Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Levonorgestrel

Proprietary Product Name: Kyleena

Sponsor: Bayer Australia Ltd

November 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACE	Angiotensin-converting enzyme
ACPM	Advisory Committee on Prescription Medicines
ADEC	Australian Drug Evaluation Committee
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
BMI	Body mass index
CCDS	Company core datasheet
CMI	Consumer Medicines Information
CSR	Clinical study report
DUS	Drug utilisation study
EMA	European Medicines Agency
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FRSH	Faculty of Sexual and Reproductive Healthcare (UK)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCP	Healthcare professional
IUD	Intrauterine device
IUS	Intrauterine (drug delivery) system
LARC	Long-acting reversible contraceptive
LCS12	Development name for Jaydess IUS
LCS16	Development name for Kyleena IUS
LLOQ	Lower limit of quantification

Abbreviation	Meaning
MEC	Medical Eligibility Criteria
MRI	Magnetic resonance imaging
PBRER	Periodic benefit-risk evaluation report
PI	Product Information
PK	Pharmacokinetic(s)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
RMP	Risk Management Plan
US	United States
WHO	World Health Organization

I. Introduction to product submission

Submission details

Type of submission:	Major variation/new strength
Decision:	Approved
Date of decision:	9 January 2017
Date of entry onto ARTG	18 January 2017
Active ingredient:	Levonorgestrel
Product name:	Kyleena
Sponsor's name and address:	Bayer Australia Ltd PO Box 182 Gordon NSW 2072
Dose form:	Intrauterine drug delivery system
Strengths:	19.5 mg
Container:	Sachet
Pack size:	1 x intrauterine drug delivery system
Approved therapeutic use:	*Contraception for up to 5 years*
Route of administration:	Intrauterine
Dosage:	Kyleena is inserted into the uterine cavity and is effective for up to 5 years
ARTG numbers:	270517

Product background

This AusPAR describes the application by the sponsor to register Kyleena levonorgestrel 19.5 mg intrauterine drug delivery system (IUS) sachet indicated for:

'Contraception for up to 5 years'.

This application was originally submitted under the proposed tradename of Sofitta and was subsequently changed as per sponsor request following the first round clinical evaluation. For continuity and clarity, Kyleena is used throughout this document except where discussion of tradename changes is relevant to the application itself.

Levonorgestrel is a second generation progestin with known anti-proliferative effects on the endometrium and is used widely as the progestogenic component of combined oral contraceptive pills, as well as progestogen-only pills and intrauterine drug delivery systems. The application represents the proposed additional strength of levonorgestrel (19.5 mg) similar to the same sponsor's currently registered drug products, Mirena (52 mg) and Jaydess (13.5 mg) levonorgestrel intrauterine drug delivery system, as currently listed on the Australian Register of Therapeutic Goods (ARTG).

Other than differences in the strength for the proposed product, the proposed indication for Kyleena differs from the current approved indications for Mirena and Jaydess, which are as follows:

The approved indication for Mirena is:

> *'Mirena is indicated for:*
>
> - *Contraception*
> - *Treatment of idiopathic menorrhagia*
> - *Prevention of endometrial hyperplasia during oestrogen replacement therapy'.*[1]

The approved indication for Jaydess is:

> *'Contraception for up to 3 years'.*[2]

Regulatory status

The Mirena IUS first received ARTG listing on 24 July 2000 followed by Jaydess on 18 September 2013; however, Jaydess is not currently marketed in Australia.

Applications to register Kyleena have been submitted to the European Union (EU) via the decentralised procedure with Sweden as the Reference Member State; the United States (US) and Canada. Regarding dataset similarities, the sponsor states: *'No significant differences exist in the data submitted with the current Australian Application compared to the data sets submitted in other countries other than the respective local regulatory requirements. The dossier submitted in Australia is based upon the data set submitted in EU'.*

As of 3 October 2016, Kyleena had received a positive outcome in the EU for the same indication as proposed in Australia and was awaiting national registrations in the individual EU countries. As of September 2016, Kyleena had been approved in the US for the following indication:

> *'Kyleena is indicated to prevent pregnancy for up to 5 years.'.*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

The Kyleena IUS consists of a whitish or pale yellow drug reservoir mounted on the vertical stem of a T-body. In addition, the vertical stem contains a silver ring located close to the horizontal arms. The white T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Blue coloured removal threads are attached to the loop. The vertical stem of the IUS is loaded into the insertion tube at the tip of the inserter. The inserter consists of a handle and slider that are integrated with flange, lock, pre-bent insertion tube and plunger. The removal threads are located within the insertion tube and handle.

The device has been evaluated and was considered acceptable.

