CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206229Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 206229	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Liletta Established/Proper Name: levonorgestrel Dosage Form: intrauterine system Strengths: 18.6 mcg/day		
Applicant: Medicines360		
Date of Receipt: April 30, 2014		
PDUFA Goal Date: February 28, 2015	Action Goal Date (if different): February 26, 2015	
RPM: Charlene Williamson		
Proposed Indication(s) intrauterine contraception for up to 3 years		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES ☐ NO ☒

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	Non-clinical and Clinical Pharmacology

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

3) The bridge in a 505(b)(2) application is information to demonstrate sufficient similarity between the proposed product and the listed drug(s) or to justify reliance on information described in published literature for approval of the 505(b)(2) product. Describe in detail how the applicant bridged the proposed product to the listed drug(s) and/or published literature[1]. See also Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

The data described in the submitted references is scientifically relevant to this drug product which was evaluated at or above the proposed human doses.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved as labeled without the published literature)?

YES ☒ NO ☐

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES ☐ NO ☒

*If "**NO**", proceed to question #5.*
*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES ☐ NO ☐

[1]For 505(b)(2) applications that rely on a listed drug(s), bridging studies are often BA/BE studies comparing the proposed product to the listed drug(s) Other examples include: comparative physicochemical tests and bioassay; preclinical data (which may include bridging toxicology studies); pharmacokinetic/pharmacodynamic (PK/PD) data; and clinical data (which may include immunogenicity studies) A bridge may also be a scientific rationale that there is an adequate basis for reliance upon FDA's finding of safety and effectiveness of the listed drug(s) For 505(b)(2) applications that rely upon literature, the bridge is an explanation of how the literature is scientifically sound and relevant to the approval of the proposed 505(b)(2) product

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES ☐ NO☒

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A ☐ YES ☐ NO ☐

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES ☐ NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a final OTC drug monograph:

d) Discontinued from marketing?

YES ☐ NO ☐

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO ☐

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms intended for the same route of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

YES ☐ NO ☒

*If "**NO**" to (a) proceed to question #11.*

*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☐ NO ☐

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A ☐ YES ☐ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES ☒ NO ☐

*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***
*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in*

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s): Mirena (NDA 21225) and Skyla (NDA 203159)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed ☐ *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES ☐ NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☒ No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s): Expiry date(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the*

NDA holder/patent owner, proceed to question #15.

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):
(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the signed certification.*

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES ☐ NO ☐

*If "**NO**", please contact the applicant and request the documentation.*

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

***Note** that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES ☐ NO ☐ Patent owner(s) consent(s) to an immediate effective date of approval ☐

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

/s/

ZETA-MAE C WILLIAMSON
02/26/2015

AUDREY L GASSMAN
02/26/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 206229
Product Name: Liletta (levonorgestrel-releasing intrauterine system)

PMR/PMC Description: PMC 2874-1: Descriptive observational cohort study to evaluate (b) (4) of the THI-002 inserter (b) (4)

PMR/PMC Schedule Milestones:

Final Protocol Submission:	02/28//2016
Study/Trial Completion:	02/28//2018
Final Report Submission:	02/28//2019
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This study is being conducted to provide additional data about the functionality of a new inserter (a device), THI-002, with the Liletta Intrauterine System (IUS). A phase 3 study was conducted to support approval of Liletta, but the product was inserted using a slightly different two-handed inserter (THI-001) in the first part of the trial and using a single-handed inserter (SHI-001) in the remainder of the trial. (b) (4), the Applicant decided to market a modified two-handed inserter (THI-002) that was not evaluated in the phase 3 study. In order to demonstrate safe use of the modified THI -002 inserter, the Applicant conducted a small phase 1 study (M360-L104) in 100 women. Although no safety signals were identified, the data on functionality of the modified inserter are limited because Liletta was inserted by very experienced healthcare providers, and because follow-up for potential adverse events was done only to seven days post-insertion. This cohort study will allow collection of data regarding adverse events associated with use of the inserter over a broad range of the intended patient population.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Experience with other IUS and accompanying inserters demonstrated that there are infrequent but serious complications related to insertion. The current Liletta IUS has been demonstrated in the phase 3 trial to be effective and safe, but the inserter (THI-002) intended for the commercial presentation was not used in this study. The small phase 1 study of the THI-002 inserter demonstrated a high rate of successful insertions, but was not large or long enough to identify less common problems or adverse events that might be insertion-related. The primary goal of this study will be to characterize insertion difficulties and reasons for insertion failures, and to determine the incidence of insertion-related adverse events associated with use of the new inserter.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**
  - ☐ Accelerated Approval (subpart H/E)
  - ☐ Animal Efficacy Rule
  - ☐ Pediatric Research Equity Act
  - ☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - ☐ Assess a known serious risk related to the use of the drug?
  - ☐ Assess signals of serious risk related to the use of the drug?
  - ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - ☐ Analysis of spontaneous postmarketing adverse events?
    Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
  - ☐ Analysis using pharmacovigilance system?
    Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
  - ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
    Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
  - ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study will be a descriptive, observational cohort study in the intended population of women who seek long-term contraception with an IUS.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials

Continuation of Question 4

☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☒ Other
This study relates primarily to evaluation of the device used to insert the Liletta IUS.

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

☐ There is a significant question about the public health risks of an approved drug
☐ There is not enough existing information to assess these risks
☐ Information cannot be gained through a different kind of investigation
☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for BLAs)

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

/s/

MEREDITH ALPERT
02/25/2015

AUDREY L GASSMAN
02/26/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: February 19, 2015 **Date Consulted:** January 30, 2015

From: Miriam Dinatale, D.O., Medical Officer
Division of Pediatric and Maternal Health

Through: Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND Associate Director
Division of Pediatric and Maternal Health

To: Division of Bone, Reproductive and Urologic Products (DBRUP)

Drug: Liletta (levonorgestrel-releasing intrauterine system)
52mg of levonorgestrel with an initial release rate of 18.6 mcg/day

NDA: 206229

Applicant: Medicines360

Subject: Pregnancy and Lactation labeling

Proposed Indication: for intrauterine contraception [redacted] (b) (4)

Materials Reviewed:

- DPMH consult request dated January 30, 2015, DARRTS Reference ID 3694791
- Sponsor's submitted background package for Liletta, NDA 206229
- Clinical Pharmacology Review: Liletta. January 30, 2015. DARRTS Reference ID 3695248
- Pharmacology/Toxicology Review: Liletta. December 10, 2014. Reference ID 3670573

Consult Question:
DBRUP requests assistance from DPMH in completing the review of the pregnancy and lactation section of labeling and conversion to the Pregnancy and Lactation Labeling Rule format.

REGULATORY HISTORY

On April 29, 2014, Medicines360 submitted a 505 (b)(2) New Drug Application (NDA) 206229 for Liletta (levonorgestrel-releasing intrauterine system (IUS)) for the proposed indication of intrauterine contraception (b) (4) for up to three years. The reference listed drug is Mirena (levonorgestrel), NDA 021225.

The Division of Bone, Reproductive and Urologic Products (DBRUP) consulted the Division of Pediatric and Maternal Health (DPMH) on January 30, 2015, to provide input for appropriate labeling of the pregnancy and lactation subsections of Liletta labeling and conversion to the Pregnancy and Lactation Labeling Rule format.

BACKGROUND

Levonorgestrel and Mechanism of Action

Liletta is a levonorgestrel-releasing IUS consisting of a T-shaped polyethylene frame with a drug reservoir containing 52 mg of levonorgestrel.

The local mechanism by which continuously released levonorgestrel enhances contraceptive effectiveness has not exclusively been demonstrated. Studies with Mirena have suggested several mechanisms that prevent pregnancy: thickening of cervical mucus preventing passage of sperm into uterus, inhibition of sperm survival, and alteration of endometrium. Levonorgestrel has local progestogenic effects in the uterine cavity and leads to morphological changes including stromal pseudodecidualization, glandular atrophy, leukocytic infiltration and a decrease in glandular and stromal mitosis. In some women, ovulation is inhibited, but most cycles are ovulatory.[1]

Pregnancy and Lactation Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[2] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[3] format to include information about the risks and benefits of using these products during pregnancy and lactation.

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[1] Mirena labeling: Drugs@FDA, accessed 2/18/2015.
[2] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[3] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

DISCUSSION

Nonclinical Experience

The applicant did not perform additional nonclinical studies for levonorgestrel. Studies used to establish the safety of the active ingredient, levonorgestrel, have been supported by reference to published literature or to studies for which the sponsor has the right to reference. Overall, the pharmacology/toxicology review noted that levonorgestrel does not adversely affect early embryonic development in the event that pregnancy is initiated during its use. In rabbits given up to 1000mcg/kg/day of levonorgestrel during organogenesis, there were no drug-related effects on fetal survival, fertility or abortion rates, and no adverse effects were seen in external, visceral or skeletal morphological development. In rats given levonorgestrel 800mcg/kg/day from gestation day 7 to 17, complete litter resorption occurred and reduction of ossification of the sternebrae and skull bones was noted.[4]

Levonorgestrel and Pregnancy

A search of the scientific literature for available published human pregnancy data on levonorgestrel was performed to update the Pregnancy subsection of labeling for this application.

In a retrospective observational cohort study conducted by Telefono Rosso, the Teratology Information Service at the Catholic University of Sacred Heart in Rome, Italy (DeSantis, *et al*.), 36 women who were exposed to levonorgestrel (1.5mg) as an emergency contraceptive and went on to become pregnant, were compared to a control group of 80 women who had contacted a teratology information service, during the same period. Of the 36 cases of first trimester levonorgestrel exposure, 25 cases had exposure that was limited to levonorgestrel alone, and 11 cases had exposure to levonorgestrel plus ethinyl estradiol. In 10 of the 36 patients, there was also exposure to other drugs. Of these ten patients, two patients were taking drugs that were teratogenic. One patient was taking valproic acid and phenobarbitone for epilepsy and another patient was taking methimazole for hyperthyroidism. Both patients delivered healthy infants. One of the 36 patients contracted rubella during pregnancy and delivered a newborn with a specific congenital syndrome related to rubella (bilateral cataracts, deafness and cardiac malformation). In the 36 cases of levonorgestrel exposure, the following outcomes were observed:

- 24 deliveries and 25 newborns (one twin pregnancy) (66.7%)
- 6 elective abortions (16.7%)
- 6 spontaneous abortions (16.7%)
- 0 ectopic pregnancies

In the control group of 80 patients the following outcomes were observed:

- 69 deliveries (86%)
- one intrauterine death (due to streptococcal infection) (1%)
- 7 elective abortions (8.75%)
- 3 spontaneous abortions (3.75%)

Of the 25 neonatal cases in the levonorgestrel-exposed group, there was one case of gastroesophageal reflux requiring medical treatment and one case of nasolacrimal duct

[4] Pharmacology/Toxicology Review. Krishan L. Raheja: Liletta, NDA 206229. December 10, 2014. DARRTS Reference ID 3670573

obstruction that required surgical drainage. There were no other cases of congenital malformations, no ectopic pregnancies, and no statistically significant differences in birth weight, length, and proportion of small-for-gestational age infants. There was no evidence of maternal complications during pregnancy in either group.[5]

In a prospective comparative cohort study (Zhang, *et al*.), a group of 332 pregnant women, who used levonorgestrel (1.5mg) as an emergency contraceptive, were compared to 332 pregnant women without exposure to levonorgestrel. There were 31 women in the study group and 28 women in the comparison group who miscarried by 14 weeks gestation. There was one stillbirth in the study group (41 week gestation, male infant with umbilical cord rupture). There were three pregnancies terminated by abortion due to fetal malformations detected during 24 week ultrasounds. One fetal malformation (congenital polycystic kidneys) was detected in the study group, and two malformations (achondroplasia and sacrococcygeal tumor) were noted in the comparison group. There were 272 and 298 infants delivered in the study group and comparison group, respectively. Three malformations were found in the study group (hip dislocation, incomplete cleft lip, facial hemangioma) and two malformations were seen in the control group (cleidocranial dysplasia, anal fistula). The rate of birth defects was 1.5% in the study group and 1.3% in the comparison group. Birth weight was slightly higher in the study group (3416 grams) when compared to the comparison group (3345 grams), but there was no statistically significant difference in fetal macrosomia (p=0.040). There were no statistically significant differences in the incidence of miscarriage (10.3% for levonorgestrel vs. 8.6% for comparison group), fetal malformation, or neonatal outcome between both groups. The authors did note that the study and comparison groups were matched with regards to last menstrual period and not gestational age because ultrasound results were not available for all subjects at the time of random matching. This may have caused comparison bias, especially for early miscarriage incidence, and may have also biased the neonatal and delivery outcome comparisons.[6]

