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RESEARCH**

APPLICATION NUMBER:

208224Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA #	NDA 208224
Applicant Name	Bayer Healthcare
Date of Submission	November 18, 2015
PDUFA Goal Date	September 16, 2016
Proprietary Name / Established (USAN) Name	Kyleena Levonorgestrel-releasing intrauterine system
Dosage Forms / Strength	19.5 mg load, with an average release rate of 9 mcg/day over 5 years
Proposed Indication(s)	Prevention of pregnancy for up to 5 years
Action	Approval

Material Reviewed/Consulted	Names of discipline reviewers
Action Package, including:	
Cross-Discipline Team Leader	Lisa Soule, M.D.
Medical Officer Review	Ronald Orleans, M.D.
Statistical Review	Weiya Zhang, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Alexander Jordan, Ph.D.
Office of Pharmaceutical Quality	Jeffrey Medwid, Ph.D., Sarah Ibrahim, Ph.D., Donna Christner, Ph.D., Yubing Tang, Ph.D., Jessica Liang, Ph.D., Juandria Williams, Ph.D., R.A.C., Grace McNally, Hansong Chen, Kelly Kitchens, Ph.D., Elizabeth Berr, Ph.D., Erika Pfeiler, Ph.D., James Laurenson, M. Scott Furness, Mark Seggel, Ph.D. and Moo-Jhong Rhee, Ph.D.
Clinical Pharmacology Review	Lin Zhou, Ph.D. and Myong-Jin Kim, Pharm.D.
Center for Devices and Radiological Health	Sharon Andrews, Christopher Brown, Francisco Vicenty, and Terry Woods, Ph.D.
Division of Medication Error Prevention and Analysis	Walter Fava, R.Ph., M.S.Ed. and Danielle Harris, Pharm.D., B.C.P.S.
Division of Medical Policy Programs	Twanda Scales, M.S.N./Ed., B.S.N., R.N., Lynn Panholzer, Pharm.D., and LaShawn Griffiths, M.S.H.S.-P.H., B.S.N., R.N.
Office of Prescription Drug Promotion	Carrie Newcomer, Pharm.D.
Office of Scientific Investigations	Roy Blay, Ph.D., Susan Thompson, M.D., Janice Pohlman, M.D., M.P.H., and Kassa Ayalew, M.D., M.P.H.

Signatory Authority Review

1. Introduction

Bayer Healthcare submitted this 505(b)(1) New Drug Application (NDA) for Kyleena (levonorgestrel-releasing intrauterine system), seeking approval for the prevention of pregnancy for up to five years. Kyleena is not marketed in any country.

This document serves as FDA's decisional memorandum for the application.

2. Background

There are three levonorgestrel-releasing intrauterine systems approved for the prevention of pregnancy, two of which – Mirena and Skyla – are also owned by Bayer. Mirena is slightly larger than Kyleena (32 x 32 mm vs. 28 x 30 mm), has a higher levonorgestrel load (52 mg vs. 19.5 mg), and is also for use up to five years. Skyla has the same overall dimensions as Kyleena, but has a lower levonorgestrel drug load (13.5 mg) and smaller drug reservoir (12 mm vs. 18 mm), and is approved only for use up to three years.

Bayer developed Kyleena and Skyla in parallel and evaluated the two products in the same Phase 3 trial.

Kyleena is a drug-device combination product. The intrauterine system is a new drug per 21 CFR 310.502(a)(8), whereas the inserter is a device.

3. CMC/Device

Kyleena consists of a T-shaped polyethylene frame (T-body) with a cylindrical drug reservoir on the vertical stem. The reservoir contains 19.5 mg of levonorgestrel in a silicone elastomer, covered with a silicone membrane (b) (4). Like Skyla, there are two features that facilitate visualization on imaging studies – barium sulfate in the polyethylene renders it radio-opaque and a silver ring on the top of the vertical stem enhances detection on ultrasound. There are removal threads consisting of polypropylene and copper phthalocyanine at the lower end of the vertical stem.