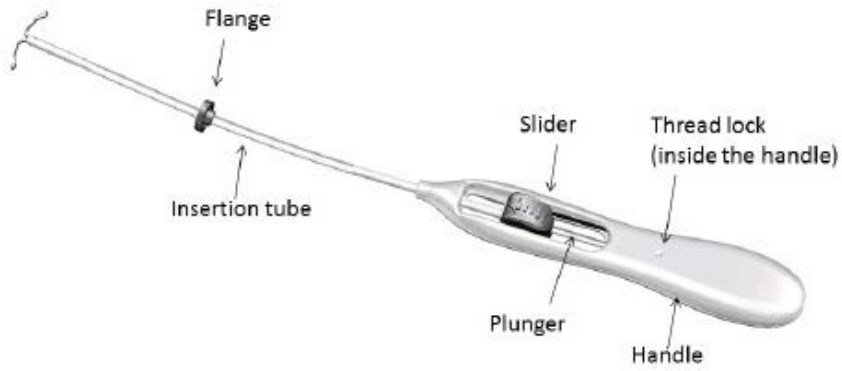
[1] Australian PI for Mirena levonorgestrel 52 mg intrauterine drug delivery system sachet. Bayer Australia Ltd

[2] Australian PI for Jaydess levonorgestrel 13.5 mg intrauterine drug delivery system sachet. Bayer Australia Ltd

The schematic representation of the Kyleena IUS and the inserter/applicator are shown below in Figures 1 and 2 respectively.

Figure 1. Schematic representation of the Kyleena IUS

Figure 2. Schematic representation of the Kyleena IUS applicator



Whilst a suitable In vitro–In vivo Correlation (IVIVC) of the levonorgestrel release rate was not established to cover the proposed 5 year duration of use for Kyleena, in vivo vs in vitro performance of Kyleena has been reported for the Phase III LCS16 batch with ex vivo products up to 5 years used in the calculations. The residual levonorgestrel content was determined in 911 intrauterine systems. There is a strong correlation between the observed and calculated cumulative percentage of levonorgestrel released which supports the conclusion that the model can reliably predict the levonorgestrel release rate. The population pharmacokinetic analysis was detailed in clinical report R-9266.

The shelf life proposed by the sponsor is considered acceptable as 24 months when stored below 30°C (unopened). Once inserted, the intrauterine system may remain in place for up to 5 years (that is, the in-use shelf life is 5 years).

Quality summary and conclusions

All outstanding chemistry and quality control issues have been satisfactorily resolved.

Approval is recommended for registration of the proposed product from a pharmaceutical chemistry and biopharmaceutics perspective, provided the tradename is considered acceptable by the clinical evaluator.

III. Nonclinical findings

Kyleena represents a mid-strength version of the sponsor's existing Mirena and Jaydess products (containing 52 and 13.5 mg levonorgestrel, respectively). The average in vivo release rate of levonorgestrel with Kyleena is 9 µg/day over 5 years, compared with 14 µg/day over 5 years with Mirena and 6 µg/day over 3 years with Jaydess. The initial rate of release and the rate of release at the end of the treatment period for Kyleena are also in-between that of Mirena and Jaydess (17.5, 20 and 14 µg/day initially for the respective products; and 9, 14 and 6 µg/day at end of use).

Nonclinical data submitted included a series of Good Laboratory Practice (GLP) compliant toxicity studies conducted with the new materials used in Kyleena. These are blue coloured polypropylene removal threads (which are in long term body contact) and a grey coloured polyethylene flange used as a component of the inserter device (in short term body contact).

Biocompatibility of the modified polypropylene removal threads was shown in tests for cytotoxicity, genotoxicity, contact sensitisation, local (intracutaneous) tolerance and systemic toxicity; and biocompatibility of the modified flange of the inserter device was demonstrated in tests for cytotoxicity, contact sensitisation and local (intracutaneous) tolerance. The suite of tests performed was as per ISO 10993 requirements for materials in long and short term body contact. [3]

The proposed Pregnancy category, B3, is appropriate and matches that for Mirena and Jaydess.[4]

The nonclinical Safety Specification contained in the sponsor's draft Risk Management Plan is acceptable.

Nonclinical summary and conclusions

There are no nonclinical objections to the registration of Kyleena pending revision of the Product Information document.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Kyleena is a low dose levonorgestrel IUS which has been developed for use as a long-acting reversible contraceptive (LARC). There are two levonorgestrel IUS currently registered. The Mirena IUS contains 52 mg of levonorgestrel with initial in vitro release rate of 20 µg/24 hours and can be used for up to 5 years. Jaydess (designated LCS12 during development) is a lower dose levonorgestrel IUS containing 13.5 mg of levonorgestrel with initial in vitro release rate of 12 µg/24 hours. Jaydess can be used for up to 3 years.

[3] ISO 10993: International Organization on Standardization, Standards for Evaluating Biocompatibility of Medical Devices.

[4] Australian Pregnancy Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

The current submission proposes to register Kyleena (designated LCS16 during development), a low dose IUS containing 19.5 mg of levonorgestrel with initial in vitro release rate of 16 µg/24 hours. The proposed duration of use is for up to 5 years. The sponsor's rationale is:

'*The smaller size of LCS16 as compared with Mirena has been designed to facilitate successful insertion in a wide range of women. The treatment duration of up to five years with LCS16 is considered to be a suitable option for women who would prefer the smaller insertion tube diameter and lower dose (compared to Mirena) but are interested in a 5 year treatment option (compared to LCS12)*'.

