OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 21-225/SE27	Submission Dates: 04/01/2009, 09/04/2009
Brand Name	Mirena
Generic Name	Levonorgestrel-releasing intrauterine system
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Bayer HealthCare Pharmaceuticals
Relevant IND	IND 22,697
Submission Type	Efficacy supplement
Formulation; Strength	Levonorgestrel-releasing intrauterine system, 52 mg
Indications	Intrauterine contraception up to 5 years / Treatment of heavy menstrual bleeding (pending)

Table of Contents

1. Executive Summary

Mirena was approved in December 2000 for the intrauterine contraception for up to 5 years.

Bayer submitted an efficacy supplement under NDA 21-225/SE27 to seek an additional indication of treatment of heavy menstrual bleeding in women who desire intrauterine contraception on April 1, 2009. The efficacy supplement consists of 11 phase 3 studies (A38313, B088, A02916, A00630, A14096, A36340, A00696, BC71, B086, AY01, AW82) with Mirena for the treatment of heavy menstrual bleeding. Studies submitted under SE27 did not contain any clinical pharmacology related information. Therefore, no review was done for this efficacy supplement. However, this review addresses on the sponsor's proposed label.

(b) (4)

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology, finds the efficacy supplement of NDA 21-225 acceptable.

1.2 Phase IV Commitments

None.

4 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

3. Appendix

3.1 Cover Sheet and OCP Filing

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-225	Brand Name	Mirena
OCP Division	DCP3	Generic Name	Levonorgestrel-releasing intrauterine system
OND Division	DRUP	Drug Class	Hormonal
OCP Reviewer	Hyunjin Kim, Pharm.D., M.S.	Indication(s)	Intrauterine contraception up to 5 years
OCP Team Leader	Myong-Jin Kim, Pharm.D.	Dosage Form	Intrauterine system
		Dosing Regimen	Once up to 5 years
Date of Submission	04/01/2009	Route of Administration	Intrauterine insertion
Estimated Due Date of OCP Review	08/01/2009	Sponsor	Bayer
PDUFA Due Date	10/01/2009	Priority Classification	
Division Due Date	08/01/2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable ?	**X**			
Comments sent to firm ?				
QBR questions (key issues to be considered)	**Are the drug product and formulation of Mirena used in the clinical study (protocol 309849) same as the to-be-marketed formulation of Mirena?**			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

Filing Memo

Clinical Pharmacology Review

NDA: 21-225, efficacy supplement
Compound: Mirena (levonorgestrel (LNG) releasing intrauterine system (IUS))
Sponsor: Bayer

Date: 05/06/2009
Reviewer: Hyunjin Kim, Pharm.D., M.S.

Background:
Mirena was approved in December 2000, for intrauterine contraception for up to 5 years. Bayer submitted an efficacy supplement to NDA 21-225 for the treatment of heavy menstrual bleeding in women who desire intrauterine contraception. The sponsor initially conducted efficacy studies; they were informed in 2002 that adequacy of these studies to support an application for the proposed indication would be a review issue. In accord with the Division's recommendation, the sponsor conducted an additional study, study A38313 (protocol 309849), to support the primary efficacy of the proposed indication.

Mirena contains LNG as the active ingredient. The pharmacological and pharmacokinetic characteristics of LNG in Mirena were already described in NDA 21-225. In addition, the Division agreed to the sponsor's proposal to cross reference previously submitted clinical pharmacology (human pharmacokinetics and bioavailability) data from the approved NDA 21-225, as long as the drug product and formulation of Mirena used in the primary clinical study (protocol 309849) are same as the marketed formulation of Mirena under NDA 21-225 (Please see meeting minutes for IND 22,697 DARRTSed on January 12, 2009).

Study A38313 (protocol 309849)
This study was conducted in 38 centers in the United States, 10 centers in Canada, 2 centers in Brazil, 3 centers in Mexico and 2 centers in Argentina. The objective of the study was to assess the safety and efficacy of the levonorgestrel intrauterine system as compared to medroxyprogesterone acetate (MPA, orally for 10 consecutive days per cycle), over 6 cycles of treatment in women with idiopathic menorrhagia.

The primary objectives of the study were:
• To determine the absolute change in Menstrual Blood Loss (MBL) from Baseline to End-of-study
• To determine the proportion of patients with successful treatment

The secondary objectives of the study were:
• To determine the absolute change and percent change from Baseline MBL to

Mid-study MBL
• To determine the percent change from Baseline MBL to End-of-study MBL
• To determine the continuation rate (ie, proportion of subjects who completed the study in the LNG IUS treatment group)
• To determine the total number of days of bleeding, spotting, bleeding and spotting, and total number of bleeding episodes
• To evaluate the percent change in hemoglobin, hematocrit, and serum ferritin from Visit 5 to Visit 8 and from Visit 8 to Visit 11 and from Visit 5 to Visit 11
• To determine the proportion of patients with improvement in the Investigator and Patient Global Assessment Scale at Cycle 3 (Visit 8) and Cycle 6 (Visit 11)

There was no measurement of serum levonorgestrel concentration in this study.

The drug product and formulation of Mirena used in the 38 centers in US and 17 foreign centers of the primary clinical study (protocol 309849) was US approved marketed product and was manufactured at the same US manufacturing site.

Information Request from Office of Clinical Pharmacology
None

Clinical Pharmacology comments to be included in the 74-day letter
None

Recommendation:
The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 21-225 efficacy supplement submitted on April 1, 2009 is fileable.

_____ _____
Hyunjin Kim, Pharm.D., M.S. Date

_____ _____
Myong-Jin Kim, Pharm.D., Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21225	SUPPL-27	BAYER HEALTHCARE PHARMACEUTICALS INC	MIRENA(LEVONORGESTREL RELEASING INTRA-UT
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYUNJIN KIM
09/30/2009

MYONG JIN KIM
10/01/2009