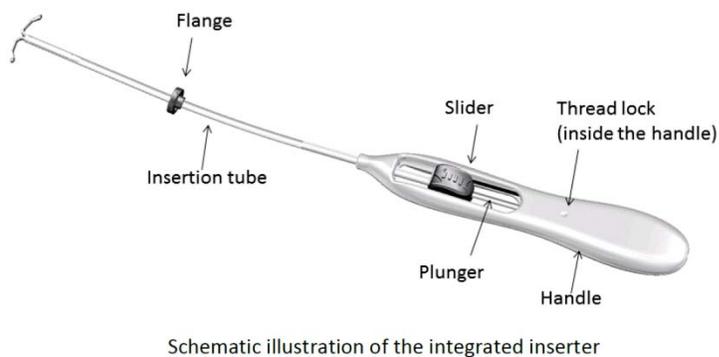
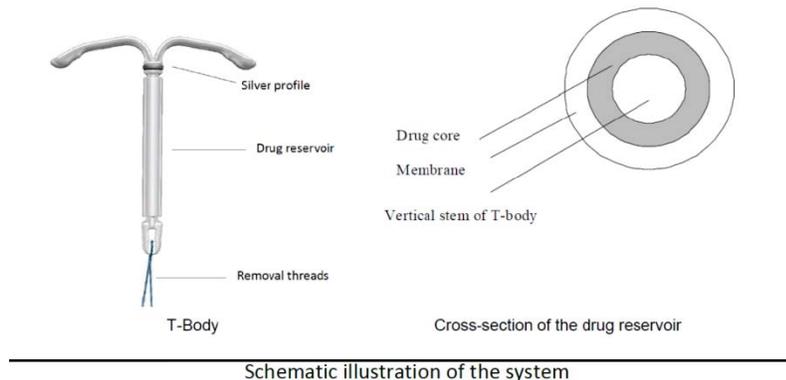
There are minor differences between the Phase 3 product (referred to as LCS16 throughout this memorandum) and the to-be-marketed product, (b) (4)

The Office of Pharmaceutical Quality (OPQ) determined that these changes do not impact the drug reservoir or drug release mechanism, and concluded that no bridging study is needed.

The Center for Devices and Radiological Health (CDRH) reviewed the inserter, which is identical to the inserter approved for Skyla except for the colorant of the slider and flange. These colorant differences are inconsequential because the slider does not come into contact with the patient and the flange is only transiently in contact with the patient. Although the to-be-marketed inserter (with a different colorant for slider and flange) has been tested with Skyla, and not Kyleena, the existing data are sufficient because there are only minor differences from the inserter used in the Kyleena Phase 3 trial, and both Skyla and Kyleena have the same T-body dimensions. CDRH concluded that the device is acceptable from an engineering perspective and meets regulations governing device Good Manufacturing Practices. See the reviews by Sharon Andrews and Chris Brown for further details.

Kyleena is pre-loaded in the inserter then both components are sterilized and co-packaged. The microbiology reviewers found the sterilization process and procedures acceptable.

The intrauterine system and inserter are shown below.



The chemistry reviewers agree with a 24-month expiration dating period for the intrauterine system and inserter, when stored at 25 degrees Celsius in the proposed commercial packaging.

The reviewers also agree with the Applicant's claim for categorical exclusion from an environmental assessment, but, in general, recommend future FDA monitoring for potential cumulative effects of progestins and other hormonally active substances beyond the actions related to this NDA.

The Office of Pharmaceutical Quality (OPQ) recommends approval of the NDA. The chemistry reviewers found the Drug Master File, acceptance criteria and analytical methods for levonorgestrel (the drug substance) to be adequate. In addition, they determined that there is sufficient data to ensure the identity, strength, quality, purity, potency and bioavailability of the product. All facilities have acceptable current Good Manufacturing Practice (CGMP) status.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewer recommends approval of the NDA. See the review by Alexander Jordan, Ph.D., for details.

We did not require nonclinical studies for levonorgestrel because it is used in numerous contraceptive products and hormone therapies, and has a well-established safety profile. In addition, Kyleena's levonorgestrel load and release rate are lower than those for Mirena. The Applicant conducted nonclinical studies to assess biocompatibility and genotoxicity of the new components in the removal threads and inserter flange that differ from those used in Skyla. Per Alexander Jordan, Ph.D., the nonclinical pharmacology/toxicology reviewer, these studies showed that the new components are well-tolerated, biocompatible, and non-mutagenic. The Applicant cross-referenced its own applications for Skyla and Mirena for the remainder of the nonclinical pharmacology/toxicology program.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology and Biopharmaceutics reviewers have found the NDA acceptable. See their reviews for details.