The sponsor's rationale is considered acceptable.

Guidance

The TGA adopted EU Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CHMP/021/97 Rev.1) was applicable to this submission.

Contents of the clinical dossier

The submission contained the following clinical information:

- 3 clinical pharmacology studies
- 8 population pharmacokinetic reports
- 1 pivotal efficacy/safety study
- 5 other efficacy/safety studies
- 1 Periodic Safety Update Report (PSUR)
- A Clinical Overview, Summary of Clinical Efficacy, and Summary of Clinical Safety.

The majority of submitted data has been evaluated previously in the submission for Jaydess [details of the Jaydess evaluation can be found in the relevant AusPAR/Attachment 2 document on the TGA website].[5] The focus of the clinical evaluation report (see Attachment 2) was the pivotal efficacy/safety Study 91665/310442 supporting use of Kyleena for up to 5 years, and additional safety data from 4 studies with Jaydess.

Paediatric data

The TGA paediatric development program form states data to support use in the paediatric population was not submitted. On review of the dossier, data for adolescent subjects has been submitted. The sponsor is asked to comment why this was not indicated as such on the application form.

Good clinical practice

The clinical expert stated all clinical studies performed in the framework of this submission were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP).

[5] AusPAR for Jaydess (intrauterine delivery system) levonorgestrel Bayer Australia Ltd; February 2014. TGA; Canberra, Australia.

Pharmacokinetics

Studies providing pharmacokinetic data

The majority of pharmacokinetic (PK) data for LCS16 was provided by the pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 (clinical study reports (CSR) A52238 and PH-37274) and the Phase II Study Protocol 308901 (CSR A46796).

Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetic (PK) profile of levonorgestrel has been described in the previous submission for the lower strength product LCS12 (Jaydess). The current submission included additional PK data from the two clinical studies to support the longer term (5 year) use of LCS16.

Release of LNG occurs immediately after insertion of LCS16. The in vivo release rates calculated over the 5 year period demonstrate a reduction over the first 12 months, with rates remaining relatively stable thereafter to 5 years. The mean release rate over the 5 year period was 9.0 µg/day. By comparison, the mean release rate over the 3 year period for LCS12 was 6.4 µg/day.

As both LCS16 and LCS12 mainly act locally, the following comments from the clinical evaluator of the Jaydess submission are endorsed:

'LCS12 acts primarily via local effects on the endometrium and cervix therefore systemic concentrations, drug interactions, pharmacogenetic factors and food are of less relevance than for oral administration of LNG such as in oral contraceptives. Further the systemic concentrations are > 30 fold more with oral contraceptive use than with the LNG IUS… There were no pharmacokinetic issues of concern in healthy fertile women as studied in the large trials and there are no further pharmacokinetic studies that need to be undertaken for the requested indication'.

Given the effect of bodyweight on levonorgestrel clearance, the clinical evaluator of Jaydess submission did raise the issue of use of LCS12 in obese women:

'On examining the pharmacometric work on clearance in the obese, it suggests it is important that pharmacovigilance is undertaken in obese women with Jaydess. Although the clinical data did not show a higher pregnancy rate in this group, it is possible from the pharmacokinetic simulation data'.

Pharmacodynamics

Studies providing pharmacodynamic data

Pharmacodynamic information included effects on ovulation, cervical mucus, endometrium, serum oestradiol concentration. Data was provided in the Phase II Study A46796, and the Phase III LCS 16 efficacy study.

Evaluator's overall conclusions on pharmacodynamics

LCS16 acts primarily via local effects within the uterine cavity and cervix. The majority of data were provided in the 3 year Study A52238, with few subjects remaining within the subset for assessment during the extension phase. However, no change in pharmacodynamic effect would be expected in the extension phase given the release rates and serum concentrations of levonorgestrel over time as discussed above. Evidence of ovulation was present in almost all subjects during the 3 year study suggesting serum levonorgestrel concentrations were not sufficient to exert an inhibitory effect on ovulation. There was variability in circulating oestradiol levels, although values remained within the range for normal menstrual cycles. A strong progestogenic effect on the

endometrium and cervix was observed indicating a high degree of endometrial suppression and thickening of cervical mucus respectively.

Efficacy

Studies providing efficacy data

The two clinical efficacy studies providing evaluable data were the Phase II Study Protocol 308901 (CSR A46796) and the pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 (CSRs A52238 and PH-37274). Study A46796 and the 3 year Study A52238 have been evaluated previously in the Jaydess submission; the clinical evaluation of Kyleena (see Attachment 2) cross references the Clinical Evaluation Report and the Delegate's Overview for Jaydess where appropriate [details of this the previous Jaydess evaluation are available via the AusPAR/Attachment 2 for Jaydess].[5] This current submission includes new data from the 5 year Study PH-37274.

