Public Assessment Report
MIRENA

INFORMASI PRODUK

Nama Obat	:	MIRENA
Bentuk Sediaan	:	Intra Uterine System (IUS)
Zat Aktif	:	Levonorgestrel 52 mg/implant
Kemasan	:	Dus, @ 1 IUS
Pendaftar	:	PT. Bayer Indonesia, Depok
Produsen	:	Bayer OY., TURKU, FINLANDIA
Kategori Registrasi	:	Registrasi obat yang sudah terdaftar dengan posologi baru
Indikasi yang diajukan	:	Mirena telah disetujui dengan indikasi sebagai berikut: - *Contraception* - *Idiopathic menorrhagia* - *Protection from endometrial hyperplasia during estrogen replacement therapy*
Posologi yang diajukan	:	Terlampir

PENGANTAR

Mirena mengandung zat aktif levonorgestrel yang telah disetujui untuk indikasi *contraception, idiopathic menorrhagia,* dan *protection from endometrial hyperplasia during estrogen replacement therapy.* Saat ini pendaftar mengajukan perubahan pada bagian posologi yaitu perpanjangan penggunaan sebagai kontrasepsi dari 5 tahun menjadi 8 tahun. Evaluasi dilakukan terhadap data studi klinik pendukung sesuai posologi yang diserahkan.

ASPEK MUTU

NA

Pengajuan registrasi berupa posologi baru pada produk obat yang sudah terdaftar. Tidak terdapat perubahan terhadap mutu obat, sehingga tidak dilakukan evaluasi pada aspek mutu

ASPEK KHASIAT KEAMANAN

Studi Non Klinik

Tidak ada studi non klinik baru untuk pengajuan posologi baru.

Studi Klinik

Studi yang diserahkan untuk mendukung pengajuan ini terdiri dari 4 studi farmakokinetika (studi CPMX 50012, 19450, 18960, dan 18579), 1 studi fase 1 (studi 92085), 1 studi fase 2 (studi 91412/308901), 5 studi fase 3 (studi PH-41827, PH-40171, PH-41316, 91655, dan 91665-a52238), serta sudi PH-41511 (studi 19682).

Pembahasan studi klinik difokuskan pada data pendukung efikasi dan keamanan penggunaan Mirena IUS berupa 1 studi fase 3 (studi PH-41827, n=362), yang dilakukan pada wanita usia 18-35 tahun. Studi dilakukan dengan desain *multi-center, open-label, uncontrolled study*. Hasil studi menunjukkan:

1. Untuk mendukung posologi kontrasepsi, penggunaan Mirena sebagai kontrasepsi selama 8 tahun dapat mencegah terjadinya kehamilan (dengan nilai *Pearl Index* tahun ke-6 adalah 0,34; 95%CI: 0,01- 1,88), tahun ke-7 adalah 0,40; 95%CI: 0,01- 2,25 dan tahun ke-8 adalah 0,00 ; 95%CI: 0,00 -1,90).
2. Untuk mendukung posologi *idiopathic menorrhagia*, hasil analisa sub grup pada subjek yang mengalami *Heavy Menstrual Bleeding* (HMB) menunjukkan bahwa subjek yang diberikan levonogestrel sampai tahun ke-8 mengalami penurunan jumlah kehilangan darah menstruasi dari baseline pada akhir tahun ke-8 (*mean change of menstrual blood loss* -0.580 mL/30 hari). Namun demikian, jumlah subjek yang dianalisa tersebut

masih terbatas (n=4 pada tahun ke-8), sehingga belum cukup untuk membuktikan efikasi levonorgestrel lebih lanjut.

3. Data keamanan menunjukkan penggunaan Mirena selama 8 tahun dapat ditoleransi dengan baik.
   - *Drug related treatment emergent adverse event* (TEAE) terjadi pada 65 wanita (18.0%), dimana 47 wanita (13%) mengalami kejadian dengan intensitas *mild*.
   - *Drug related* TEAE yang dilaporkan dialami oleh lebih dari 2% subjek adalah *heavy menstrual bleeding, vaginal haemorrhage,* dan *pelvic pain*, yang sebagian besar adalah *mild*.
   - *Serious drug related* TEAE yang dilaporkan adalah *embedded device* (n=1), *ectopic pregnancy with contraceptive device* (n=1), dan *uterine perforation* (n=2), yang menyebabkan penghentian studi.
   - Dilaporkan tidak terjadi kematian selama studi.