In a systemic review of published literature, Brahmi, *et al*., reviewed nine studies to determine the safety of removing an IUD versus leaving an IUD in place when a woman becomes pregnant and desires to continue her pregnancy. Based on three randomized studies,[789] the estimated failure rate for levonorgestrel-containing intrauterine devices (IUDs), such as Mirena, is 0.2%. Labeling information for other IUDs notes that pregnancy with an IUD in place is a risk factor for adverse pregnancy outcomes, including miscarriage and preterm labor. Brahmi, *et al.,* reviewed the following studies:

- 7 retrospective cohort studies of copper-IUD users[101112131415]

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[5] DeSantis, et al. Failure of the emergency contraceptive levonorgestrel and the risk of adverse effects in pregnancy and on fetal development: an observational cohort study. Fertility and Sterility. 2005; 84 (2): 296-299.
[6] Zhang, et al. Pregnancy outcome after levonorgestrel-only emergency contraception failure: a prospective cohort study. Human Reproduction. 2009, 24(7), 1605-1611.
[7] Sivin, *et al.* Long-term contraception with the Levonorgestrel 20 mcg/day (LNG-IUS) and the Copper T 380Ag intrauterine devices: a five-year randomized study. Contraception. 1990; 42: 361–378.
[8] Luukkainen, et al. Effective contraception with the levonorgestrel-releasing intrauterine device: 12-month report of a European multicenter study. Contraception, 1987; 36: 169-179.
[9] Cox, et al. Clinical performance of the levonorgestrel intrauterine system in routine use by the UK Family Planning and Reproductive Health Research Network: 12-month report. Br J Fam Planning. 2000; 26: 143–147.
[10] Chaim, et al. Pregnancy with an intrauterine device in situ and preterm delivery. Arch Gynecol Obstet. 1992; 252: 21-24.

- 1 prospective study of copper-IUD users[16]
- 1 case series describing pregnancy outcomes in levonorgestrel-IUD users[17]

See Appendix A for details of the comparative studies of pregnancy outcomes following exposure to copper IUDs and Appendix B for pregnancy outcomes following levonorgestrel-IUD exposure.

The nine studies reviewed demonstrated that pregnancies conceived with an IUD in place were associated with adverse pregnancy outcomes, with the greatest risk among those pregnancies in which the IUD was not removed. When compared to women who conceived without an IUD, women with a retained IUD had a higher risk of spontaneous abortion (SAB), preterm delivery (PTD) and chorioamnionitis. When compared with women whose IUDs were removed early in pregnancy, women with a retained IUD were at a higher risk of SAB, PTD and septic abortion. Although some of the studies reported fetal malformations, there was not enough data to draw any conclusions on an association between conception with an IUD *in situ* and risk of malformations.[18]

Reviewer Comments:
Overall, there are few published studies that look at the effect of levonorgestrel taken during pregnancy on a developing fetus. The two studies reviewed above (DeSantis, et al. and Zhang, et al.) did not demonstrate any evidence of congenital malformations or adverse fetal outcomes noted in infants exposed to levonorgestrel as an emergency contraceptive during the first trimester of pregnancy. However, each study has limitations.

The study by DeSantis, et al. was a retrospective observational study and was limited by a small number of levonorgestrel users (n=36) that were compared to control patients (n=80). The women in the study were contacted by telephone after the expected date of delivery, and information about perinatal and postnatal complications, birth weight and length, and malformations was ascertained. Since information was obtained from the mother, and not from a medical chart, there may have been recall bias, which may have affected the results. Also, the rate of spontaneous abortions was higher in the levonorgestrel group but was not statistically

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[11] Ganer et al. Pregnancy outcome in women with an intrauterine contraceptive device. Am J Obstet Gynecol. 2009; 201: e1-5.
[12] Inal, et al. The evaluation of 318 intrauterine pregnancy case with an intrauterine device. Eur J Contracept Reprod Health Care. 2005; 10: 266-271.
[13] Kim et al. The prognosis of pregnancy conceived despite the presence of an intrauterine device. J Perinat Med. 2010; 38: 45-53.
Mermet et al. Outcome of pregnancies with an intrauterine device and their management. Rev Fr Gynecol Obstet. 1986; 81: 233-5
[14] Tatum, et al. Management and outcome of pregnancies associated with copper T intrauterine device. Am J Obstet Gynecol. 1976; 126: 869-879.
[15] Von Theobald, et al. The outcome of continuing pregnancies in patients with intrauterine devices. A retrospective study from the Maternity Unit of the University Hospital Center at Caen during the period 1985-1988. J Gynecol Biol Reprod. 1990; 19: 863-8.
[16] Deveer, et al. Comparison of C-reactive protein levels in pregnancies with retained or removed intrauterine devices. J Matern Fetal Neonatal Med. 2011.
[17] Backman, et al. Pregnancy during the use of levonorgestrel intrauterine system. Am J Obstet Gynecol. 2004; 190: 50-54.
[18] Brahmi, et al. Pregnancy outcomes with an IUD in situ: a systemic review. Contraception. 2012; 85: 131-139.

significant (p >0.05); this may be due to women reporting a spontaneous abortion when they may, in fact, have chosen to terminate their pregnancy.

The study by Zhang, et al., was a prospective comparative cohort that compared 332 women who had been exposed to levonorgestrel during pregnancy versus 332 women who did not have exposure. The study by Zhang, et al. had a larger sample size than the study by DeSantis, et al. and did not show any significant difference in the number of miscarriages, fetal malformations, or neonatal outcomes between both groups. However, neonatal outcomes were collected from hospital records or by telephone for patients who delivered at another hospital. Relying on maternal reports may have introduced recall bias, which may have affected the number and types of fetal malformations seen. In addition, Zhang, et al., did note that the study and comparison groups were not matched by gestational age, which may have caused comparison bias, especially for early miscarriage incidence, and may have also biased the neonatal and delivery outcome comparisons.

There were nine studies that evaluated pregnancy outcomes in women who became pregnant with an IUD in place. In the eight studies that reviewed removal versus retaining copper-IUDs during pregnancy, the study strengths and weaknesses can be reviewed in Addendum A. In the only study reviewed that evaluated pregnancy outcomes in women who became pregnant with a levonorgestrel-IUD in place (Backman, et al), a cross-sectional questionnaire was utilized. Out of 17, 630 women with a levonorgestrel IUD, there were 40 confirmed pregnancies. In women with a retained IUD, there were 63% ectopic pregnancies, 37.5% intrauterine pregnancies, 20% SABs, and 5% healthy infants delivered. The study by Backman, et al. had several weaknesses including: patient self-reporting, which led to a recall bias rate of 63%, and a high loss to follow-up of 18%.

Overall, the studies reviewed above demonstrated that there is no evidence of congenital malformations or adverse fetal outcomes when a fetus is exposed to levonorgestrel as an emergency contraceptive; however, the studies do have limitations and further research is needed to further demonstrate that there is no or little risk with levonorgestrel use during pregnancy. However, when an IUD (copper or levonorgestrel) is retained during pregnancy, numerous studies have demonstrated a statistically significant increase in the risk for spontaneous abortions, preterm deliveries, and ectopic pregnancies.

Levonorgestrel and Lactation

There were no formal lactation studies of Liletta in nursing mothers conducted by the applicant. The Drugs and Lactation Database (LactMed)[19] was searched for available lactation data on the use of levonorgestrel. Although non-hormonal methods are preferred during breastfeeding, progestin-only contraceptives, such as levonorgestrel, are considered the hormonal contraceptive of choice because levonorgestrel does not adversely affect milk composition, milk supply or the

[19] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

growth and development of the infant.[20] The information reviewed below includes a review of the studies that were presented in LactMed.

In a small lactation study done by Heikkila, *et al.,* ten women had IUDs that released 10 mcg or 30mcg of levonorgestrel daily placed at six-weeks postpartum. Maternal plasma and breast milk samples were collected eight times over a three-month period and the concentrations of levonorgestrel were determined by radioimmunoassay. One week after IUD insertion the plasma to milk ratio was 6.6:1, but by twelve weeks after IUD insertion, the plasma to milk ratio was 4:1. The total amount of levonorgestrel excreted per day in 600ml of breast milk was about 0.1% of the daily dose of 30 mcg. All milk levels were less than 0.1mcg/L, regardless of the dose the mother was receiving.[21] This single small study suggests that levonorgestrel is present in breast milk at low doses.

In another small lactation study by Nilsson, *et al.,* 15 women who were breastfeeding and eight weeks postpartum were given three oral contraceptives, containing different amounts of levonorgestrel (30 mcg, 150mcg, or 250mcg). In women receiving the 30mcg dose, the drug was undetectable in all women in foremilk. The following results were seen for the 150mcg and 250mcg doses of levonorgestrel:

150mcg of levonorgestrel

	3 hours after dose	23 hours after dose
Foremilk	0.34 mcg/L	0.11 mcg/L
Hindmilk	0.54 mcg/L	0.017 mcg/L

250mcg of levonorgestrel

	3 hours after dose	23 hours after dose
Foremilk	0.51 mcg/L	0.22 mcg/L
Hindmilk	1.05 mcg/L	0.38 mcg/L

The authors calculated the milk:plasma ratio to be 6.6:1 and determined that 0.3mcg and 0.15 mcg of levonorgestrel would be transferred to breast milk per day for the 250mcg and 150mcg dose of levonorgestrel, respectively. The authors estimated that breastfed infants would 0.1% of the total maternal dose. Three out of the 15 infants also had levonorgestrel concentrations measured. The mothers of two infants were taking 250mcg daily and infant plasma levels were measured five hours after the maternal dose and two hours after breastfeeding. (Peak milk levels for levonorgestrel occur at three hours after maternal dose.) Infant plasma levels of levonorgestrel were 0.058mcg/L and 0.115 mcg/L in the two infants. A third infant whose mother was taking 30mcg of levonorgestrel per day had undetectable levonorgestrel in its plasma.[22]

[20] Anon. FFPRHC Guidance (July 2004): Contraceptive choices for breastfeeding women. J Fam Plann Reprod Health Care. 2004;30:181-9.
[21] Heikkila M, Haukkamaa M, Luukkainen T. Levonorgestrel in milk and plasma of breast-feeding women with a levonorgestrel-releasing IUD. Contraception. 1982; 25 (1): 41-49.
[22] Nilsson S, Nygren K-G, Johansson EDB. d-Norgestrel concentrations in maternal plasma, milk, and child plasma during administration of oral contraceptives to nursing women. Am J Obstet Gynecol. 1977;129:178-84

In a lactation study by Shikary, *et al*., the transfer of levonorgestrel from the maternal plasma via breast milk was studied in 38 breastfeeding women at 4-6 weeks postpartum for a duration of 28 days. The women in this study had levonorgestrel delivered via three routes: IUD (n=14), Norplant subdermal implant (n=14) and minipills, 30mcg daily (n=10). On the first day after IUD or implant insertion, maternal blood and breast milk samples were collected at 2, 4 and 8 hour intervals. This was followed by daily collection of maternal blood, breast milk samples (both foremilk and hindmilk), as well as infant blood samples from days two to four, and thereafter on days 7, 14, and 28. For infant blood samples from minipill users, only a single four-hour sample was collected on the first day and no samples were collected on days three and four. The rest of the collection of maternal blood and breast milk as well as infant blood samples was the same in minipill users as for the other two treatment groups. The authors expected very low levels of levonorgestrel in serum samples from infants that would be below the detection limit of levonorgestrel in their assay system (50pg/ml) and decided to pool the infant's serum samples separating infants into their respective groups. The serum levels of infants averaged 0.046 mcg/L and 0.03mcg/L in infants whose mothers used Norplant and the IUD, respectively. Infants whose mothers used oral levonorgestrel had peak serum levels (2-hours post-nursing and 4 hours after maternal ingestion) of 0.2mcg/L. Infant serum levels averaged 2.9-4.6% (Norplant), 6.7% (IUD), and 2.2% (oral tablets) of maternal serum levels.[23]

Reviewer's Comment
The relative infant dose (RID) of levonorgestrel ranged from 2.2% to 6.7% in the study by Shikary, et al; when the RID is less than 10% of the maternal dose, the medication is considered generally safe for breastfeeding. The study, however, has several limitations. First, the study is an older study done in 1987 and current lactation studies would not collect infant blood samples as frequently as performed in this study. Also, the assays were done over 30-years ago and are not as accurate as today's assay methods.