Evaluator's conclusions on efficacy

The pivotal Phase III LCS16 efficacy study provided data for 1452 women, 707 of which continued in to the 5 year extension phase. The overall LCS16 study population included healthy women aged 18 to 35 years, mostly Caucasian, with mean age 27.1 years, mean body mass index (BMI) 25.3 kg/m^2. There were 39.5% of women who were nulliparous. The study population is considered representative of the target population for marketing.

There were 13 pregnancies over the course of the study. The primary efficacy endpoint was the overall Pearl Index, which was 0.29 (95% CI: 0.16, 0.50). The Pearl Indices for each year ranged from 0.15 to 0.45 with no trend in the Pearl Index observed over time. All Pearl Indices met the European Medicines Agency (EMA) guidelines efficacy requirement that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1. The cumulative failure rate over the 5 years was 1.4%.

The Pearl Indices for subgroups stratified by age, parity and BMI were generally similar to the overall population. It is noted the number of subjects in the BMI subgroup ≥ 30 kg/m^2 was small by comparison. Although the PI and upper limit of the 95% CI met EMA efficacy guideline requirements (that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1; Pearl Index 0.56, 95% CI: 0.15, 1.42), the upper limit of the 95% CI was above 1. Whilst a wide confidence interval can reflect the small sample size, it is difficult to draw conclusions regarding efficacy in this subgroup.

The bleeding profile for LCS16 is considered favourable, with an increase in amenorrhoea and infrequent bleeding over time, together with a reduction in prolonged and frequent bleeding. Return to fertility data demonstrate over 70% of women who ceased LCS16 due to desire for pregnancy conceived within 12 months after removal of LCS16.

Overall, proof of efficacy is considered demonstrated.

Safety

Studies providing safety data

The pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 and the comparative Phase II Study Protocol 308901, as presented for demonstration of contraceptive efficacy, are relevant for the safety evaluation.

Patient exposure

Phase III LCS16 efficacy Study Protocol 91665/310442

The extent of exposure at 3 years was as follows: 1452 subjects received LCS16 with a total exposure of 3353.42 women years.

The 5 year data (based on Report PH-37274 where LCS16 was extended to 5 years) for the pivotal efficacy study is shown in Table 1 below.

Table 1. Extent of exposure, all subjects treated with LCS16 (FAS)

	No-extension group N = 745 (100%)	Extension group N = 707 (100%)	Total N = 1452 (100%)
Treatment duration (days)			
Mean (SD)	603.6 (377.5)	1745.8 (173.3)	1159.8 (643.3)
Min, Max	1, 1248	1083, 1953	1, 1953
Woman years [a]			
Mean (SD)	1.65 (1.03)	4.78 (0.47)	3.18 (1.76)
Min, Max	0, 3.4	3.0, 5.4	0, 5.4
Total	1232.05	3381.55	4613.61

FAS = Full analysis set; N = Total number of subjects (100%)
a: A woman-year equals 365 days

Study A46796 (Protocol 308901)

The extent of exposure to LCS16 (that is, Kyleena) is shown below in Table 2.

Table 2. Extent of total exposure by study phase in women years (FAS)

	LCS12	LCS16	Mirena
Year 1	N = 239	N = 245	N = 254
Total exposure in WY	226.07	233.30	239.35
Year 2	N = 215	N = 215	N = 219
Total exposure in WY	196.48	197.93	201.06
Year 3	N = 187	N = 189	N = 193
Total exposure in WY	176.25	177.25	184.75
Overall	N = 239	N = 245	N = 254
Total exposure in WY	601.68	611.48	627.94

N = number of women, numbers = total exposure in women years (WY) based on the unadjusted Pearl Index (1WY = 365 days)

Safety issues with the potential for major regulatory impact

Known risks of levonorgestrel IUS include unplanned pregnancy; ectopic pregnancy, expulsion and uterine perforation; ovarian cyst; pelvic inflammatory disease; pain on insertion; changes in bleeding pattern; and progesterone related effects. These are characterised and comparable to other IUS (see Attachment 2 for further details).

It is noted that in relation to nulliparous women: 36.7% of the women in the LCS16 group were nulliparous with a higher percentage recorded in the pivotal study (39.5% in the LCS16 efficacy study versus 20.0% in the Phase II study). Adverse events (AE) were reported more frequently overall in nulliparous women: 93.7% of the nulliparous women in the LCS16 pool had adverse events (AE) compared with 85.8% of the parous women. Acne (17.3% versus 12.3%), dysmenorrhea (11.7% versus 5.8%), pelvic pain (11.4% versus 6.1%), nasopharyngitis (10.4% versus 6.5%), and vulvovaginal mycotic infection (8.8% versus 7.1%) were specific AEs reported more frequently in nulliparous women, and the pattern was similar across treatment groups.

Safety in magnetic resonance imaging (MRI) is discussed in the clinical questions section of Attachment 2 and later in this document.