KEPUTUSAN

Berdasarkan hal tersebut di atas, rapat KOMNAS Penilai Obat merekomendasikan bahwa registrasi posologi baru Mirena IUS **diterima dengan perbaikan posologi,** sebagai berikut :

Posologi yang disetujui:

Dosage and method of administration

Method of administration

Mirena is inserted into the uterine cavity. It is effective for 8 years for contraception and for 5 years in the indications Idiopathic menorrhagia and protection from endometrial hyperplasia during estrogen replacement therapy. For timing regarding removal/replacement, see section Removal/replacement.

The in vivo levonorgestrel release rate 24 days after insertion is approximately 21 µg/day, decreasing continuously to approximately 19 µg/day after 1 year, to 11 µg/day after 5 years and to 7 µg/day after 8 years of use. The average daily levonorgestrel release rates are approximately 20 µg/day during the first year, 15 µg/day during the first 5 years and 13 µg/day over the complete 8 year period of use.

In women under hormonal replacement therapy, Mirena can be used in combination with oral or transdermal estrogen preparations without progestogens.

The contraceptive efficacy of Mirena up to 8 years, when inserted according to the insertion instructions, is presented in table 4 below.

Table 4: Contraceptive efficacy

Contraceptive Efficacy within the first 5 years (N= 3330, Pooled data of contraceptive trials up to 5 Years)	
Year 1 Pearl Index	*0.2*
Years 1-5 cumulative failure rate (%)*	***0.7***
Contraceptive Efficacy beyond 5 years (N=362, Mirena Extension Trial)	
Year 6 Pearl Index	*0.34*
Year 7 Pearl Index	*0.40*
Year 8 Pearl Index	*0.00*
Years 6-8 cumulative failure rate (%)*	***0.68***

***** *Kaplan-Meier estimate*

Insertion and removal/replacement
Insertion
Use of Mirena as a contraceptive: In women of fertile age, Mirena is to be inserted into the uterine cavity within seven days of the onset of menstruation. Mirena can be replaced by a new system at any time in the cycle. The system can also be inserted immediately after first trimester abortion.

Postpartum insertions should be postponed until the uterus is fully involuted, however not earlier than six weeks after delivery. If involution is substantially delayed, consider waiting until 12 weeks postpartum. In case of a difficult insertion and/or exceptional pain or bleeding during or after insertion, the possibility of perforation should be considered and appropriate steps should be taken, such as physical examination and ultrasound.

Mirena is not recommended as the contraceptive method of first choice for young women who have never given birth.

Mirena in the treatment of idiopathic menorrhagia: In women of fertile age, Mirena is to be inserted into the uterine cavity within seven days of the onset of menstruation. Mirena can be replaced by a new system at any time in the cycle.

Mirena as a local progestin treatment in conjunction with estrogen replacement therapy: A sample should be taken from the uterine cavity to check the endometrium before insertion of Mirena because spotting is common during the first months of therapy. Mirena can be inserted at any time in an amenorrheic woman, or during the last days of menstruation or withdrawal bleeding. New specimens are not usually required during the 12 months following insertion. Vaginal ultrasonography is recommended 12 months after insertion. An endometrial sample should be taken if the endometrium is thicker than 5 mm or the patient has had extra bleedings. In the treatment of menorrhagia and in local progestin treatment in conjunction with estrogen replacement therapy Mirena releases a sufficient amount of levonorgestrel during a five-year period to prevent proliferation of the endometrium. A sample should be taken from the uterus to check the endometrium before insertion of a new Mirena, even if there has been no bleeding.

It is recommended that Mirena should only be inserted by physicians/health care professionals who are experienced in Mirena insertions and/or have undergone sufficient training for Mirena insertion.

Removal/replacement
Contraception
The system should be removed or replaced after 8 years.

If pregnancy is not desired, the removal should be carried out within 7 days of the onset of menstruation in women of fertile age, provided the woman is experiencing regular menses. If the system is removed at some other time during the cycle or the woman does not experience regular menses and the woman has had intercourse within a week, she is at a risk of pregnancy. To ensure continuous contraception a new system should be immediately inserted or an alternative contraceptive method should have been initiated.

Idiopathic menorrhagia
The system should be removed or replaced in case symptoms of idiopathic menorrhagia return. The system should be removed or replaced after 5 years.

Protection from endometrial hyperplasia during estrogen replacement therapy
The system should be removed or replaced after 5 years.

Mirena is removed by gently pulling on the threads with forceps. The use of excessive force during removal may cause damage to the device. After removal of Mirena, the system should be examined to ensure that it is intact.

During difficult removals, single cases have been reported of the hormone cylinder sliding over the horizontal arms and hiding them together inside the cylinder. This situation does not require further intervention once completeness of the IUS has been ascertained. The knobs of the horizontal arms usually prevent complete detachment of the cylinder from the T-body.