In a prospective, randomized, controlled trial by Heikkila and Luukkainen, IUDs that released levonorgestrel were inserted 6 weeks after delivery in 110 women. Thirty patients had levonorgestrel IUDs that released 10 mcg per day; 40 patients had levonorgestrel IUDs that released 30 mcg per day; 40 women served as the control and had copper-releasing IUDs. The infants were monitored monthly for weight gain and growth, age of eruption of the first tooth, and age of being able to walk without support. There were no differences seen in infant height, weight, or development. Plasma samples were collected from 13 children at the age of eight months, while the mothers were still breastfeeding. Six mothers had levonorgestrel-releasing IUDs and the seven others the copper-IUD. There were no differences noted between groups in Na, K, Cl, Ca, P, protein, albumin, creatinine, urate, iron, cholesterol, triglycerides, bilirubin, AST, ALT. The authors noted that levonorgestrel plasma concentrations were not measured in infant blood samples because levonorgestrel concentrations were expected to be beyond the detection limit of the assay and large volumes of blood could not be drawn from infants due to ethical reasons.[24]

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[23] Shikary ZK, Betrabet SS, Patel ZM, Patel S, Joshi JV, Toddywala VS et al. ICMR task force study on hormonal contraception. Transfer of levonorgestrel (LNG) administered through different drug delivery systems from the maternal circulation into the newborn infant's circulation via breast milk. Contraception 1987; 35(5):477-486.

[24] Heikkila M, Luukkainen T. Duration of breast-feeding and development of children after insertion of a levonorgestrel-releasing intrauterine contraceptive device. Contraception. 1982; 25:279-92.

In a prospective, controlled and randomized trial, Shaamash, *et al*., randomly assigned 320 lactating women requesting initiation of contraception in the early postpartum period into two groups: levonorgestrel-releasing 20mcg IUD (Mirena) (n= 163) and copper-IUD (n=157). Each participant was followed up at three monthly intervals after insertion and until the first birthday of her baby. During these visits, the breastfeeding pattern was assessed, certain infant growth parameters (length, weight, head circumference, mid-arm circumference, skin-fold thickness) were measured and a set of infant development tests were performed. Follow-up of infants for one year found no differences in growth and development or in duration of breastfeeding.[25]

In a prospective study by Shaaban, *et al*., Norplant (levonorgestrel subdermal implant) was inserted in 50 lactating women between postpartum days 30 and 42. Two control groups of breastfeeding mother (50 women with copper-IUDs and 50 women with barrier or no contraception) were included. Although there was no difference in lactational performance between the three groups, the rates of weight and height gain were lower in the Norplant group compared to the control groups. By the sixth postpartum month, there was no significant difference in these growth parameters.[26]

Discussion

The studies reviewed above indicate that levonorgestrel is present in the breast milk of treated mothers. Two studies reviewed above (Nilsson, et al. and Heikkila, et al.) determined the plasma- to-milk (M/P) ratio to be 6.6:1 for levonorgestrel immediately after IUD insertion with an M/P of 4:1 after 12 weeks noted by Heikkila, et al. Overall, an M/P demonstrates the proportion of drug concentration in the milk versus plasma, and a ratio less than one indicates that a drug is safe to use during breastfeeding.[27]

Nilsson, et al. and Heikkila, et al. calculated that the infant would receive 0.1% of the maternal dose, while Shikary, et al. calculated a relative infant dose (RID) ranging between 2.9-6.7%. This discrepancy may be due to the different assay method used by the authors. Overall, a RID less than 10% of the maternal dose indicates that a medication is safe for breastfeeding.[28]

Nilsson, et al., also measured the concentration of levonorgestrel in two infants of mothers taking 250mcg/day of levonorgestrel at five hours after the maternal dose and found infant plasma levels to be significantly lower (0.058-0.115mcg/L) than levonorgestrel levels measured in foremilk (0.51mcg/L) and hindmilk (1.05mcg/L) measured three hours after the maternal dose. This suggests that levonorgestrel does not accumulate in the infant's plasma, and the infant is able to metabolize levonorgestrel.

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[25] Shaamash AH, Sayed GH, Hussien MM, Shaaban MM. A comparative study of the levonorgestrel-releasing intrauterine system Mirena(R) versus the Copper T380A intrauterine device during lactation: breast-feeding performance, infant growth and infant development. Contraception. 2005;72:346-51

[26] Shaaban, et al. Influence of levonorgestrel contraceptive implants, NORPLANT, initiated early postpartum upon lactation and infant growth. Contraception. 1985; 32 (6): 623-635.

[27] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94

[28] Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94

Although levonorgestrel is present in breastmilk in small amounts, levonorgestrel appears to produce limited, if any, effects on breast milk volume and quality. There was one study by Shaaban, et al., which suggested that levonorgestrel may decrease milk supply since infants whose mothers had Norplant had lower weight gain compared to mothers using different forms of contraception; however, by six months of age there was no difference with infant height and weight, which may be due to introduction of solid foods around that age. Other studies have not found any difference in infant growth or development. The studies done by Heikkila, Luukkainen, and Shaamash, et al., showed that there were no adverse effects on breastfeeding infants of mothers using levonorgestrel with normal infant growth and development. Since this NDA is a 505(b)(2) application, not all published data can be reflected in the labeling.

Levonorgestrel and Infertility

On average, conception rates in the U.S. are 85% in the normal population at the end of one year; 15% of couples are unable to get pregnant after one year of unprotected intercourse.[29]

In a European randomized multicenter study (Andersson, *et al.)*, levonorgestrel (LNG)-IUD, 20mcg (n=138 women) was compared to the copper (Cu)-IUD (n=209 women) to evaluate the return of fertility after the IUD removal in women planning pregnancy. For the Cu-IUD group the rate of conception was 71% after 12 months and 79.7% after 24 months. The conception rate for the LNG-IUD group was 79% after 12 months and 86.6% after 24 months. There was no statistically significant difference between both groups. Of those women who got pregnant, there were no difference in the percentage of live births (84%: Cu-IUD vs. 85.6%: LNG-IUD), still births (2%: Cu-IUD vs. 0: LNG-IUD), SABs (6%: Cu-IUD vs. 5.8%: LNG-IUD), and ectopic pregnancies (1%: Cu-IUD vs. 1%: LNG-IUD).[30]

In a randomized multicenter prospective study (Sivin*, et al*.), Norplant implants(30mcg/day), LNG-IUDs (20mcg/day) and Cu-IUDs were compared to evaluate return of fertility after implant or IUD removal in women planning pregnancy. Pregnancy rates for all three contraceptive devices were 82% and 89% at 12 and 24 months, respectively.[31]

Reviewer Comments:
Based on the above randomized trials comparing levonorgestrel-IUDs to copper-IUDs and Norplant, there is no evidence that levonorgestrel has permanent effects on female fertility. At 12 and 24 months, LNG-IUDs had pregnancy rates that were comparable to other methods of contraception and were similar to fertility rates in the general population.

CONCLUSIONS AND RECOMMENDATIONS

Liletta labeling has been updated to comply with the PLLR. Since review of the literature for relevant data revealed no new data with levonorgestrel use in pregnant or lactating women, DPMH recommends that information in Liletta labeling be consistent with Mirena labeling. DPMH has the following recommendations for Liletta labeling:

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[29] http://www nlm nih.gov/medlineplus/infertility html. Infertility. Accessed 2/4/15

[30] Andersson, et al. Return to Fertility after Removal of a Levonorgestrel Releasing Intrauterine Device and Nova-T. Contraception. 1992;46: 575-584.

[31] Sivin, et al. Rates and outcomes of planned pregnancy after use of Norplant capsules, Norplant II rods, or levonorgestrel-releasing or copper TCu380Ag intrauterine contraceptive devices. Am J Obstet Gyncecol. 1992; 166: 1208-1213.

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of Liletta labeling was formatted in the PLLR format to include the "Risk Summary" subsection.[32]
- **Lactation, Section 8.2**
  - The "Lactation" subsection of Liletta labeling was formatted in the PLLR format to include the "Risk Summary" subsection[33].

DPMH LILETTA LABELING

DPMH discussed labeling recommendations with DBRUP, and DPMH labeling recommendations are below. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here. (See Appendix A for the applicant's proposed pregnancy and lactation labeling.)

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------CONTRAINDICATIONS----------

- Pregnancy or suspected pregnancy (4)
- Post-coital contraception (emergency contraception) (4)

----------WARNINGS AND PRECAUTIONS----------

- Remove LILETTA if pregnancy occurs with LILETTA in place and LILETTA is in the uterus. If pregnancy occurs, there is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death) and premature labor and delivery. (5.1, 5.2)

FULL PRESCRIBING INFORMATION

4 CONTRAINDICATIONS

The use of LILETTA is contraindicated when one or more of the following conditions exist:

- Pregnancy or suspected pregnancy. (b) (4)
- For use as post-coital contraception (emergency contraception)

5 WARNINGS AND PRECAUTIONS

5.1 Ectopic Pregnancy

Evaluate women for ectopic pregnancy if they become pregnant with LILETTA in place because the likelihood of a pregnancy being ectopic is increased with LILETTA. Approximately half of pregnancies that occur with LILETTA in place are likely to be ectopic. Also consider the possibility of ectopic pregnancy in the case of lower abdominal pain, especially in

[32] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

[33] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.

association with missed periods or if an amenorrheic woman starts bleeding. If an ectopic pregnancy is confirmed, LILETTA should be removed.

The incidence of ectopic pregnancy in the clinical trial with LILETTA, which excluded women with a history of ectopic pregnancy who did not have a subsequent intrauterine pregnancy, was approximately (b) (4). The risk of ectopic pregnancy in women who have a history of ectopic pregnancy and use of LILETTA is unknown. Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection have a higher risk of ectopic pregnancy. Ectopic pregnancy may require surgery and may result in loss of fertility.

5.2 Intrauterine Pregnancy

If pregnancy occurs while using LILETTA, determine if LILETTA is in the uterus. If LILETTA is in the uterus, attempt to remove LILETTA because leaving it in place may increase the risk of spontaneous abortion and preterm labor. Removal of LILETTA or probing of the uterus may also result in spontaneous abortion. In the event of an intrauterine pregnancy with LILETTA, consider the following:

Septic abortion

In patients becoming pregnant with an IUS in place, septic abortion – with septicemia, septic shock, and death – may occur. Septic abortion typically requires hospitalization and treatment with intravenous antibiotics. Septic abortion may result in spontaneous abortion or a medical indication for pregnancy termination. Should severe infection of the uterus occur, hysterectomy may be required which will result in permanent infertility.

Continuation of pregnancy

If a woman becomes pregnant with LILETTA in place and if LILETTA cannot be removed or the woman chooses not to have it removed, warn her that failure to remove LILETTA increases the risk of miscarriage, sepsis, premature labor, and premature delivery. Prenatal care should include counseling about these risks and that she should report immediately any flu-like symptoms, fever, chills, cramping, pain, bleeding, vaginal discharge or leakage of fluid, or any other symptom that suggests complications of the pregnancy.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

LILETTA is contraindicated for use in pregnant women because there is no need for pregnancy prevention in a woman (b) (4) is already pregnant and LILETTA may cause (b) (4). If a woman becomes pregnant with LILETTA in place, there is an increased risk of miscarriage, sepsis, premature labor, and premature delivery. Published studies report no harmful effects on fetal development with long-term use of contraceptive doses of oral progestins in a pregnant woman. The background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies. Advise a woman of the potential fetal risks if pregnancy occurs with LILETTA in place.

8.2 Lactation

Risk Summary

Published studies report the presence of levonorgestrel in human milk (b) (4) approximately 0.1% of the total maternal dose. There are no reports of adverse effects in breastfed infants with maternal use of progestin-only contraceptives. Isolated cases of decreased milk production have been reported with (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LILETTA and any potential adverse effects on the breastfed child from LILETTA or from the underlying maternal condition.

