CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208224Orig1s000

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

NDA: 208224

Supporting documents: IND 73,505; NDA 21225 (Mirena); NDA 203159 (Skyla)

Letter date: November 18, 2015

Product: Kyleena (LCS16 levonorgestrel-releasing intrauterine system, 19.5 mg)

Indication: Prevention of pregnancy for up to 5 years

Applicant: Bayer Health Care Pharmaceuticals, Inc

Review Division: Division of Bone, Urologic and Reproductive Products

Reviewer: Alex Jordan, PhD

Supervisor/Team Leader: Kim Hatfield, PhD

Division Director: Hylton Joffe, MD

Project Manager: Charlene Williamson

Disclaimer

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Executive Summary

Recommendation

Approvability

Nonclinical data support approval of LCS16, levonorgestrel intrauterine delivery system 19.5 mg, for the prevention of pregnancy for up to 5 years.

Additional Nonclinical Recommendations

No additional nonclinical studies are recommended.

Labeling

The Sponsor's proposed LCS16 (Kyleena) labeling is modeled off of the approved physicians labeling for Mirena and Skyla (Bayer is the Sponsor for Kyleena, Mirena and Skyla). The labeling is in the PLLR format and is acceptable as proposed.

Drug Information

Generic name: LCS16

Pharmacological Class: levonorgestrel-releasing intrauterine system

Brief Discussion of Nonclinical Findings

LCS16 is a drug delivery device designed for intrauterine insertion, releasing small amounts of LNG over time. LCS16 is modeled after the approved IUS's Mirena and Skyla. Kyleena contains 19.5 mg LNG and can be used for up to 5 yrs. Mirena contains 52 mg LNG for 5 yrs of use. Skyla contains 16 mg LNG and can be used up to 3 yrs.

Levonorgestrel has been extensively used as an approved product in a variety of oral contraceptives, hormone replacement therapy and LNG-releasing intrauterine systems, and its pharmacology is well known. LNG is a metabolically stabilized 19-nortestosterone derivative, a potent progestin with some androgenic activity but is devoid of glucocorticoid and estrogenic activity in vivo, and is a potent inhibitor of ovulation.

LCS16 is a low-dose levonorgestrel (LNG) intrauterine system (IUS) that has been developed for use as a long-acting (5 year), reversible contraceptive. The LCS16 IUS consists of a hormone-elastomer reservoir mounted on the vertical stem of a T shaped polyethylene frame. The drug reservoir is composed of a mixture of 19.5 mg LNG ((b) (4)%) and polydimethylsiloxane (PDMS, (b) (4)%). The reservoir is covered by a PDMS membrane (b) (4) The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. The vertical stem contains a silver ring located close to the horizontal arms. Removable threads are attached to the loop of the T body.

In vivo LNG release rate 24 days after insertion is approximately 17.5 ug/24 hrs. This drops to 9.8 ug/24 hrs after 1 yr, 7.9 ug/hr after 3 yrs and 7.4 ug/24 hrs after 5 yrs. The average LNG in vivo release rate is approximately 9 ug/24 hr over the 5 yr period. This results in tissue concentrations that make the endometrium insensitive to circulating estradiol implying an antiproliferative effect.

Except for the removal thread and the flange of the inserter, the components of LCS16 IUS and body-contact components of the inserter are the same as those approved for use with Skyla (NDA 203159), including T-body core elastomer, membrane elastomer, silver ring, and the insertion tube of the inserter.

The novel components of the LCS16 are described below.

Table 1: New components of LCS16*

Component of IUS	Code number
Removal threads (polypropylene, pigmented with ≤ 0.5 wt% [phthalocyaninato(2-)]copper)	LE1401C LE1402C**
Flange (b) (4)	LE1403C

* further details are described in module 3 section 3.2.P.2.1
** material from different polypropylene suppliers

The type of studies conducted to assess biocompatibility and genotoxicity of the new PP removal thread and PE flange used in LCS16, are presented in Table 3 and Table 4.

Table 3: Overview on biocompatibility tests used to assess the safety of the new LNG-IUS components

Biocompatibility tests	Sample type used for the test	Testing standard or guideline
In vitro cytotoxicity test (elution test)	Extract in cell culture medium	ISO 10993-5 (Tests for *in vitro* cytotoxicity), USP <87> Biological reactivity tests *in vitro* (Elution test)
Intracutaneous test in rabbits	Extract in saline	ISO10993-10 (Tests for irritation and delayed-type hypersensitivity). USP <88> Biological reactivity tests *in vivo*
Test for delayed contact hypersensitivity using the guinea pig maximization test	Extract in saline	ISO10993-10 (Tests for irritation and delayed-type hypersensitivity). USP <88> Biological reactivity tests *in vivo*
Subcutaneous implantation in rats over 4 and 26 weeks	Implant of material	ISO10993-6 (Tests for local effects after implantation) ISO10993-11 (Tests for systemic toxicity)

Table 4: Overview on genotoxicity tests used to assess the safety of the new LNG-IUS components

Genotoxicity tests	Sample type used for the test	Testing standard or guideline
In vitro bacterial reverse mutation test	Extract in saline and DMSO	ISO10993-3 (Test for genotoxicity, carcinogenicity and reproductive toxicity) OECD guidelines 471
In vitro mammalian cell gene mutation test	Extract in cell culture medium	ISO10993-3 (Test for genotoxicity, carcinogenicity and reproductive toxicity) OECD guideline 476

Table 3: Results of biocompatibility studies of new LCS16 materials

Test article	Cytotox.	Contact sensitization	Local tolerance. (i.c.)	Ames test	Mouse lymphoma	Chronic implantation (s.c.)
		guinea pigs	rabbits			rat
LE1401C	neg.	neg.	neg.	neg.	neg.	neg.
LE1402C	neg.	neg.	neg.	neg.	neg.	neg.
LE1403C	neg.	neg.	neg.	-	-	-

neg. no relevant findings
\- not determined

The results of the biocompatibility tests indicate that the new LCS16 components are well-tolerated locally and systemically, were biocompatible under the conditions of the tests employed, and were not mutagenic.

Summary and Safety Evaluation

LCS16 (Kyleena) is the third IUS developed by Bayer Health Care after Mirena and Skyla. All three IUS's release levonorgestrel as the progestin and levonorgestrel is not a safety issue. Kyleena is similar to Skyla except that it is designed to last 5 years vs 3 years for Skyla. It contains an intermediate amount of LNG between Mirena and Skyla. The differences between the IUS's of Skyla and Kyleena are the polypropylene removal threads and the polyethylene flange of the inserter. For testing of these products, recommendations of ISO standards (ISO 10993-Part 1) for the testing of medical devices and USP guidelines for testing the biocompatibility of materials used in drug containers, medical devices and implants were followed. With regard to the new flange used for the inserter, studies required for limited contact duration were performed. Results of those studies gave no indication of any toxic effect, neither when tested after subcutaneous implantation nor when tested in the form of extracts in the investigation of toxicity of leachables.

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/s/

ALEXANDER W JORDAN
08/02/2016

KIMBERLY P HATFIELD
08/02/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208224 **Applicant:** Bayer Healthcare **Stamp Date:** Nov. 18, 2015

Drug Name: LCS16 **NDA/BLA Type:** NDA

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies (in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes__X__

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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/s/

ALEXANDER W JORDAN
01/13/2016