Post-marketing data

Jaydess (LCS12), though registered in Australia is not marketed here. It is noted that the results of EURAS-IUD study were discussed at the Pharmacovigilance Risk Assessment Committee (PRAC) during its meeting of 7 to 10 April 2014. The PRAC recommended that the product information for Mirena and Jaydess be updated to reflect the final 1 year follow-up results of the EURAS-IUD study. In addition, the sponsor was asked to submit additional data and information, which was provided by the company together with a labelling variation in June 2014.

Actions arising from the EU Decentralised Procedure for Jaydess include additional risk minimisation measures in form of appropriate communication to raise prescribers' awareness of the risk of ectopic pregnancy, emphasising the importance of early diagnosis, and to help to differentiate between different types of levonorgestrel IUS (with different approved duration of use) via ultrasound. Consequently, educational material to address communication measures regarding awareness of the risk of ectopic pregnancy and to help to differentiate between different types of levonorgestrel IUS (that is, Jaydess or Mirena) was developed for all EU countries included in the EU Decentralised Procedure. The educational material was nationally submitted in the EU and approved depending on national regulations during 2013 and 2014, and was made available for launch in the individual EU countries during 2014.

It is stated in the PSUR that the company core datasheet (CCDS) for Jaydess was updated to include the main results of EURAS-IUD regarding uterine perforation. This included perforation rates (for the entire study population and for the Mirena and copper intrauterine device (IUD) cohorts) and an update of the existing warning on risk factors for uterine perforation in the Jaydess CCDS with numerical information deriving from EURAS-IUD on the risk factors breastfeeding, and time since last delivery. A section was modified to include information on the frequency of perforation in the populations at higher risk.

There were no other safety related issues identified in the PSUR of 2014.

The estimated cumulative post-marketing exposure is estimated to be more than 774,000 woman-years for Jaydess at the time of database lock point for this periodic benefit-risk evaluation report (PBRER)/PSUR. Close to 535,000 woman-years accumulated during 2015.

No further safety changes or risk minimisation activities were undertaken during this period.

Evaluator's conclusions on safety

The pivotal Study Protocol 91665 (310442) was designed to compare LCS12 and LCS16 and was the study used in the registration dossier for Jaydess, that is, the safety and efficacy of these studies have been evaluated in the previous submission.[5] The 3 year results of safety showed a trend to reducing the number of AEs over the duration. All AEs were similar between groups except for ovarian cysts which were 13.0% versus 20.9% in the LCS12 and LCS16 groups respectively. Other adverse events of special interests did not reveal any clinically significant increase in the LCS16 group. Report PH-37274 deals with the uncontrolled extension study of Protocol 91665 on 707 subjects using LCS16. Whilst these data have limited significance due to the nature of being uncontrolled in design, there were no untoward concerns identified in relation to safety.

The Phase II Study A46796, (Protocol 308901) where LCS12 (n = 239), LCS16 (n = 245) and Mirena (n = 254) were studied for three years, supported the safety findings of the pivotal study.

Safety of the inserter device: It is noted that the device to 'be marketed' is different to that used in the LCS16 studies that support efficacy. Three studies using this insertion device are discussed under the section 'Clinical Safety: Studies using the same Evolution Inserter' (see Attachment 2). A total of 965 subjects have been involved and provide a crude index that the device is safe and does not provide any untoward side effects. This is considered supportive information only.

A comprehensive evaluation of the device is required from a quality point of view to recommend registration.

Overall, the safety of the LCS16 appears acceptable.

First Round Benefit-Risk Assessment

First round assessment of benefits

At the first round, the identified benefits of Kyleena levonorgestrel IUS are:

- Kyleena provides effective contraception for 5 years, a longer duration of action than the currently registered low dose levonorgestrel IUS Jaydess.
- The daily levonorgestrel release rates are lower than Mirena, the currently registered levonorgestrel IUS product which can be used for 5 years. This may theoretically be associated with a more favourable adverse effect profile, although in the absence of direct comparison to Mirena over 5 years no conclusions can be drawn.
- The bleeding profile over 5 years demonstrates a trend towards infrequent bleeding over time. Again, there is no direct comparison to Mirena over the same duration.
- Less systemic progesterone exposure than oral products therefore less risk of progesterone related adverse events.

First round assessment of risks

At the first round, the identified unknown risks of Kyleena levorgestrel IUS are:

- efficacy in women with a BMI ≥ 30 kg/m^2
- safety in MRI

The known risks of Kyleena levorgestrel IUS are:

- unplanned pregnancy
- ectopic pregnancy, expulsion, uterine perforation
- ovarian cyst
- pelvic inflammatory disease
- pain on insertion
- changes in bleeding pattern
- progesterone related effects.

Clinical Questions and Second Round Evaluation of clinical data submitted in response to questions

For details of the clinical questions for the sponsor, the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Kyleena in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Kyleena in the proposed usage are unchanged from those identified in the first round assessment of risks.