17 PATIENT COUNSELING INFORMATION

17.1 INFORMATION FOR PATIENTS

- Inform the patient about the risks of ectopic pregnancy, including the loss of fertility. Teach her to recognize and report to her healthcare provider promptly any symptoms of ectopic pregnancy.
- Counsel the patient that if pregnancy occurs while using LILETTA:
    - LILETTA will likely need to be removed because leaving it in place may increase the risk of spontaneous abortion and preterm labor; however, removal of LILETTA or probing of the uterus may also result in spontaneous abortion.
    - a septic abortion may occur. Warn her that if LILETTA cannot be removed or she chooses not to have it removed, there may be an increased risk of miscarriage, sepsis, premature labor, and premature delivery.

Appendix A: Comparative studies of pregnancy outcomes following exposure to copper IUD

Brahmi, et al. Pregnancy outcomes with an IUD in situ: a systemic review. Contraception. 2012; 85: 131-139.

Reference	Study Design	Population	Outcomes Measured	Results	Strengths/weaknesses
Tatum, et al (1976)	Retrospective Cohort; 1970-1976; Canada, Puerto Rico, USA	918 pregnancies with Cu-IUD *in situ* at conception. -275 continued pregnancies: • 157 retained IUD • 118 removed IUD	SAB, preterm delivery (PTD), live birth stillbirth	*IUD retained* -SAB: 85 (54%); p-value <0.005 -PTD: 12 (17%); p-value <0.02 -Live birth: 69 (44%) -Stillbirth: 3 (2%) *IUD removed* -SAB: 24 (20%) -PTD: 4 (4%) -Live birth: 93 (79%) -Stillbirth: 1 (1%)	*Strengths* -Adequate sample of IUD pregnancies -Comparison of outcomes between IUDs left in place and IUDs removed *Weaknesses* -Moderate loss to follow-up (13%) -Contacted patients directly regarding outcomes -Timing of IUD removal/ expulsion not matched with outcomes -No adjustment for potential confounders
Inal, et al (2005)	Retrospective Cohort; 1994-1999, Turkey	318 pregnancies with Cu-IUD in situ at conception. -89 continued pregnancies • 26 retained IUD • 56 removed IUD 300 Cu-IUD controls not pregnant	SAB, septic abortion, PTD	*IUD retained (n=26)* - -SAB 20 (77%), RR 2.9 -Septic abortion 0 -PTD 6 (23%), RR 3.2 *IUD removed* (n=56) -SAB 15 (27%) -Septic abortion 0 -PTD 4 (7%)	*Strengths* -Comparison of outcomes between IUDs left in place and IUDs removed *Weaknesses* -Relied upon medical charts for information -IUD removal procedure not specified
Deveer, et al (2001)	Prospective Cohort, June 2009-April 2010, Turkey	48 women using a Cu- IUD • 30 retained • 18 removed IUD	SAB, Vaginal bleeding, Placental abruption, Premature rupture of membranes (PROM), PTD, Small for gestational age (SGA)	*IUD retained (n=30)* -SAB: n=16 (53%), p-value= 0.005. RR 3.2 -Vaginal bleeding: n= 12 (40%), p-value: 0.391, RR 1.4 -Placental abruption: n= 2 (7%), p-value: 0.263 -PROM: n=12 (40%), p-value.002 -PTD: n= 7 (23%), p-value 0.000, RR 4.2 -SGA: n=2 (7%), p-value=0.590, RR 0.6 *IUD removed (n=18)* -SAB: n=3 (17%) -Vaginal bleeding: n=5(28%) -placental abruption: 0 -PROM: 0 -PTD: n=1 (6%) -SGA: n=2 (11%)	*Strengths* -Comparison of outcomes between IUDs left in place and IUDs removed -Prospective study likely improved reporting of outcomes *Weaknesses* -Small sample size -IUD removal procedure not specified -No adjustment for potential confounders

Mermet et al. (1986)	Retrospective Cohort, 1979-1985	157 women with IUD in situ at conception -67 (36%) continued pregnancies • 29 retained IUD • 38 removed IUD in 1st trimester • 34 pregnancies without IUD	SAB, Septic abortions, Vaginal bleeding, PROM, PTD, Congenital malformations	*IUD retained (n=29)* -SAB: 14 (48%), RR 6.1 -Septic abortion: 2 (7%) -PROM and PTD: 2 (7%) *IUD removed* (n=38) -SAB: 3 (8%) -Septic abortion: 0 -7/52: congenital malformations in combined IUD group *No IUD (n=34*) Vaginal bleeding 10 (30%)	*Strengths* -Comparison of outcomes between IUDs left in place and IUDs removed -IUD removed under ultrasound guidance and with 2-mm grasper if located above pregnancy *Weaknesses* -Limited information about complications -Poorly defined outcomes and not all reported -Small sample size
Von Theobald, et al (1990)	Retrospective cohort, 1985-1988	12 pregnancies with retained Cu-IUDs 41 removed IUDs in first trimester 14,442 pregnancies without IUD Included only "viable fetus," i.e., excluded ectopic pregnancy and SAB but does not define gestational age	Vaginal bleeding PROM PTD Congenital malformations	*IUD retained (n=12*) -Vaginal bleeding 2 (16%) p-value: <0.02, RR 2.3 -PROM: 1 (9%), RR 0.7 -PTD: 3 (25%), p-value: <0.05, RR 1.5 -Malformations: 1 (0.08%) *IUD removed (n=41)* -Vaginal bleeding 3 (8%), p-value: <0.05 -PROM: 5 (12%) -PTD 7 (17%), p-value: <0.05 -Malformations; 1 (0.02%) *No IUD (n=14,442)* -VB (10%) -PROM (3%) -PTD (7%) -Malformations (7%)	*Strengths* -Comparison of outcomes between IUDs left in place and IUDs removed *Weaknesses* -Results of some outcomes not reported or unclear -Small sample size -IUD removal procedure not specified -No adjustment for Potential confounders

Garner, et al (2009)	Retrospective Cohort, 1988-2007, Israel	98 pregnancies with retained Cu-IUD 194 removed IUDs in early pregnancy 141,191 pregnancies without IUD Included all singleton pregnancies N22 weeks	Placenta previa Placental abruption Chorioamnionitis PROM PTD Low birth weight (b2.5 kg) Congenital malformations	*IUD retained (n=98)* -Placental previa 4% p-value: <0.001, RR 0.8 -Placental abruption 4%, p-value: <0.001, RR 2.0 -Chorioamnionitis 7%, p-value: <0.001, RR 0.2 -PROM 10%, p-value: 0.021, RR 1.3 -PTD 18, p-value < -0.001, RR 1.2 Birth weight <2.5 kg: 11%, p value <0.001, RR 0.8 Malformations 10%, p-value 0.041, RR 1.8 *IUD removed (n=194)* -Placental previa 4% -Placental abruption 2% -Chorioamnionitis 4% -PROM 8% -PTD 14% -Birth weight <2.5 kg: 7% Malformations 6% *No IUD (n=141,191)* -Placental previa 4% -Placental abruption 1% -Chorioamnionitis 1% -PROM 6% -PTD 7% -Birth weight <2.5 kg 7% -Malformations 5%	*Strengths* -Comparison of outcomes between IUDs left in place and IUDs removed -Adjustment for potential Confounders *Weaknesses* -Limited discussion of methods -Outcomes not clearly defined -Unknown timing of IUD removal -IUD extraction procedure not specified
Chaim and Mazor, et al (1992)	Retrospective Cohort Study, Israel	16 pregnancies with Cu-IUD at conception, then removed 48 pregnancies without IUD matched for age, parity and gravidity	PTD	*Removed IUD (n=16)* -PTD: n= 3 (19%) p=0.045 compared to no IUD OR, 10.8 (95% CI, 0.8–78.1) *No IUD (n=48)* PTD: n=1 (2%)	*Strengths* -Outcome clearly defined *Weaknesses* -Small sample size -IUD removal timing not specified -IUD removal procedure not specified -No adjustment for potential Confounders

Kim et al. (2010)	Retrospective cohort study, December 1997-June 2007, Chile	-196 pregnancies with retained Cu-IUD -121,101 pregnant women no IUD Singleton pregnancies and parous women Excluded women post-IUD removal in early pregnancy	SAB >12 weeks, Placental previa, Placental abruption, Chorioamnionitis, PROM, PTD, SGA, Congenital malformations	*IUD retained: (n-196)* -SAB: n=31, OR 16.8 -Placental previa: n= 4, OR 0.7 -Placental abruption: n=16, OR 3.4 Chorioamnionitis: n= 16, OR 4.1 -PROM: n= 68, OR 9.4 -PTD: n=110, OR 5.8 -SGA: n=10, OR 0.7 -Malformations : n=15, OR 1.4 *No IUD (n=121,101)* SAB: n=146 Placental previa n=186 PROM n=714 Placental abruption: n= 249 Chorioamnionitis: n= 209 PTD: n= 2503 SGA: n= 1141 Malformations: n= 828	Strengths -Outcomes clearly defined -Adjustment for potential confounders *Weaknesses* -No comparison group of women who removed IUD in early pregnancy

Appendix B: Observational study of pregnancy outcomes following exposure to levonorgestrel IUD

Brahmi, et al. Pregnancy outcomes with an IUD in situ: a systemic review. Contraception. 2012; 85: 131-139.

Reference	Study Design	Population	Outcomes Measured	Results	Strengths/Weakness
Backman, et al (2004)	Cross-sectional questionnaire, 1996, Finland	132 pregnancies reported by 17,630 LNG-IUD users -108 pregnancies confirmed -68 were not LNG-IUD pregnancies -40 confirmed LNG-IUD pregnancies	Ectopic pregnancy, Intrauterine pregnancy, Induced abortion, (SAB Healthy-term delivery	*Retained IUD (n=40)* -Ectopic pregnancy: n=25 (63%) -Intrauterine pregnancy n=15 (37.5%) -Induced abortion n=5 -SAB n=8 (20%) -Healthy-term delivery n=2 (5%)	*Strengths* -Population-based sample of LNG-IUD users in Finland, follow-up of medical records -large sample *Weaknesses* -Relied on self-reported pregnancy to identify cases, -18% loss to follow- up -recall bias for 63% who reported pregnancy but was not a LNG-IUD pregnancy

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/s/

MIRIAM C DINATALE
02/19/2015

TAMARA N JOHNSON
02/19/2015

LYNNE P YAO
02/20/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug
Administration

Review Memorandum

Date: January 28, 2015

To: Charlene Williamson CDER\DBRUP

From: Terry O. Woods, Ph.D.
OSEL\DAM
301-796-2503

Terry O. Woods -S

Digitally signed by Terry O. Woods -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Terry O. Woods -S, 0.9.2342.19200300.100.1.1=1300085350
Date: 2015.02.02 11:17:10 -05'00'

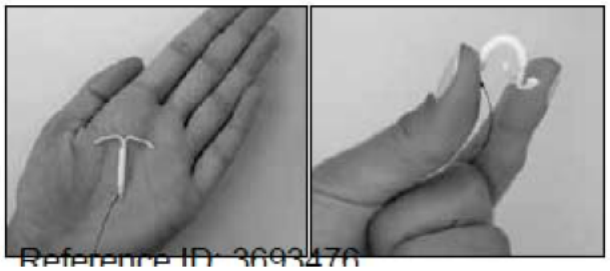
Re: NDA 206229 Medicines 360 Liletta IUS, MRI safety evaluation and labeling

Recommendation: Deficiencies and recommendation are at the end of the memo.

DEVICE DESCRIPTION (from the patient information leaflet)

"Liletta is an IUC LILETTA is a small, flexible plastic T-shaped system that slowly releases a progestin hormone called levonorgestrel that is often used in birth control pills. Because LILETTA releases levonorgestrel into your uterus, only small amounts of the hormone enter your blood.
LILETTA does not contain estrogen. Two thin threads are attached to the stem of LILETTA. The threads are the only part of LILETTA you should feel when LILETTA is in your uterus; however, unlike a tampon string, the threads do not extend outside your body."

An e-mail from Andrea Olariu of Medicines 360 confirms that the device contains no metal.



