation tests of the T body frame and removal thread a very thin encapsulation of test article implants was detected by Day 5 which correlates with minimal to slight fibrosis, minimal necrosis and/or minimal hemorrhage. These results indicated local tissue toleration.

Conclusions: The expected local pharmacologic effects of LNG on the endometrium were observed in cynomolgus monkeys implanted with a modified formulation D LNG IUS for 9 months and in Rhesus monkeys with intrauterine implants of modified formulation C for 1 yr. Comprehensive testing of formulation D LNG IUS including the PDMS and PE components suggests that the to be marketed formulation will be well tolerated. No evidence of genotoxicity was demonstrated. Local or systemic intolerance was not observed in rats following SC implantation of the composition D PDMS rods for 6 months or in cynomolgus monkeys following intrauterine implantation of Composition D LNG IUS or placebo IUS for 9 months.

Considering the biocompatibility, absence of genotoxicity and absence of preneoplastic changes observed with the drug product and its components in addition to

the extensive nonclinical/clinical experience with levonorgestrel the carcinogenic potential of formulation D LNG-IUS is low. Some rabbits with exposures 3X human had an increased incidence (not given) of uterine cysts and papillary hyperplasia.

The absence of compound related maternal toxicity, embryotoxicity, teratogenicity or effect on fetal development in pregnant rabbits with intrauterine implants or modified early formulations suggests that the LNG IUS is not a reproductive toxicant.

Considering the safety profile of levonorgesterel in animals and humans, the inert behavior of the PDMS and PE components, the tolerance in rats implanted with PDMS rods for 6 months and cynomolgus monkeys implanted with LNG IUS (D) for 9 months no nonclinical findings preclude use in humans.

Labeling Review: The Carcinogenicity section of the label refers to the Warning section, which is deficient in pertinent information regarding carcinogenicity.

Recommendations to Sponsor: Please amend the carcinogenicity section of the label with the following: An 18 Month rabbit study indicates a significantly greater frequency of uterine cysts and endometrial papillary hyperplasia at exposures estimated to be 3X human (based on release rates). See Warning Section.

Reviewer/Team Leader Signatures: LS 8/16/10

LS 8/21

Cc: HFD-580 file/Davis-Bruno/Jordan/Best

Addendum to review:

3 Page(s) Withheld

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

Carcinogenicity Review is NA for this Product.

APPEARS THIS WAY
ON ORIGINAL

NDA 21-225
Mirena® (levonorgestrel-releasing intrauterine system)
Berlex Laboratories, Inc.

There was no CAC/Executive Committee Meeting held for this drug product.