- Although body weight can affect levonorgestrel clearance, the available data, albeit limited, for women with BMI ≥ 30 kg/m^2 do not suggest a clinically significant effect of body weight on contraceptive efficacy of levonogestrel IUS. This is not unexpected given the predominant local effect of Kyleena.
- Use in MRI remains an unknown risk. Mirena does not contain metallic components and Jaydess (which does contain the silver ring) is not marketed in Australia. Appropriate information regarding this risk needs to be adequately communicated in the PI/Consumer Medicines Information (CMI) documents and patient card.
- Use in heart disease is an uncertain risk; the Sponsor is asked to clarify the discrepancy regarding the proposed text in Kyleena and that in the current Mirena PI, the latter recommending antibiotic prophylaxis when inserting or removing Mirena.

Second round assessment of benefit-risk balance

The benefit-risk balance of Kyleena, given the proposed usage, is favourable.

Contraceptive efficacy over 5 years with LCS16 has been demonstrated with an overall Pearl index of 0.29 (95% CI: 016, 0.50). There was no trend observed with pregnancy rate over time. The cumulative failure rate at 5 years (1.4%) was similar to the cumulative failure rate at 3 years for the LCS16 arm (1.0%).

There were no new or unexpected safety findings. Ectopic pregnancy is a known safety issue with levonorgestrel IUS. The unadjusted 5 year Pearl Index for ectopic pregnancy for LCS16 in the pivotal study was 0.18 (95% CI: 0.08, 0.36), which is slightly higher than the overall incidence of ectopic pregnancy for Jaydess (0.11 per 100 women-years), although lower than the rates in women not using any contraception (0.3 to 0.5 per 100 women-years).[2] The increased likelihood of a pregnancy being ectopic if pregnancy occurs with Kyleena in situ is clearly documented in the proposed PI. Further, the known risks of pelvic infection, expulsion and perforation are well characterised in the proposed PI.

Second round recommendation regarding authorisation

Approval of the application to register the product Kyleena is recommended for the indication 'Contraception for up to 5 years'.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP version 3; dated 15 October 2015, with a database lock point of 15 July 2015; and an Australian Specific Annex (ASA) version 4 dated February 2016.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 3.

Table 3. Sponsor supplied summary of safety concerns for Kyleena IUS

Summary of safety concerns for Kyleena	
Important identified risks	Pelvic inflammatory disease
	Ectopic pregnancy
	Uterine perforation
	Unintended pregnancy with LCS
	Ovarian cysts
	Expulsion
	Bleeding changes
Important potential risks	Potential for medication error
	Potential for off-label use in indications other than contraception
Missing information	Not applicable

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance for all safety concerns. This includes a targeted questionnaire for the important identified risk of 'uterine perforation'. This questionnaire will be used to collect comprehensive and standardised follow-up information for any post-marketing adverse event reports arising in Australia which are suspicious for these events. For completeness, this form should be appended to the ASA.

The targeted follow up of pregnancy outcomes is also conducted routinely according to Global Standard Operating Procedures. As part of this follow up, Pregnancy Monitoring forms are completed. These forms have been provided in the ASA.

There are no ongoing pharmacovigilance studies for Kyleena. However, the sponsor has provided a list of ongoing studies with Jaydess listed below in Table 4. The protocols are provided in the EU-RMP (studies ongoing since 2014).

Table 4. Ongoing pharmacovigilance studies for Jaydess

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
Ongoing studies			
Pelvic inflammatory disease, ectopic pregnancy,	Outcomes study including DUS component (EURAS-LCS12)	Assess risk of contraceptive failure including ectopic pregnancy, pelvic inflammatory disease	Q2/2021 Annual interim reports

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
unintended pregnancy		and other clinical outcomes in LCS12 users as compared to users of other IUDs/IUSs in real life.	
Off-label use in indications other than contraception, off-label use beyond 3 years	Pharmaco-epidemiological study of LCS12 use in routine clinical practice (Sweden)	Drug utilisation study	Q4/2021

Q2=second quarter; Q4=fourth quarter

Risk minimisation activities

The proposed risk management activities planned for Australia are routine except for the important potential risk of medication error, which will have additional activities.

The sponsor also commits to update the CMI/PI if any safety signal is identified from the PBRERs/PSURs if applicable.

The additional activities planned are similar to that proposed in the EU-RMP and include physician education materials and a patient reminder card to minimise the risk of premature removal of Kyleena (medication error). The sponsor will provide the physician education material to the TGA when available. The education material is proposed only for physicians, and not for other healthcare professionals such as pharmacists. As this product will be inserted by a physician this approach is reasonable.

The patient reminder card has been provided and is based on the reminder card for Jaydess, which is appropriate. The reminder card will capture a record of the date of insertion, latest date for removal and space to record yearly check-ups.

The EU-RMP version 3 includes additional risk minimisation activity for the important identified risk of 'ectopic pregnancy' (Jaydess only). Prescriber educational material is to be provided in the form of an ectopic pregnancy fact sheet. This is not being considered for Australia.