Reference ID: 3693170

INDICATIONS FOR USE (from the patient information leaflet)

(b) (4)

SCOPE of REVIEW

I reviewed information related to MRI safety testing and labeling.

Testing:

The company provided an extended abstract from the Journal of Magnetic Resonance in Medicine which discusses the MR safety of IUDs. This publication contains insufficient information to be able to determine the safety of any of the listed devices in MRI. In addition, it contains insufficient information to demonstrate that the referenced testing may be applied to LILETTA.

However, because the LILETTA contains no metal and is composed entirely of polymeric materials, it may be labeled as MR Safe without performing any testing.

Proposed MR Safety Labeling:

M360 added the statement "Liletta is MR safe" to the labeling. The consumer-friendly statement "It is safe to have a MRI following LILETTA insertion" was also added to the patient information booklet.

DEFICIENCY

Your labeling indicates: "LILETTA is MR safe. It is safe to have a MRI following LILETTA insertion." The standard MRI safety term from ASTM F2503 is "MR Safe," where the "S" in "Safe" is a capital letter. Please use the term MR Safe in your labeling.

RECOMMENDATION

Because the Liletta contains no metal and is composed entirely of polymeric materials, it may be labeled as MR Safe without performing testing. I recommend you send the deficiency above requesting the minor change in the labeling.

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/s/

ZETA-MAE C WILLIAMSON
02/02/2015

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 30, 2015

To: Charlene Williamson
Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA: 206229
LILETTA (levonorgestrel-releasing intrauterine system)

Background

On July 3, 2014, DBRUP consulted OPDP to review the proposed package insert (PI), patient package insert (PPI), and carton/container labeling for the original NDA submission for LILETTA (levonorgestrel-releasing intrauterine system).

Please note that OPDP has reviewed the proposed PI and our comments are based on the substantially complete version of the draft label dated December 26, 2014, and retrieved from sharepoint on January 29, 2015. Our comments are provided in the attachment.

OPDP will provide comments on the proposed carton/container labeling under separate cover.

The Division of Medical Policy Programs and OPDP provided comments on the PPI under separate cover in a joint review on January 29, 2015.

Thank you for your consult. If you have any questions on the PI, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
01/30/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 28, 2015
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LILETTA (levonorgestrel-releasing intrauterine system)
Application Type/Number:	NDA 206-229
Applicant:	Medicines 360 Inc.

1 INTRODUCTION

On April 29, 2014, Medicines 360 Inc., submitted for the Agency's review an original New Drug Application (NDA206-229) for LILETTA (levonorgestrel-releasing intrauterine system) for the proposed indication of the prevention of pregnancy for up to 3 years.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on July 03, 2014, and July 3, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LILETTA (levonorgestrel-releasing intrauterine system).

2 MATERIAL REVIEWED

- Draft LILETTA (levonorgestrel-releasing intrauterine system) PPI received on April 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on January 22, 2015.
- Draft LILETTA (levonorgestrel-releasing intrauterine system) PPI received on April 30, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on January 22, 2015.
- Draft LILETTA (levonorgestrel-releasing intrauterine system) Prescribing Information (PI) received on April 30, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on January 22, 2015.
- Draft LILETTA (levonorgestrel-releasing intrauterine system) Prescribing Information (PI) received on April 30, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on January 22, 2015.
- Approved MIRENA (levonorgestrel-releasing intrauterine system) comparator labeling dated May 29, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Verdana font, size 11.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
01/28/2015

CARRIE A NEWCOMER
01/28/2015

MARCIA B WILLIAMS
01/29/2015

LASHAWN M GRIFFITHS
01/29/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Office of Device Evaluation

DATE: November 4, 2014,
revised January 23, 2015

FROM: Veronica Price, Biomedical Engineer
CDRH/ODE/DRGUD/OGDB
301-796-6538

TO: Charlene Williamson
CDER/DBRUP

RE: **NDA#206229**
(b) (4) IUS (levonorgestrel intrauterine system)
Medicines 360

I. Review Summary:

Medicines 360 submitted an NDA for a levonorgestrel intrauterine system, (b) (4) IUS, which is intended for prevention of pregnancy for 3 years. The IUS incorporates a drug (levonorgestral loaded onto a T-frame) and a drug delivery device (inserter). This review is limited to an evaluation of the inserter.

An initial review of the (b) (4) IUS was provided as part of a Pre-NDA submission from the firm. Written comments to the firm were included as part of the meeting minutes from a September 17, 2013.

The Phase 3 study of the (b) (4) IUS included two different inserters: a two handed inserter referred to as the THI-001; and a single handed inserter referred to as the SHI-001. The THI-001 was used initially in the Phase 3 study (~700 patients); however, based on feedback from the clinical investigators regarding patient discomfort and difficulty in insertion, the study was stopped (b) (4) . The single handed inserter, SHI-001, was successfully used in the remainder of the study (~900 patients). In spite of the successful use of the SHI-001 inserter, the firm developed a modified two handed inserter, THI-002. (b) (4) . During the Pre-NDA interactions, the firm was notified that a clinical study would be necessary to support the use of the THI-002 with the to-be-marketed (b) (4) IUS.

The scope of this review includes the design of the THI-002, shelf-life testing, design verification/validation testing and clinical testing. The evaluation of the sterility and biocompatibility of the inserter is outside the scope of this review. An in-depth review of this information identified deficiencies related to the shelf life testing, and design verification/validation. These deficiencies were conveyed to the firm and responses were provided in a submission dated November 24, 2014. I have reviewed these responses and have no outstanding concerns. The information provided on the THI-002 is sufficient to support its approval as part of the NDA for the (b) (4) IUS.

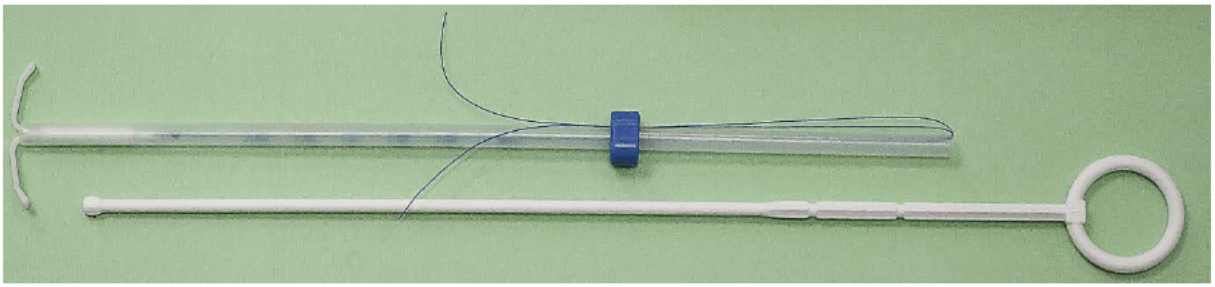
II. Proposed Indication

The proposed indication for (b) (4) IUS is prevention of pregnancy for up to 3 years (b) (4)

III. Device Description:

The [redacted] IUS contains levonorgestrel in a cylindrical-shaped drug reservoir. The drug reservoir is mounted on a vertical T-shaped frame that has two side arms and a vertical stem with an eyelet at the bottom. A thread is attached to the eyelet at the base of the vertical stem of the T-frame.

The [redacted] inserter is a sterile, single-use inserter preloaded with [redacted] for intrauterine administration. The inserter consists of an inserter tube [redacted], [redacted] with a graduated scale), a flange [redacted], and a plunger or insertion rod [redacted]. It is referred to as the Two-Handed Inserter (THI-002). **The focus of this review is limited to the inserter.**



The graduation marks on the inserter tube range from 5 cm to 9 cm to assist the user with controlling the depth of penetration of the inserter tube into the uterus during IUS insertion. The inserter tube has a curved rounded tip with 4 little incisions. The table below identifies the key dimensions:

Tube	
Inserter Tube Tip Incision Length (mm)	1 ± 0.2
Inserter Tube Length	196-198 mm
Inserter Tube OD	4.70 – 4.90 mm
Inserter Tube ID	4.00 – 4.20 mm
Plunger (rod, pusher, stem)	
Plunger length without ring (mm)	206 – 208 mm
Plunger Stem Diameter (mm)	3.5 – 3.7 mm
Plunger tip diameter	3.91 – 4.19 mm
Flange	
Flange inside dimensions	4.68 – 4.88 mm
Flange outside dimensions (mm)	11.65 – 11.95 mm
Flange Height (mm)	5.75 – 6.25 mm

The following table summarizes the materials included in the Two-Handed Inserter:

Component	Material	Trade Name	Supplier
Tube	[redacted] (b) (4)		
Plunger			
Flange			

The firm also identifies the following colorants:

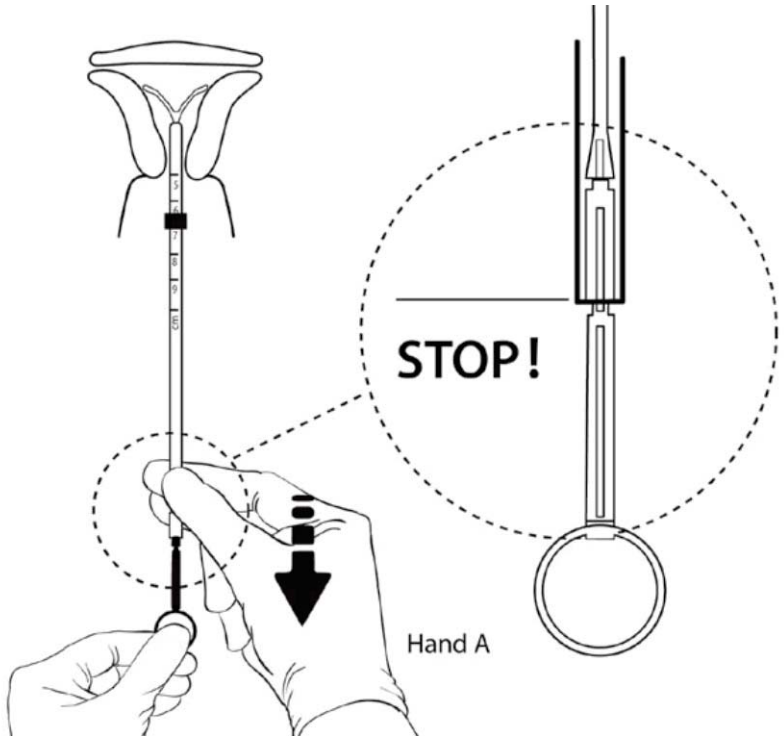
Component	Color	Manufacturer	% colorant by weight	Regulation
Tube Ink	[redacted] (b) (4)			

Plunger colorant	(b) (4)	(b) (4)
Flange colorant		

The material safety review is being conducted by CDER.

Principle of Operation:

The inserter is used as a delivery device for the drug, (b) (4) Intrauterine Contraceptive (IUC). After determining the uterine cavity length with a uterine sound, the flange is set to the uterine depth. With the contraceptive retracted within the insertion tube, the tube with rod inserted is introduced through the cervix into the lower uterine segment. The IUC is deployed within the lower uterine segment by pulling the insertion tube back until it reaches the second groove on the rod.



The insertion tube and rod are then pushed forward until the flange touches the cervix and the IUC reaches the uterine fundus. The insertion tube is then pulled back to the ring of the rod. The rod is removed and then the insertion tube is removed. The string of the IUC can then be cut to an appropriate length (about 3 cm from the cervix).

IV. Risk Analysis

The firm provided a design Failure Mode and Effect Analysis (dFMEA) that included the inserter and a user FMEA (uFMEA) which evaluated the inserter. All identified risks have been adequately controlled through design verification, training and labeling.

V. Comparison to Inserter used in Phase 3 Clinical Study

The THI-002 proposed for use with the to-be-marketed (b) (4) IUS was developed following completion of the Phase 3 clinical study. The THI-002 is manufactured by (b) (4).
The Phase 3 study of the (b) (4) IUS included two different inserters: a two handed inserter referred to as the THI-001; and a single handed inserter referred to as the SHI-001. The THI-001 was used initially in the Phase 3 study; however, based on feedback from the clinical investigators regarding patient discomfort and difficulty in insertion, the study was stopped (b) (4). The following characteristics of the THI-001 were not optimal and were determined to contribute to the difficulty noted during insertion:

(b) (4)

One of the goals of optimizing the device design was to reduce the potential need for dilation. The firm also noted that some of the design modifications for the THI-002 were made at the suggestion of MHRA during the review process in the UK for approval in the European Union.