The Applicant did not conduct dedicated clinical pharmacology studies, but used dense and sparse population pharmacokinetic sampling in the Phase 3 trial. Twelve patients in the LCS16 treatment arm were planned for the dense population pharmacokinetic subset; only six had three year pharmacokinetic data and three had five year data. In contrast, the sparse pharmacokinetic subset contained data from ~1,300 subjects with ~2,300 serum levonorgestrel concentrations and ~850 measurements of levonorgestrel residual content, and was used to calculate the *in vivo* levonorgestrel release rates over time. Although the sparse sampling method involves many more patients, the pharmacokinetic profiles are better defined from dense sampling; therefore, labeling will describe pharmacokinetic data from both sampling methods.

About 20% of the levonorgestrel load remains in the intrauterine system at the end of five years. The calculated *in vivo* levonorgestrel delivery rate is initially 16 mcg/day, then 17.5 mcg/day at day 25, declining to 9.8 mcg/day at one year and 7.4 mcg/day after five years, averaging 9 mcg/day over the five year period. We did not require renal or hepatic impairment

pharmacokinetic studies or drug-drug interaction studies given these very low release rates and a mechanism of action predominantly due to local effects.

6. Clinical Microbiology

See the CMC/Device section of the memorandum.

7. Clinical/Statistical-Efficacy

The Applicant conducted one Phase 2 dose-finding European trial and one Phase 3 multinational trial. This section focuses on the Phase 3 study design and efficacy findings. For further details, see the clinical review by Ronald Orleans, M.D., the statistical review by Weiya Zhang, Ph.D., and the Cross-Discipline Team Leader Memorandum by Lisa Soule, M.D., all of whom recommend approval.

The Applicant conducted one open-label, Phase 3 trial that randomized 2,885 healthy women 18-35 years old to LCS16 (n=1,453; about one-third from the United States) or the Skyla formulation, LCS12 (n=1,432). The trial was initially planned with a three-year treatment period, but was subsequently amended after all patients had been recruited to include an extension phase to collect data up to five years for LCS16. The data from the LCS12 arm supported the Skyla approval.

A total of 707 patients (49%) received LCS16 for three years and agreed to continue in the extension phase for up to two additional years, with 550 patients (38%) completing a total of five years. In the LCS16 arm, the mean age was 27 years, about 80% were Caucasian and 11% were Hispanic, about 20% were obese (body mass index ≥ 30 kg/m²), and about 40% were nulliparous.

The efficacy and safety analyses were based on all randomized patients who had at least one insertion attempt. For efficacy, the time period at risk for pregnancy excluded intervals when patients used another contraceptive method, but pregnancies during these intervals were counted. The primary efficacy endpoint was the Pearl Index, the standard endpoint used for contraceptive trials, which counted pregnancies occurring on treatment and those that had an estimated date of conception within seven days after removal or expulsion of Kyleena (this seven day window was included to account for variability in pregnancy dating). A secondary endpoint was the cumulative failure rate (probability of getting pregnant), calculated using the Kaplan-Meier method, censoring patients who were not pregnant at the date of dropout or study end.

Efficacy Results: There were 13 reported pregnancies with LCS16 during the five-year study (occurring nine months to four years after insertion), eight of which were ectopic. Of the remaining five pregnancies, two were normal and carried to term, two ended in spontaneous abortion, and one ended in missed abortion. Drs. Orleans and Soule discuss the pregnancies in detail. The overall Pearl Index as well as the Pearl Index by year are shown in Table 1, based

on FDA’s preferred analysis with 28-day cycles. Results are well within the acceptable range for contraceptive efficacy, and were essentially unchanged when the Pearl Indices were calculated using women-year exposures. The cumulative five-year pregnancy rate based on the Kaplan-Meier method was 1.4 (95% confidence interval 0.8-2.5) per 100 women.