The sponsor provides the following justification:

- *'This safety concern is considered well-established amongst prescribers as a class effect of intrauterine contraceptives. In particular, Mirena (another levonorgestrel releasing IUS) has been registered and marketed in Australia since July 2000 and the positive risk/benefit ratio has remained unchanged. Mirena also contains a higher dose of levonorgestrel compared to Jaydess and Kyleena.*
- *The risk of ectopic pregnancy in case of contraceptive failure with IUDs is considered low. From clinical studies, the overall incidence of ectopic pregnancy with Jaydess is approximately 0.11 per 100 women-years. This rate is lower than in women not using any contraception (0.3 to 0.5 per 100 women-years). From clinical studies, the overall incidence of ectopic pregnancy with Kyleena is approximately 0.20 per 100 women-years. This rate is lower than in women not using any contraception (0.3 to 0.5 per 100 women-years)'.*

Ectopic pregnancy is covered adequately in the PI and CMI and therefore the additional risk minimisation activity for ectopic pregnancy does not seem warranted given that Kyleena is similar to Mirena but a lower dose. In addition, the ASA for Jaydess (version 3.4, March 2015) was updated with the removal of 'Ectopic Pregnancy' as requiring additional risk minimisation activities; that is education material. This has been previously approved by the TGA.

It is noted that for the important identified risk 'ectopic pregnancy' and important potential risk 'medication error' in the ASA states that there are no additional RMP activities planned for the EU or for Australia. However, the sponsor proposes physician education material and a patient reminder card to address medication error in both the EU and Australia and communication with health care professionals for ectopic pregnancy in the EU (Jaydess only). These additional risk minimisation activities should be accurately reported in the EU-RMP and ASA.

Reconciliation of issues outlined in the RMP report

Table 5 below, summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA and the RMP evaluator's evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report

Reconciliation of issues outlined in the RMP report
Recommendation 1: Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
Sponsor's response: The sponsor confirms that any safety concerns identified by the clinical or nonclinical evaluators that impact the safety specifications will be addressed in the RMP.
RMP evaluator's comment: The sponsor's response is noted. However, the sponsor has not included *'Safety with MRI'* in Missing information of the Summary of Safety Concerns as per the clinical evaluator's recommendation. The sponsor states in their response that patients with Kyleena in-situ can be safely scanned using MRI and the PI has been updated with this information. The sponsor provided *Design Verification Reports: Evaluation of Magnetic Field Interactions, Heating, and Artefacts at 3-Tesla for the IUD, LCS, Ultra Low Dose Levonorgestrel Contraceptive System for Kyleena and Kyleena/Jaydess* to support the inclusion of this precautionary statement in the PI. Kyleena is MR-conditional, similar to Jaydess. The inclusion of 'Safety with MRI' in Missing Information of the Summary of Safety Concerns is an outstanding issue and should be addressed by the sponsor.
Recommendation 2: In the ASA, the wording regarding what to do if expulsion occurs reproduced from the CMI has been superseded (states '[the sponsor] Drug Safety should be contacted'). This should be changed to reflect the revised wording in the draft CMI.
Sponsor's response: The ASA has been updated as per the revised wording in the draft CMI.
RMP evaluator's comment: The table has been updated appropriately.
Recommendation 3: In the ASA, for the important identified risk 'ectopic pregnancy' and important potential risk 'medication error', the table states that there is no additional RMP activities planned for the EU or for Australia. However, the sponsor

Reconciliation of issues outlined in the RMP report
proposes physician education material and a patient reminder card to address medication error in both the EU and Australia and communication with health care professionals for ectopic pregnancy (EU only). This table should be corrected.
Sponsor's response: The sponsor wishes to clarify that no additional risk minimisation activities are proposed for the important identified risk 'ectopic pregnancy' in the EU for LCS16. However, the table in the ASA has been amended to include the physician educational material and patient reminder card to address medication error for both the EU and Australia.
RMP evaluator's comment: The table has been updated. However, the sponsor now proposes only a patient reminder card as an additional risk minimisation activity to address 'Medication Error' and does not propose health care professional educational material as it no longer proposes to market Jaydess. The RMP evaluator considers that the health care professional education material, as well as the Physician Questionnaire, should be adapted to provide information about Mirena and Kyleena.
Recommendation 4: The sponsor should clarify if it intends to make similar changes to the CMI for Jaydess and Mirena with regards to the drug interactions and what to do if the product is expelled.
Sponsor's response: It is planned to make similar changes to the drug interactions sections for the Mirena and Jaydess PIs in early 2017. The Mirena and Jaydess CMIs will also be updated to include the information regarding what to do in the event of a product expulsion.
RMP evaluator comment: The sponsor's response is acceptable.
Recommendation 5: The PI includes additional information under the following headings in the 'Precautions' section: Paediatric Use and Interactions with Other Medicines, and Ethnic Differences. The Delegate should consider whether similar PI changes should be made for Mirena and Jaydess to reflect the proposed changes in the draft PI for Kyleena.
Sponsor's response: Not addressed.
RMP evaluator comment: The Delegate is responsible for the final wording of the PI/CMI.
Recommendation 6: The CMI refers to medicine interactions with angiotensin-converting enzyme (ACE) inhibitors and anticoagulants. However, the PI does not mention these medicines. The Delegate should consider if the PI should include all the medicine interactions reflected in the CMI.
Sponsor's response: The sponsor would like to clarify that in the initially submitted CMI for LCS16, the drug interactions with anticoagulants, medicines for pain and inflammation and ACE inhibitors was incorrectly included. The CMI has been updated to reflect the information in the proposed PI.
RMP evaluator comment: The draft PI/CMI has been amended.
Recommendation 7: Under 'Taking Other Medicines': The Delegate should consider changing the wording in the CMI from 'hydantoin' to 'phenytoin' for clarity for the consumers.

