NDA 208224/S-002

GENERAL ADVICE

Bayer HealthCare Pharmaceutical Inc.
Attention: Leslie Harden, Pharm.D.
Associate Director, Regulatory Affairs Strategy
P.O. Box 915
Whippany, NJ 07981-0915

Dear Dr. Harden:

Please refer to your supplemental new drug application (sNDA) dated and received September 9, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kyleena (levonorgestrel-releasing intrauterine system).

We also refer to our approval letter dated April 13, 2021, which contained an error. We have updated the letter to correct the error and provide more clarity to language in the April 13, 2021, approval letter.

The original letter stated that the Prior Approval supplemental new drug application provides for revisions to the following:

- Warnings and Precautions section, subsection Risks with Intrauterine Pregnancy, Use in Specific Populations section, subsection Pregnancy and, and the Patient Counseling Information section in the Prescribing Information (PI)
- Removal of all references to the Patient Information Booklet, Consent Form, Follow-up Reminder Card, from the PI and the corresponding Patient Package Information (PPI) and carton labeling
- Harmonization of the PI and PPI labeling with the Mirena label

This letter reflects the revisions to the Prescribing Information (PI) Patient Package Insert (PPI), Carton and Patient Information Booklet as follows:

Dosage and Administration Section:

- Removal of all references to Patient Information Booklet and Consent Form
- Relocated recommendation for pre-insertion evaluation

Warning and Precautions section:

- Updated subsection Risk with Intrauterine Pregnancy with the risk of virilization

Use in Specific Populations section:

- Updated the Pregnancy subsection with the risk of virilization

- Added a Females and Males of Reproductive Potential subsection

Patient Counseling Information section:

- Updated the Risk of Intrauterine Pregnancy section with the risk of virilization
- Removal of reference to Reminder Card

Patient Package Insert (PPI):

- "*What if I become pregnant while using Kyleena?*", "*Can I use tampons with Kyleena?*" and "*What are the possible side effects of Kyleena?"* subsections text updated
- Added text on the use of menstrual cups
- Updated the Perforation and Expulsion subsections.

Carton and Patient Information Booklet:

- Removal of all references to the Consent Form and Reminder Card

This General Advice letter acknowledges the error described above and incorporates the correction of the error as well as an overview of the labeling changes. The effective approval date will remain April 13, 2021, the date of the original letter.

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (310) 796-1025.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Urology, Obstetrics and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

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/s/

AUDREY L GASSMAN
04/30/2021 10:37:21 AM

NDA 208224/S-002

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/s/

AUDREY L GASSMAN
04/26/2021 10:00:36 PM

NDA 208224/S-002

SUPPLEMENT APPROVAL

Bayer HealthCare Pharmaceutical Inc.
Attention: Jo-Ann M. Ruane
Director, Regulatory Affairs Strategy
100 Bayer Blvd., P.O. Box 915
Whippany, NJ 07981-0915

Dear Ms. Ruane:

Please refer to your supplemental new drug application (sNDA) dated and received September 9, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kyleena (levonorgestrel-releasing intrauterine system).

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APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on September 9, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 208224/S-002**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Charlene Williamson, Regulatory Project Manager, at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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/s/

AUDREY L GASSMAN
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