The Applicant identified problems at two clinical sites – one with compliance issues (e.g., protocol deviations, enrollment of ineligible patients) and another implicated in fraudulent behavior. These two sites enrolled a total of about 20 patients. As expected with such a small number of patients, the efficacy analyses with and without these sites yielded similar results.

Table 1. Pearl Indices in the Phase 3 Trial Based on 28-Day Cycles (Adapted from Table 6 in Dr. Zhang’s statistical review)			
	Number of Pregnancies	Relevant Exposure Cycles	Pearl Index (95% Confidence Interval)
Overall PI (n=1452)	13	57,335 ¹	0.29 (0.16-0.50)
Year 1 (n=1452)	2	16,207	0.16 (0.02-0.58)
Year 2 (n=1206)	4	13,853	0.38 (0.10-0.96)
Year 3 (n=1010)	4	11,610	0.45 (0.12-1.15)
Year 4 (n=773) ²	1	8,556	0.15 (0.00-0.85)
Year 5 (n=636)	2	7,087	0.37 (0.04-1.33)

¹Number of evaluable 28-day cycles over the five-year treatment period was 57,313.
²Some patients in the three year trial had treatment exposure longer than three years and were considered at risk at the beginning of Year 4.

Subgroup Analyses: The population pharmacokinetic data showed lower levonorgestrel exposures in women with increasing body weight. The cumulative five-year Pearl Index was 0.55 (95% confidence interval 0.15-1.42) among the 250 patients with BMI ≥30 kg/m², and 0.24 (95% confidence interval 0.11-0.46) among the 1198 patients with BMI <30 kg/m², a trend that is consistent with the pharmacokinetic data described above, but nonetheless, still more than adequate for use in overweight or obese women.

The cumulative five-year Pearl Index and the upper bound of its associated 95% confidence interval was less than 1.00 for nulliparous and parous women, for younger and older women, and for U.S. and non-U.S. sites; across these subgroups, the Pearl Index ranged from 0.18-0.36 and the upper bound of the associated 95% confidence interval ranged from 0.53-0.81. These data suggest no meaningful differences in efficacy among these various subgroups.

Bleeding Patterns: Characterization of Kyleena’s bleeding profile was a secondary efficacy endpoint in the Phase 3 trial, assessed using daily diaries. These data are discussed in detail by Drs. Orleans and Soule. Some of these data are summarized in Table 2. Briefly, based on 90-day reference periods using pooled data from the Phase 2 and Phase 3 trials, the incidence of amenorrhea with LCS16 increased from 0.2% during the first 90 days following insertion to 12% in the 90-day reference period for Year 1, and about 20% in the 90-day reference periods for Years 3 and 5. The incidence of normal menstrual bleeding increased from about 20%

during the first 90 days to about 40% during the 90-day reference assessments for the remainder of the treatment period through five years. In addition, after the first 90 days, the incidence of undesirable bleeding patterns (e.g., irregular, prolonged, or frequent bleeding) declined (Table 2).

	First 90 Days N=1,566	Second 90 Days N=1,511	End of Year 1 N=1,371	End of Year 3 N=975	End of Year 5 N=530
Amenorrhea	<1%	5%	12%	20%	23%
Infrequent bleeding	10%	20%	26%	26%	26%
Frequent bleeding	25%	10%	4%	2%	2%
Prolonged bleeding	57%	14%	6%	2%	1%
Irregular bleeding	43%	25%	17%	10%	9%

8. Safety

Drs. Orleans and Soule discuss the safety findings in detail. Generally, these analyses used pooled data from the Phase 2 and 3 trials.

The extent of patient exposures is adequate. There were a total of 1,697 women randomized to LCS16 with a mean treatment duration of 3.1 women-years representing a total of nearly 70 thousand 28-day equivalent cycles. As noted previously, 550 patients were treated with LCS16 for five years.