Although the single handed inserter, SHI-001, was successfully used in the remainder of the study. The firm (b) (4) modified design of the two handed inserter and developed the THI-002. During interactions with the firm under the Pre-NDA, the firm explained that they need to pursue marketing of (b) (4) IUS with the THI-002 (b) (4).

(b) (4)

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(b) (4)

VIII. Clinical Experience with THI-002 Inserter

During the Pre-NDA interactions, the firm was notified that a clinical study would be necessary to support the use of the THI-002 with the to-be-marketed (b) (4) IUS. A Phase 1 study has been provided in this submission: Multi-Center Study to Assess the Performance of a LNG20 Intrauterine System Inserter (M360-L104). This study was conducted at 6 sites in the US between February and March 2014. A very brief overview is provided here with the emphasis on the technical performance of the inserter.

Study objectives

Primary Objective:

To assess the proportion of successful placement of LNG20 IUS utilizing an inserter (THI-002) in women 18-45 years old.

Secondary Objectives:

- Safety as evidenced by the assessment of adverse events related to the IUS placement procedure
- Adjunctive procedures needed for IUS placement:
  o Cervical anesthesia
  o Cervical dilation
- Uterine perforations
- IUS expulsions
- Ease of IUS placement into the uterus
- Subject acceptance of procedure
- Pain associated with IUS placement procedure (VAS)
- Adverse events during the 24 hours after placement

Additionally, the Investigators performed an assessment of the Instructions for Use.

Study Population/Procedure

The study procedure included insertion of the LNG20 IUS by a study investigator with removal after 24 hours. There was a follow-up phone call 6 days later (7 days after insertion) to assess any adverse events.

One hundred women were enrolled, 57 of whom were nulliparous and 43 of whom were parous.

Results/Analyses

The primary analysis was the proportion of subjects with successful placement (first or second attempt).

The firm reports that 99.0% (99/100) patients had a successful placement of the LNG20 IUS. One subject (parous) was discontinued after an unsuccessful first attempt. Success with first attempt was 95.0% (95/100). The four failed attempts were attributed to: bleeding into insertion tube and IUS/IUS came out with tube (1); IUD did not release from the inserter (2); and cervical canal abnormalities due to previous myomectomy and premature IUS deployment (1).

The following table summarizes some of the key outcomes for the THI-002 and compares it to the previously reported results of the Phase 3 study:

	THI-001 N=759	SHI-001 N-990	THI-002 N=100
Successful Placement	96.2%	99.2%	99%
First attempt success rate	90.0%	96.3%	95.0%
Failed Insertion*	9.0%	3.6%	1.0%
Difficult insertion	17.2%	7.3%	19%
Use of dilation	20.6%	11.8%	18.0%
Use of local anesthesia	28.7%	41.9%	44%

*It is important to note that in another 4 cases of THI-002 two attempts were required.

Enrollment in the Phase 3 study was stopped and the inserter redesigned to address the reports of patient discomfort and difficulty in insertion. The redesign was intended to optimize the design and reduce the need for dilation. While this seems to have been achieved with the SHI-001 design, the THI-002 seems to have comparable rates of difficulty in insertion and use of dilation to the THI-001. In spite of this, the reported rate of failed insertion has been reduced for the THI-002 and there is a slight improvement in the rate of successful placement.

In addressing the high rate of reported difficult insertion, the firm points out that they used a more rigorous ease of placement determination when compared to the previous studies; therefore, it is not possible to directly compare the rates. The investigators in this trial completed an Ease of Placement Questionnaire which required a more thoughtful assessment of device performance as either easy, neutral or difficult. The following is a summary of the results:

Easy	55% (55/100)
Neutral	26% (26/100)
Difficult	19% (19/100)

Of the 19 noted "difficult" insertions, the following reasons were given:

- Problem with inserter getting through cervical canal (n=13)
  - Inserter tube reported as being too flexible to pass through cervical canal (n=8)
  - Kinking of the tube (n=3)
  - Inserter tube too rigid (n=1)
- IUS remaining within inserter upon withdrawal from uterus (n=4)
- Additional dilation needed because of difficulty with placement (n=3)

- Multiple attempts with same inserter to go through cervical canal due to extreme uterine flexion (n=2)
- Need for U/S guidance (n=1)
- Inability to pass inserter into cervical canal due to stenosis (n=1)

The firm indicates that they can address the 4 cases of the IUS coming out with the inserter through training. They point out that the users had the lowest scores for the portion of the instructions dealing with the release/fundal positioning. In spite of the difficulties noted, all but one subject ultimately had a successful insertion

With respect to the noted differences in use of local anesthesia, the firm points out that the use of local anesthesia was at the discretion of the investigator. They point out that in no case was it used out of clinical necessity.

Finally, with respect to the use of dilation, the firm points out that in the majority of these cases, only "low grade" dilation was necessary (b) (4). The other subjects required a (b) (4) dilator. Nulliparous subjects required dilation more often than parous (21.1% v. 14.0%). The higher observed rate of use of dilation with THI-002 when compared to the SHI-001 may have been due to the large percentage of nulliparous subjects enrolled in this study.

I agree with the firm that there are a number of confounding factors that make a direct comparison across inserters difficult. The high rates of first attempt success and successful placement provide clinical validation of the effectiveness of the inserter as a delivery system for the LNG20.

Complications/Adverse Events

There were no uterine perforations or IUS expulsions noted during the study.

IUS Removal: Of the 99 subjects with the IUS successfully placed, 98 returned for the scheduled visit. All of these 98 subjects had successful removal of the device. One subject who did not return for the 24 hour removal, was reported to have "presyncope" after leaving the clinic following IUS insertion. This subject had the IUS removed in an emergency department. This event was considered moderate and the removal was not attributed to a safety reason.

The one serious adverse event noted during the study was a case of gastroenteritis that required hospitalization. This event was not attributed to the procedure.

The remainder of the reported adverse events are known adverse events/complications associated with IUS systems, i.e., abdominal pain, cramping, and bleeding.

I defer to the CDER clinical reviewer as to whether the rates of adverse events reported in this study suggest any concerns with the safety of the inserter.

IX. Deficiencies

The deficiencies identified in my original consulting review along with a summary of the firms' responses are identified below:

I. The specification for the frictional force necessary to move the flange along the inserter tube has been modified as a result of the early findings of the stability study. As part of the justification for the change in the specification, you have provided a detailed discussion of the information used to initially set the specification. What was not included in this discussion was any reference to the frictional force of the THI-001. (b) (4)

[redacted] **the dimensions of the THI-002 were modified. Please provide a comparison between the frictional force measured on final, finished THI-001 samples and final, finished THI-002 samples. This information should be factored into the justification for the new specification, i.e., frictional force [redacted].**

In the response dated 11/24/14 the firm clarified that the frictional force specification is [redacted] not [redacted] They reiterate that the specification was set based on an evaluation of the "design input reference device." As previously indicated in this review, the reference device is the inserter used on the product marketed [redacted]. While the firm did not provide the comparison that I would have liked to see, it is reasonable to accept the friction force on product marketed [redacted] as a benchmark for the friction force for the proposed inserter. ***No follow-up is necessary.***

II. **As part of the examination of the change in frictional force over time, you compared the [redacted] friction force observed in samples that underwent accelerated aging to samples that underwent real time aging. In both cases, a [redacted] in friction force was noted between samples evaluated at time zero and at the first follow-up point. For samples that underwent accelerated aging, the decrease can be attributed to the [redacted] Please discuss what factors might contribute to the decrease in frictional force of samples of THI-002 that have undergone real time aging.**

The firm provided data which demonstrates that the frictional force does not significantly degrade over time in the real time aged samples. The following summary table was provided:

Table 2 Real-Time Aging Studies: Frictional Force Data

Frictional Force (N) – Global mean of 10 units					
Timepoint (Months)	**0**	**1.8[1]**	**3**	**6**	**9**
Finished Product	[redacted]				
Components					

[1] 8-week timepoint

[2] Testing performed at t=8 weeks per MEM-UPH-14002, annex 6 and annex 7; value is the global mean of 20 units

The firm pointed out that the degradation in frictional force was seen when comparing sterilized and non-sterilized samples. There was no significant degradation in real time aged samples over time. ***No follow-up is necessary.***

III. **As part of the conclusion of your evaluation of the frictional force of the THI-002, you indicate that less aggressive accelerated aging conditions should be considered; however, the current aging studies can be continued. While we appreciate that the samples tested to date meet your new acceptance criteria, we are concerned that with**

additional storage time [redacted] (b) (4), samples may fail at later time points. Please note that in that case, the shelf life of your product will be limited to the time point at which samples passed. The shelf life can only be extended when sufficient real time data become available. Please either acknowledge your intention to proceed with the testing as planned or provide a new accelerated aging test plan.

See response to question 4 below.

IV. Please provide the results from any additional aging test time points that have become available since filing the NDA.

The firm has provided the results of the accelerated aging studies out to 162 days which simulates 5 years. The following table is a summary of the results of the frictional force:

Table 1 Accelerated Aging Studies: Frictional Force Data

Frictional Force (N) – Global mean of 10 units							
Timepoint (Days)	0	33	49	65	97	129	162
Finished Product	[redacted] (b) (4)						
Components							

[1] Value is the global mean of 20 units (Stage 2 testing)

[2] Testing performed at t=49 days per MEM-UPH-14001, annex 6 and annex 7; value is the global mean of 20 units

From the data provided, it can be seen that there is a [redacted] (b) (4) in force from time zero to the first accelerated aged time point. However, after the initial drop, the force does not change appreciably over the remaining time out to the 5 year simulated aging time period. Furthermore, at all time points the results exceed the specification. ***No follow-up is necessary.***

V. As part of the design verification of the THI-002, the dimensional requirements were assessed. You have not provided any information on how many devices were assessed or the results. Please provide this information for review.

The firm indicates that 30 samples from the production run were evaluated against the requirements. The results were provided in the response. ***No follow-up is necessary.***

VI. Design verification also included an evaluation of kink resistance. No information was provided on the results of this test. Please provide this information for review.

[redacted] (b) (4) **We suggest conducting this test on 10 samples of each inserter.**

The firm indicates that the THI-001 inserters were not evaluated for kink resistance. [redacted] (b) (4) *The purpose was to test the "ability of the inserter to pass*

through a simulated cervix model without any buckling resulting in permanent deformation of the tube or plunger that effects a successful insertion." Samples that underwent accelerated aging out to 129 days (simulating 5 years real time) and samples that have undergone a total of 9 months of real time testing all passed this testing. ***No additional follow-up is necessary.***

X. Conclusion

All of the deficiencies identified in my original review have been resolved. I have no outstanding issues on the THI-002 inserter.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Veronica A. Price -S 2015.01.23 10:00:17 -05'00'
Branch Chief Sign-Off	Becky Robinson, PhD Acting Branch Chief 2015.01.23 10:18:25 -05'00'
Division Director Sign-Off	Herbert P. Lerner -S 2015.01.23 11:22:21 -05'00'

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/s/

ZETA-MAE C WILLIAMSON
01/26/2015

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 5, 2015

TO: Charlene Williamson, Regulatory Project Manager
Daniel Davis, M.D., Medical Officer
Lisa Soule, M.D., Medical Team Leader
Division of Bone, Reproductive, and Urologic Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 206229

APPLICANT: Medicines 360, Inc.

DRUG: (b) (4) (levonorgestrel releasing intrauterine system)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Contraception

CONSULTATION REQUEST DATE: July 7, 2014
CLINICAL INSPECTION SUMMARY DATE: January 9, 2015
DIVISION ACTION GOAL DATE: February 27, 2015
PDUFA DATE: February 28, 2015

I. BACKGROUND:

The Applicant submitted this NDA to support the use of (b) (4)® (LNG20) for safe and effective contraception for (b) (4) years. The primary objective of this study was to assess the efficacy of a levonorgestrel-releasing intrauterine system (LNG20) in (b) (4) females of child-bearing potential who requested long term, reversible contraception.

The pivotal study M360-L102 entitled, "A Phase 3, Randomized, Multi-Center, Open-Label Study of a Levonorgestrel-Releasing Intrauterine System (20 mcg/day) and Mirena® for Long-Term, Reversible Contraception up to Five Years" was inspected in support of the indication.

