Cross-Discipline Team Leader Memo

Date	October 23, 2019
From	Gerald Willett, MD
NDA # / Supplement #	206229 / S008
Applicant	Medicines360
Date of Submission	Dated December 22, 2018 Received December 26, 2018
PDUFA Goal Date	October 26, 2019
Proprietary Name	Liletta
Established or Proper Name	Levonorgestrel (LNG)-releasing intrauterine system (IUS)
Dosage Form(s)	IUS containing 52 mg of LNG,
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy for up to 6 years
Applicant Proposed Dosing Regimen(s)	IUS inserted into the uterine cavity
Recommendation on Regulatory Action	Approval
Recommended Population	Women at risk for pregnancy

Background

Liletta is a levonorgestrel-releasing contraceptive intrauterine system (LNG IUS). This long-acting reversible contraceptive (LARC) was initially approved by the FDA on February 26, 2015, for prevention of pregnancy for up to three years of use by parous and nulliparous women of any body weight. Liletta received FDA approval for extending duration of use up to four years on August 3, 2017, and up to five years on October 15, 2018. The Applicant seeks to extend duration of use up to six years with this NDA Efficacy Supplement S008 (hereafter referred to as Supplement 008).

Supplement 008 focused on clinical effectiveness and safety data from the phase 3 trial (L102). No new subjects were enrolled in the trial and no changes were made to the protocol prior to final data lock. A total of 65 new financial disclosures were provided and these were reviewed and determined to be acceptable by the clinical reviewer (refer to Clinical Review dated October 21, 2019).

Effectiveness for LARCs after initial approval is based on the Yearly Pearl Index, cumulative Pearl Index and Life Table method of Analysis. The Applicant provided sufficient evaluable cycles (> 10,000) and number of subjects (200) in women 16-35 years of age with successful IUS placement and at least one subsequent assessment of pregnancy status at year 6 necessary for review.

The primary effectiveness results from Year 6 of Liletta use demonstrated the following:

- A year 6 Pearl Index is 0.00 (95% confidence interval = 0.00, 0.94).

- A cumulative Pearl Index for 6 years is 0.18 (95% confidence interval = 0.08, 0.33).
- A Six Year Life Table Pregnancy rate of 0.89% (95% CI 0.45, 1.75)

These Pearl Indices and Life Table pregnancy rate are acceptable for a LARC and demonstrate a clinically meaningful benefit for women who use during the sixth year.

From a safety perspective, there was sufficient overall exposure of women to Liletta in the sixth year to allow review (greater than 10,000 cycles in 566 women). There were no deaths reported in year 6 of the phase 3 trial. No serious adverse events in the supplement submission or 120-Day Safety Update were identified that appeared related to use of the IUS. The new adverse event related discontinuations did not introduce any clinically significant change to the overall safety profile for Liletta. Postmarketing safety reports for Liletta have not indicated any new safety concerns that would entail labeling changes. Based on the additional safety data from use during the sixth year, the safety profile of Liletta remains unchanged and is therefore, acceptable.

From a tolerability perspective, the Applicant collected bleeding and spotting data from Trial L102 through summary questionnaires through subject interviews every 3 months for 72 months. The bleeding and spotting data from these questionnaires were submitted in previous supplements and reviewed. These data demonstrated a consistent diminished menstrual pattern with use of Liletta over time. The rates of bleeding, spotting and amenorrhea were described in labeling. For this review cycle, it was not expected that these rates would be significantly different. A review of adverse bleeding events that resulted in discontinuation during year 6 did not identify any new signal or pattern in tolerability that would lead to requiring additional data.

Clinical pharmacology data was updated through year 6. The Applicant also provided additional *ex vivo* LNG release data that was updated through 7 years of use. There was no new product quality, nonclinical or device information in Supplement S008 that required review. All the disciplines involved with this supplement have recommended approval.

The Applicant has received a pediatric waiver for premenarchal girls and boys. As there are no physiologic reasons why Liletta would work differently in adolescents as opposed to adults, a pediatric study was not required. To comply with PREA, the Applicant submitted clinical data from year 6 from subjects 16-17 years of age from Phase 3 trial L102. The Division also conducted a literature and a FAERS search to evaluate pediatric safety in postmenarchal adolescents. After review, there were no outstanding concerns with approval for the sixth year of use from a pediatric standpoint.

There are no ongoing or outstanding postmarketing commitments or requirements for this application.

For more detail regarding Supplement S008, the reader is referred to the following primary reviews:

Clinical: Caren Kieswetter MD MPH
Biostatistics: Weiya Zhang PhD
Clinical Pharmacology: Peng Zou PhD

Labeling

The principal labeling changes submitted by the Applicant involved providing new clinical information related to extending use to 6 years. The label also provided updated clinical pharmacology information. The Division reviewed the label and patient package insert and recommended several changes related to labeling requirements and consistency with other product labels for intrauterine contraception. Agreed upon labeling for the PI and PPI was obtained with the Applicant.

Regulatory Conclusion

I recommend approval of NDA 206229 (S008) which extends use of Liletta for prevention of pregnancy for up to 6 years.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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10/24/2019 09:22:56 AM

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10/25/2019 12:59:13 PM