These trials did not include a placebo arm, which limits conclusions. Nonetheless, the overall findings are consistent with the known safety profile of other levonorgestrel-containing intrauterine systems, do not raise new safety concerns, and will be labeled. Class effects include:

- An increased risk of ectopic pregnancy: This occurred in 0.6% of LCS16-treated patients in the pooled safety database (0.8% in nulliparous women vs. 0.5% in parous women)
- A small residual risk of pregnancy while the intrauterine system is in place – see the Efficacy section – increasing the risk of spontaneous abortion, sepsis, or preterm labor
- Pelvic inflammatory disease: This occurred in 0.5% of LCS16-treated patients in the pooled safety database.
- Uterine perforation or embedment in the uterine wall or cervix: Partial perforation occurred in 0.2% of LCS16-treated patients in the Phase 3 trial.
- Expulsion: This was reported in about 4% of LCS16-treated patients in the Phase 3 trial. The probability of expulsion was numerically lower in nulliparous women despite their having a smaller uterus than parous women.

- Compatibility with only certain magnetic resonance imaging systems
- Potential side effects related to the progestin component

The first-time insertion success rate in the pooled Phase 2 and 3 trials was 96%. Second attempt success rates were 97%. There was no apparent difference between nulliparous and parous women. The vast majority (>90%) of insertions and removals (~90%) were characterized as “easy” by investigators.

The Applicant contacted 163 patients who had discontinued LCS16 prematurely because of a desire for pregnancy. About 70% of these patients had become pregnant within one year, suggesting that prolonged infertility is not generally expected following removal of the intrauterine system.

Drs. Orleans and Soule discuss other safety findings, including uterine biopsy data, bone mineral density changes, transvaginal ultrasound imaging, laboratory parameters and vital signs. None of these data raise a particular concern.

In summary, the safety findings are consistent with those of approved levonorgestrel intrauterine systems, and will be labeled. It is also reassuring that the drug load and release rates for Kyleena are lower than those of Mirena, and that the Kyleena design is virtually identical to that of Skyla.

9. Advisory Committee Meeting

We did not take this application to advisory committee; it did not raise efficacy or safety issues needing input from outside experts.

10. Pediatrics

This application does not trigger the Pediatric Research Equity Act because it does not propose a new active ingredient, indication, dosage form, dosing regimen or route of administration.

11. Other Relevant Regulatory Issues

Tradename: The Division of Medication Error Prevention and Analysis has concluded that the proposed tradename, Kyleena, is acceptable. See the review by Walter Fava, R.Ph., M.S.Ed., for details.

All three approved levonorgestrel intrauterine systems have the established name “levonorgestrel-releasing intrauterine system.” OPQ recommends the same established name for Kyleena to minimize the risk of confusion even though the 2014 USP nomenclature guidelines recommend “levonorgestrel intrauterine system” for the established name. OPQ

recommends revising the established name for all products simultaneously if/when the USP monograph becomes official and legally recognized under the Federal Food, Drug, and Cosmetic Act.

Inspections: The Office of Scientific Investigations inspected three clinical sites, two of which were classified as No Action Indicated (NAI) and one was classified as Voluntary Action Indicated (VAI). The site with the VAI classification enrolled 97 patients into the Phase 3 trial and had numerous documentation discrepancies. See the review by Roy Blay, Ph.D., for details. Dr. Blay concluded that the data generated by the site, nonetheless, appear acceptable in support of the indication, and Dr. Soule agreed. See Dr. Soule's memorandum for details.

12. Labeling

Labeling is in the Physician Labeling Rule format with content similar to that of Skyla and other levonorgestrel intrauterine systems. There is also a Patient Package Insert, as required by the regulations for contraceptives, which has been reviewed by the Division of Medical Policy Programs. See the review by Twanda Scales, M.S.N./Ed., B.S.N., R.N., for details. The Office of Prescription Drug Promotion reviewed both the Prescribing Information and Patient Package Insert for promotional text. See the review by Carrie Newcomer, Pharm.D. for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

I concur with the recommendations from all review disciplines and the Cross-Discipline Team Leader that this NDA be approved. The Applicant has demonstrated excellent contraceptive efficacy for both parous and nulliparous women with use up to five years. The safety findings are consistent with those of approved levonorgestrel intrauterine systems and show acceptable findings regardless of parity. Kyleena is smaller and has a lower levonorgestrel load and release rate than Mirena. Either can be used for contraception for up to five years. This approval provides patients with another reasonable option for contraception.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable.

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/s/

HYLTON V JOFFE
09/16/2016