If the threads are not visible, determine the location of the system via ultrasound or other method. If the system is in the uterine cavity, it may be removed using narrow forceps. This may require dilatation of the cervical canal or other surgical intervention.

If the user wishes to continue using the same method, a new system can be inserted at the time of removal.

Instruction for use and handling and disposal:
Mirena is supplied in a sterile pack which should not be opened until required for insertion.
The exposed product should be handled with aseptic precautions. lf the seam of the sterile package is broken, the product should be discarded. Detailed instructions for insertion are in the package.

Additional information on special populations
Geriatric patients
Mirena has not been studied in women over the age of 65 years.

Patients with hepatic impairment
Mirena is contraindicated in women with acute liver disease or liver tumor (see Contraindications).

Patients with renal impairment
Mirena has not been studied in women with renal impairment.

Pediatric population
Use of this product before menarche is not indicated.

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PRODUCT INFORMATION

Drug Product Name	:	MIRENA
Dosage Form	:	Intra Uterine System (IUS)
Active Substance	:	Levonorgestrel 52 mg/implant
Packaging	:	Dus, @ 1 IUS
Applicant	:	PT. Bayer Indonesia, Depok
Manufacturer	:	Bayer OY., TURKU, FINLANDIA
Registration Category	:	Registration of drug product that have been registered with the new posology
Indication Proposed	:	Mirena has been approved for the following indications: - Contraception - Idiopathic menorrhagia - Protection from endometrial hyperplasia during estrogen replacement therapy
Posology Proposed	:	Enclosed

INTRODUCTION

Mirena contains the active substance of levonorgestrel which has been approved for the indications of contraception, idiopathic menorrhagia, and protection from endometrial hyperplasia during estrogen replacement therapy. Currently, the applicant is proposing changes on the posology section, namely extending use as a contraceptive from 5 years to 8 years. Evaluation is carried out on supporting clinical study data according to the posology submitted.

QUALITY ASPECTS

NA

Submission of registration in the form of a new posology for an already registered drug product. There were no changes to the quality of the drug product, so no evaluation was carried out on the quality aspect

ASPECTS OF SAFETY EFFECTIVENESS

Non-Clinical Studies

There are no new non-clinical studies for the proposed new posology.

Clinical Studies

The studies submitted to support this application consisted of 4 pharmacokinetic studies (study of CPMX 50012, 19450, 18960, and 18579), 1 phase 1 study (study of 92085), 1 phase 2 study (study of 91412/308901), 5 phase 3 stuides (study of PH-41827, PH-40171, PH-41316, 91655, and 91665-a52238), as well as study of PH-41511 (study of 19682).

The discussion on clinical studies focuses on data supporting the efficacy and safety of using the Mirena IUS in the form of 1 phase 3 studies (study of PH-41827, n=362), which was conducted in women aged 18-35 years. The study was conducted with a multi-center, open-label, uncontrolled study design. Study results show:

1. To support contraceptive posology, using Mirena as a contraceptive for 8 years can prevent pregnancy (with the Pearl Index value in the 6th year being 0.34; 95%CI: 0.01- 1.88), in the 7th year being 0.40; 95%CI: 0.01- 2.25 and year 8 is 0.00; 95%CI: 0.00 -1.90).

2. To support the posology of idiopathic menorrhagia, the results of subgroup analysis of subjects who experienced Heavy Menstrual Bleeding (HMB) showed that subjects who were given levonogestrel until the 8th year experienced a decrease in the amount of menstrual blood loss from baseline at the end of the 8th year (mean change of menstrual blood loss -0.580 mL/30 days). However, the number of subjects analyzed was still limited (n=4 in year 8), so it was not enough to further prove the efficacy of levonorgestrel.

3. Safety data shows that use of Mirena for 8 years is well tolerated.
   - Drug related treatment emergent adverse events (TEAE) occurred in 65 women (18.0%), of which 47 women (13%) experienced mild intensity events.
   - Drug related TEAEs reported to be experienced by more than 2% of subjects were heavy menstrual bleeding, vaginal hemorrhage, and pelvic pain, most of which were mild.
   - Serious drug related TEAEs reported were embedded device (n=1), ectopic pregnancy with contraceptive device (n=1), and uterine perforation (n=2), which led to study discontinuation.
   - It was reported that no deaths occurred during the study.

DECISION
Based on the above, the KOMNAS Drug Product Appraisal meeting recommended that the registration of the new Mirena IUS posology **be accepted with improvements to the posology**, as follows:

Approved posology:

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