The clinical sites of Drs. Eisenberg and Westhoff were selected for inspection because they were among the highest enrolling sites and lacked previous inspection histories.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
David Eisenberg, M.D. Washington University School of Medicine 4921 Parkview Place St. Louis, MO 63110	M360-L102/ 108/ 186	2-8 Oct 2014	NAI
Carolyn Westhoff, M.D. Columbia University Medical Center 630 West 168th St., PH 16 NYC, NY 10032	M360-L102 / 141/ 119	17-30 Sep 2014	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. David Eisenberg, M.D.
Washington University School of Medicine
4921 Parkview Place
St. Louis, MO 63110

a. What was inspected: At this site for Protocol M360-L102, 198 subjects were screened, 186 subjects were enrolled, and 133 subjects remained enrolled at the time of the inspection.

The records of 40 subjects were reviewed. Informed consent was obtained from these subjects prior to any study procedures. Study records were compared with electronic case report forms (eCRFs) and line listings. The records reviewed included, but were not limited to, financial disclosure, delegation of authority, laboratory accreditation, study training, inclusion/exclusion criteria, randomization, visit documentation, IRB, monitor and sponsor correspondence, protocol deviations, adverse event reporting, and test article accountability and storage.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Carolyn Westhoff, M.D.
Columbia University Medical Center
630 West 168th St., PH 16
New York City, NY 10032

a. What was inspected: At this site for Protocol M360-102, 132 subjects were screened and 120 subjects were enrolled. No subjects had completed the study at the time of the inspection.

The records of 24 subjects were reviewed in depth. These subjects signed consent forms prior to the initiation of any study-related procedures. Source documents were compared against line listings. Other records reviewed included, but were not limited to, sponsor and IRB correspondence, financial disclosure forms, inclusion/exclusion criteria, treatment assignments, subject discontinuations, adverse events, protocol violations, efficacy data, and drug accountability and storage.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. Observations included but were not limited to the following:

Deviations from the investigational plan were noted. Examples include the lack of a urine pregnancy test at Month 1 for Subject 0016; the conduct of incomplete pelvic examinations at Months 12, 48, and 12 for Subjects 0001, 0007, and 0016, respectively; an uncollected plasma levonorgestrel sample at Month 42 for Subject 0007; unmonitored room temperature storage conditions for levonorgestrel or Mirena for the period between August 23 and November 15, 2010; and unmonitored freezer temperature storage conditions for used intrauterine systems between August 3 and November 15, 2010 (freezer temperatures were only documented on three occasions during this period).

Not all case histories were prepared or maintained adequately. For example, Subject 2071 experienced a serious adverse event (SAE) on December 5, 2012; however, an initial SAE report form was not available for review though a faxed confirmation and updated SAE reports were present in the source documents.

Not all adverse events possibly related to investigational drug administration were reported. An example includes Subject 2112 who experienced dizziness, clamminess, and a vasovagal reaction post-IUD insertion, in addition to a period of unconsciousness, on November 7, 2012, but whose source document reported only nausea.

c. **Assessment of data integrity:** The observations noted during this inspection, including the examples above, would not be expected to adversely affect safety and/or efficacy considerations. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Eisenberg and Westhoff were inspected in support of this NDA. Dr. Eisenberg was not issued a Form FDA 483, and the final classification of this inspection was No Action Indicated (NAI). Dr. Westhoff was issued a Form FDA 483; however, the deficiencies noted were isolated and would not appear to have adversely affected safety or efficacy considerations, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H.
Branch Chief
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Office of Scientific Investigation

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/s/

ROY A BLAY
01/07/2015

JANICE K POHLMAN
01/07/2015

KASSA AYALEW
01/07/2015

A. All Label and Labeling (container label, carton and patient information booklet labeling, patient reminder card and sticker)

   a. [redacted] (b) (4) Consider increasing the prominence of the strength statement presentation through the use of bolding, darker font color, or some other means to improve its readability.

   b. Ensure that the established name is stated as “levonorgestrel-releasing intrauterine system” on all label and labeling as this is the appropriate established name for this product.

B. Container Label

   a. Increase the prominence of important drug-identifying information on the principal display panel (PDP) by re-locating the inactive ingredients statement to the side or back panel. This will improve readability of the content statement and reduce information crowding on the PDP. Relocating this information will also allow space for recommendation C (b) below.

C. Container Label and Carton Labeling

   a. To decrease clutter and allow for easier retrieval of important information, [redacted] (b) (4) ” located on the principal display panel to read “Not made with natural rubber latex”. Ensure that there is white space between the content statement and the rubber latex statement to improve readability.

   b. Add the statement “Insert Liletta no later than the expiration date printed on this carton” to the principal display panel and in proximity to the expiration date stated on the container label and carton labeling. We recommend this to minimize the risk of using the system beyond the product’s expiration date.

   c. Add a usual dosage statement: “Usual dose: See package insert” to the side panel in accordance with 21 CFR 201.55.

D. Carton Labeling

   a. Add a ‘carton contains’ statement to the side panel which states: “Each carton contains one sterile unit of Liletta (levonorgestrel-releasing intrauterine system) 52 mg, one Physician Labeling, one Consent form, one Patient Information Booklet, and one Follow-up Reminder Card”. Adding this information will allow the prescriber or their assistant to check the carton for completeness.

[redacted] (b) (4)


(b) (4)

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/s/

ZETA-MAE C WILLIAMSON
01/02/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 5, 2014
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 206229
Product Name and Strength:	Liletta (Levonorgestrel-releasing Intrauterine System) 52 mg
Product Type:	Drug-Device Combination Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Medicines 360
Submission Date:	April 30, 2014 and October 3, 2014
OSE RCM #:	2014-1034
DMEPA Primary Reviewer:	Denise V. Baugh, PharmD, BCPS
DMEPA Acting Team Leader:	Tingting Gao, PharmD

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Bone, Reproductive, and Urologic Products (DBRUP) to review the Liletta (Levonorgestrel-releasing Intrauterine System) [redacted], carton, insert and patient booklet cover labeling, [redacted] for NDA 206229 for vulnerabilities to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Human Factors Study	D (N/A)
ISMP Newsletters	E (N/A)
Regulatory History	F
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Liletta [redacted], carton and insert labeling, as well as the [redacted]

We also note that Liletta has the same active ingredient, shares the same dosage form, and has similar indications to the approved products Skyla (NDA 203159) and Mirena (NDA 021225).

[1] Baugh D. Proprietary Name Review for [redacted] (NDA 206229). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 AUG 6. 26 p. OSE RCM No.: 2014-17369.

Therefore, we reviewed the recommendations in our previous label and labeling reviews for these products to maintain consistency in their labeling where appropriate. Additionally, we completed a FAERS search to identify any medication errors that have occurred with Skyla and Mirena and which may be likely to occur with Liletta.

Based upon all these sources of information, we identified improvements to the proposed container label, carton, insert, and (b) (4) that can be made to minimize their vulnerability to medication errors. Specifically, we identified expired drug errors involving Skyla where an expired product was used for insertion. Adding statements to the container label, carton and insert labeling may help to reinforce the importance of checking the expiration date prior to opening the package and before insertion to minimize the risk of expired drug errors. Additionally, we identified a possible drug-drug interaction that may have contributed to an unintentional pregnancy. Although there is a list of medications in Section 7 (Drug Interactions) of the Liletta prescribing information, the Patient Information Section does not inform the patient that they should communicate such information to their healthcare providers. Therefore, patients are likely unaware of the importance of communicating their medication regimens to prescribers while using this product. This is especially important if the prescriber who inserted the intrauterine system is not the same one who prescribes medications for other purposes. (b) (4)

4 CONCLUSION & RECOMMENDATIONS

Based upon 1) our review of the proposed label and labeling; 2) our review of the recommendations for Skyla and Mirena; and 3) the retrieval of expired drug errors and monitoring errors involving Skyla and Mirena, we conclude that improvements can be made to the label and labeling to minimize errors. We recommend these improvements be implemented prior to approval of NDA 206229.

4.1 RECOMMENDATIONS TO THE DIVISION

We recommend the Division consider the following prior to approval of this NDA:

A. Dosage and Administration, Full Prescribing Information

   a. Add the following statement in Section 2.1 (Insertion Instructions): "Check the expiration date on the box before opening it. (b) (4) . (b) (4)

B. Patient Information

b. To facilitate the discussion of their medication regimens with their prescribers, we recommend adding a statement to the Patient Information which tells the patient to discuss their medications during visits with all of their healthcare providers. We make this recommendation because we retrieved two monitoring errors involving Mirena where the patients were prescribed medications that were included in the medication list in Section 7 (Drug Interactions) of the prescribing information. One of these patients became pregnant and experienced a spontaneous abortion. Since an identical list is included in the proposed PI for this product, adding this information to the Patient Information section may alert patients to communicate with their physicians about their medications.

4.2 RECOMMENDATIONS FOR MEDICINES 360

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. All Label and Labeling (container label, carton and (b) (4) labeling, (b) (4)

a. (b) (4) Consider increasing the prominence of the strength statement presentation through the use of bolding, darker font color, or some other means to improve its readability.

b. Ensure that the established name is stated as "levonorgestrel-releasing intrauterine system" on all label and labeling as this is the appropriate established name for this product.

B. Container Label

a. Increase the prominence of important drug-identifying information on the principal display panel (PDP) by re-locating the inactive ingredients statement to the side or back panel. This will improve readability of the content statement and reduce information crowding on the PDP. Relocating this information will also allow space for recommendation C(b) below.

C. Container Label and Carton Labeling

a. To decrease clutter and allow for easier retrieval of important information, (b) (4)

[redacted] (b) (4) located on the principal display panel to read “Not made with natural rubber latex”. Ensure that there is white space between the content statement and the rubber latex statement to improve readability.

b. Add the statement “Insert Liletta no later than the expiration date printed on this carton” to the principal display panel and in proximity to the expiration date stated on the container label and carton labeling. We recommend this to minimize the risk of using the system beyond the product’s expiration date .

c. Add a usual dosage statement: “Usual dose: See package insert” to the side panel in accordance with 21 CFR 201.55.

D. Carton Labeling

a. Add a ‘carton contains’ statement to the side panel which states: “Each carton contains one sterile unit of Liletta (levonorgestrel-releasing intrauterine system) 52 mg, one Physician Labeling, one Consent form, one Patient Information Booklet, and one Follow-up Reminder Card”. Adding this information will allow the prescriber or their assistant to check the carton for completeness.

[redacted] (b) (4)

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Liletta that Medicines 360 submitted on October 3, 2014.

Table 2. Relevant Product Information for Liletta	
Active Ingredient	levonorgestrel
Indication	Prevention of pregnancy for up to 3 years
Route of Administration	intrauterine
Dosage Form	Intrauterine system
Strength	52 mg
Dose and Frequency	Insert one intrauterine system into the uterus every 3 years
How Supplied	Levonorgestrel-releasing intrauterine system is packaged together with an inserter in a pouch; a carton contains one sterile unit
Storage	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light until ready to use.

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

Since the marketed products, Skyla and Mirena share similar product characteristics with Liletta, we searched the FDA Adverse Event Reporting System (FAERS) for Skyla and Mirena medication error cases on June 25, 2014 using the criteria in Table 3, and then individually reviewed each case. We assessed these cases for their potential to translate to similar errors with Liletta and limited our analysis to cases that described errors possibly associated with label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[2]

Table 3: FAERS Search Strategy	
Date Range	June 20, 2013 (from the date of the previous search) through June 25, 2014
Drug Names	Product Name: Skyla Produce Name: Mirena
MedDRA Search Strategy	Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Quality Issues (NEC)[HLT]

B.2 Results

Our search identified 6 (of 7) cases involving errors with Skyla and 31 (of 74) cases involving errors with Mirena relevant to this review.

We excluded 1 case involving Skyla because it described an adverse event unrelated to a medication error.

We excluded 43 cases involving Mirena because they described: an adverse event unrelated to medication error (n = 8), events unrelated to medication error such as healthcare provider cutting themselves on the packaging or difficult insertion/removal procedures (n = 15), dislocation of the device unrelated to a medication error (n = 17), expulsion unrelated to a medication error (n = 2), and insufficient information to assess (n = 1).

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www.nccmerp.org/pdf/taxo2001-07-31.pdf.

Expired Drug Use with Skyla (n = 6)

There were six cases which identified the insertion of Skyla after it had expired. Contributing factors and outcomes were not reported in any of these cases.

In the How Supplied/Storage and Handling Section (16) of Prescribing Information for Liletta, there is the statement "Insert before the end of the month shown on the package." We did not find this statement repeated on the Liletta container label or carton labeling. Additionally, adding it to the insertion instructions in the dosage and administration section of the PI may serve as an additional reminder to the prescriber.

Maternal Exposure with Mirena (n = 14)

There were fourteen U.S. cases involving accidental exposure of pregnant patients to the Mirena device.

In those 14 cases, the results of the pregnancy tests in these cases were positive (n = 1), negative (n = 4), no test was performed (n = 3), and the reporter did not state whether a pregnancy test was performed prior to insertion (n = 6).

Reported outcomes were termination (n = 6), continued pregnancy (n = 2), and miscarriage (n = 1). In the remaining cases (n = 5), the outcome was not stated.

Pregnancy is a contraindication to the use of Liletta as stated in the Dosage and Administration, Contraindications, Special Populations, and Patient Information subsections of the Full Prescribing Information. Although we anticipate that this medication error type is likely to occur with Liletta, we note that this contraindication is repeatedly stated and has adequate redundancy in the PI and therefore this error will not be evaluated further for this product.

Wrong Technique Errors (n = 2)

There were 2 cases where the device was inserted prior to the discovery of potential contraindications to the use of Mirena.

In the first case the prescriber found uterine tissue postulated to have been a blood clot or a residual of placenta material. Mirena is contraindicated in patients who are pregnant or suspected to be pregnant, congenital or acquired uterine anomalies, postpartum endometriosis, known or suspected uterine neoplasia, or conditions associated with increased susceptibility to pelvic infections.

In the second case the patient's uterine cavity sounded less than 5.5 cm which may place the patient at risk for expulsion, bleeding, pain, perforation, and possibly pregnancy.

Contributing factors were not stated in either of these cases. The prescriber removed the device in the first case and the final outcome was not stated in the second case.

In our review of the Liletta insertion and preparation instructions in the dosage and administration section of the prescribing information, the list of clinical diagnoses (and their decision points) is clearly stated. Additionally, there is a list of diagnoses and clinical conditions in the contraindications section of the prescribing information to which the prescriber can

refer. Therefore, the PI is adequately labeled and we will not evaluate these isolated cases further.

Monitoring Error with Mirena (n = 2)

There were 2 cases which involved the simultaneous use of topiramate with Mirena. In one of these cases, the patient was prescribed topiramate for migraines after the insertion of Mirena and subsequently became pregnant. This patient experienced a spontaneous abortion presumably as a result of this drug-drug interaction. In the second monitoring error case, a patient was on topiramate and Mirena simultaneously, but details were not provided and the final outcome was unknown.

Although a list of drugs and herbal products are included in Section 7 (Drug Interactions) of the Full Prescribing Information, this list is not repeated in the patient information section of the labeling. In view of the potential for patient harm, repeating this information in the patient information section may make the patient aware of the necessity to communicate this information to their prescribers. This may be especially important given that the health care provider responsible for inserting Liletta may not be the same provider who prescribes another drug product that may interfere with the effective or safe use of Liletta.

Wrong Duration with Mirena (n = 13)

Thirteen cases involved the insertion of Mirena for longer than 5 years. The duration of insertion was 10 years (n = 2), and 5 to 6 years (n = 11). No contributing factors were stated in any of these cases.

Outcomes included itchiness (n = 1), no adverse events (n = 2), perforated uterus (n = 1), pregnancy (n = 1), amenorrhea (n = 1), adverse event not related to labeling (n = 1), and no outcome reported (n = 5). The outcome of the remaining case (which was foreign) was a stroke.

The duration of use for Liletta is stated in the Dosage and Administration Section of the FPI as well as in the Patient Information Labeling section. Additionally, none of the reporters indicated that the reasons for the wrong duration errors were related to labeling confusion. Therefore, these error types will not be evaluated further.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case numbers and manufacturer control numbers for the cases relevant for this review.

Case Number	Version	Manufacturer Control Number
10228589	1	US-BAYER-2014-085549
10228592	1	US-BAYER-2014-085385
10242428	1	US-BAYER-2014-090470

10243463	1	US-BAYER-2014-090931
10249447	1	US-BAYER-2014-092595
10255043	1	US-BAYER-2014-094263
10207388	1	US-BAYER-2014-036469
10218372	1	US-BAYER-2014-080459
9360596	3	US-BAYER-2014-081403
9491683	4	US-BAYER-2013-073915
9529661	1	US-BAYER-2013-105004
9543567	1	US-BAYER-2013-114465
9549124	1	US-BAYER-2013-114964
9592552	1	US-BAYER-2013-118098
9607757	2	US-BAYER-2013-121185
9641650	1	US-BAYER-2013-127815
9656232	1	US-BAYER-2013-131726
9858158	1	US-BAYER-2014-012426
9888523	1	US-BAYER-2014-018511
9893639	3	US-BAYER-2014-020217
10007270	1	US-BAYER-2014-036469
9745898	1	US-BAYER-2013-148034
9916430	1	US-BAYER-2014-027669
9995329	1	US-BAYER-2014-034048
10006715	1	US-BAYER-2014-036287
10011629	1	US-BAYER-2014-038477
10013723	2	US-BAYER-2014-036744
10110564	1	US-BAYER-2014-058317
10191562	1	US-BAYER-2014-076495
10228219	1	US-BAYER-2014-083164
10242154	1	US-BAYER-2014-090965

9432720	1	US-BAYER-2013-092299
9725704	1	US-BAYER-2013-140167
9921554	1	US-BAYER-2014-028304
9970228	1	US-BAYER-2014-034018
9970250	1	US-BAYER-2014-033197
9538369	2	FR-BAYER-2013-113490

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the DMEPA shared drive (also known as the "L" drive) on June 20, 2014 using the terms, "Skyla" and "Mirena" to identify labeling reviews of approved levonorgestrel-releasing intrauterine devices performed by DMEPA. Our intent is to maintain consistency in label and labeling among these products where feasible.

C.2 Results

Our search identified 2 previous reviews[2,3], and we reviewed these recommendations for Skyla and Mirena to assess whether they would be applicable to this Liletta review.

[2] Park A. Label and Labeling Review for Skyla (NDA 203159). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 September 21, 10 p. OSE RCM No.: 2011-4677; and

[3] Siahpoushan, M. Label and Labeling Review for Mirena (NDA 021225). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 June 25, 15 p. OSE RCM No.: 2013-1437.

APPENDIX F. Regulatory History

This proposed levonorgestrel releasing intrauterine system will be the third device of its kind to be approved. Products approved previously include Mirena (NDA 021225 approved December 6, 2000) and Skyla (NDA 203159 approved January 9, 2013). DMEPA reviewed the label and labeling for Skyla (OSE Review # 2011-4677 dated September 21, 2012) and for Mirena (OSE Review # 2013-1437 dated June 25, 2013).

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[4] along with postmarket medication error data, we reviewed the following Liletta labels and labeling submitted by the Applicant, Medicines 360 on October 3, 2014.

- (b) (4)
- Carton labeling
- (b) (4)
- (b) (4)
- (b) (4)

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[4] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

DENISE V BAUGH
11/05/2014

TINGTING N GAO
11/05/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 206229 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) Intrauterine System Established/Proper Name: levonorgestrel Dosage Form: intrauterine Strengths: 18.6 mcg/day		
Applicant: Medicines360 Agent for Applicant (if applicable):		
Date of Application: April 30, 2014 Date of Receipt: April 30, 2014 Date clock started after UN:		
PDUFA Goal Date: February 28, 2015	Action Goal Date (if different): February 27, 2015	
Filing Date: June 29, 2014	Date of Filing Meeting: June 12, 2014	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed indication(s)/Proposed change(s): Prevention of pregnancy for up to 3 years		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.***	**X Standard** ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted ☐ Pediatric Rare Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s):

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☐ Exempt (orphan, government) ☒ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒	☐	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	X	☐	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:	☐	☒	☐	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	X	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☐	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☐	

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	

Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☐	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note**: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☐	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☒	☐	☐	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☐	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☐		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide)			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Carton labels ☒ Immediate container labels ☐ Diluent ☒ Other (Patient Brochure)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined?	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	CDRH – May 19, 2014
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** September 17, 2013 ***If yes, distribute minutes before filing meeting***	X	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☐		

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 12, 2014

NDA #: 206229

PROPRIETARY NAME: [redacted] (b) (4) intrauterine system

ESTABLISHED/PROPER NAME: levonorgestrel releasing intrauterine system

DOSAGE FORM/STRENGTH: 18.6 mcg/day

APPLICANT: Medicines360

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): prevention of pregnancy for up to 3 years

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Williamson	Y
	CPMS/TL:	Mercier	Y
Cross-Discipline Team Leader (CDTL)	Soule		Y
Clinical	Reviewer:	Davis	Y
	TL:	Soule	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Miller, Denise	Y
	TL:		

Clinical Pharmacology	Reviewer:	Kim, Hyunjin	N
	TL:	Kim, Myong-Jin	Y
Biostatistics	Reviewer:	Dwyer, Kate	Y
	TL:	Sobhan, Mahboob	
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Raheja, Krishan	Y
	TL:	Jordan, Alex	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Ni, Nina	Y
	TL:	Christner, Donna	N
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
• 505(b)(2) filing issues:	☐ Not Applicable
○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☒ NO
○ Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?	☒ YES ☐ NO
Describe the scientific bridge (e.g., BA/BE studies):	For the components of the intrauterine drug delivery system, Medicines360 conducted 1 biocompatibility study on the LNG-IUS drug reservoir and release controlling membrane, and 3 biocompatibility studies on the LNG-IUS inserter. The remaining toxicology data to support the use of the polymer components of the drug delivery system are from studies in the public domain and studies to which Medicines360 has right of reference.
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments	☒ Not Applicable

List comments:	
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**:	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable

Comments:	☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation	☐ Not Applicable ☒ YES ☐ NO

of sterilization? (**NDAs/NDA supplements only**) **Comments**:	
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☒ N/A ☐ YES ☐ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	

• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Charlene Williamson

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V):

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

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

/s/

ZETA-MAE C WILLIAMSON
07/03/2014

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 206229

Application Type: New NDA

Name of Drug/Dosage Form: (b) (4) Intrauterine System

Applicant: Medicines360

Receipt Date: April 30, 2014

Goal Date: February 28, 2015

1. Regulatory History and Applicant's Main Proposals

(b) (4) is an intrauterine contraceptive (IUC) for prevention of pregnancy for up to 3 years.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified:

Highlights:

1. Dosage Forms and Strength missing
2. Under Adverse Reactions the dash is missing in the FDA phone number
3. Horizontal Line is missing separating the TOC from the FPI
4. HL headings are not presented in the center of the horizontal line
5. Dosage Form and Strengths are missing
6. Under Indication and Usage Section - Name of established pharmacologic class is missing

Table of Content:

1. FULL PRECRIBING INFORMATION**:CONTENTS** is missing

Full Prescribing Information:

1. Revision date is missing at the end of the patient labeling (21 CFR Part 208)

2. Under Post-Marketing Experience the following verbatim statement is missing - *The following adverse reactions have been identified during post-approval use of* (b) (4) *Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure is missing*.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter/an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **August 8, 2014**. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

NO 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
Comment: *Horizontal Line is missing separating the TOC from the FPI*

NO 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: *HL headings are not presented in the center of the horizontal line*

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

NO 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Dosage Form and Strenths are missing*

NO 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment: *Dosage Forms and Strenghts missing*

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S.**

Approval:" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.****"*).

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

NO 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment: *Name of established pharmacologic class is missing*

Dosage Forms and Strengths in Highlights

NO 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment: *Missing*

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

NO 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment: *1-800FDA (missing -)*

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

NO 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment: *:CONTENTS missing*

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

YES 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

NO 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment: *The following adverse reactions have been identified during post-approval use of* (b) (4) *. Because these reactions are reported voluntarily drom a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure is missing.*

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ZETA-MAE C WILLIAMSON
06/25/2014