Reconciliation of issues outlined in the RMP report
Sponsor's response: Not addressed.
RMP evaluator comment: A revised CMI (dated October 2016) has been provided which implements this change.

Summary of recommendations

Following the second round evaluation, the following recommendations were made in relation to the RMP and were subsequently addressed by the sponsor. These recommendations, along with the sponsor's responses are discussed in Table 6, below.

Table 6. Reconciliation of recommendations in the post-second round RMP evaluation

Reconciliation of issues outlined in the post-second round RMP report
Recommendation 8: The inclusion of '*Safety with MRI*' in Missing Information of the Summary of Safety Concerns is an outstanding issue and should be addressed by the sponsor.
Sponsor's response: Non-clinical testing has been conducted with a similar levonorgestrel IUS with the same size silver ring and T-body and has demonstrated that the intrauterine system can be used in commercially available MRIs under specific conditions. This type of non-clinical testing is consistent with the testing recommended by the US Food and Drug Administration (FDA) in '*Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment*'. Therefore, the sponsor considers the safety of Kyleena during a MRI to be sufficiently demonstrated based on the non-clinical testing as recommended by ASTM in Standard F2503-08 and the abovementioned FDA guidance document.[6,7]
RMP evaluator's comment: The sponsor has provided evidence that there is sufficient information regarding Kyleena to ensure safety with MRI and therefore, from an RMP perspective 'Safety with MRI'' does not need to be included under Missing Information of the Summary of Safety Concerns.
Recommendation 9: The RMP evaluator considers that the healthcare professional education material, as well as the Physician Questionnaire, should be adapted to provide information about Mirena and Kyleena. **Recommendation 10**: Healthcare professional material should be added as an additional risk minimisation activity for Medication Error in the ASA.
Sponsor's response (to recommendations 9 and 10): The principle of the safety concern 'potential for medication error' in the EU-RMP for Jaydess and Kyleena (Version 3.0) is to differentiate between Jaydess, an IUS with the contraceptive efficacy of 3 years, and the IUSs with the contraceptive efficacy of five years, Mirena and Kyleena, as use

[6] American Section of the International Association for Testing Materials (ASTM International) Standard F2503-08: Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.
[7] FDA Guidance related to MR safety evaluation (2014): 'Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment'.

Reconciliation of issues outlined in the post-second round RMP report
beyond the approved duration may no longer provide full contraceptive efficacy. In the EU, Jaydess is marketed with Mirena (Kyleena will also be marketed soon) and additional risk minimisation activities for the safety concern 'potential for medication error' were deemed necessary for healthcare professionals due to the different duration of use between Jaydess and Mirena. However, as Jaydess will not be marketed in Australia, the potential for medication error is not applicable as both Mirena and Kyleena have the same duration of use for contraceptive efficacy. Therefore, the sponsor considers educational material regarding medication error for healthcare professionals to be not required. Furthermore, the contraceptive efficacy (Pearl Index) of Mirena is 0.21 at 1 year and 0.14 at 5 years while for Kyleena, it is 0.16 at 1 year and 0.29 at 5 years. The Pearl Index shows that the two IUSs have similar contraceptive efficacy. Nonetheless, the sponsor will be providing promotional materials to healthcare professionals in the form of a quick reference guide which will highlight the differences between the two IUSs such as the silver ring and the thread colour. The Kyleena PI also has an image of the IUS with labels highlighting the silver ring and the blue thread colour. The sponsor will also recommend to external training providers to update their training materials to include Kyleena.
RMP evaluator's comment: The educational material for insertion of Kyleena and understanding the various circumstances in which to use the various available contraceptive products is generally provided by external training providers and not the sponsor. A large majority of the IUS insertions are carried out at family planning clinics and they are responsible for training protocols as the sponsor has advised. In addition, medication error is less of a concern between Mirena and Kyleena as they both have the same duration of action (that is, 5 years). The sponsor has committed to ensure that educational materials provided by the external training providers are updated to include Kyleena. In addition, it is noted that the sponsor intends to provide promotional material for the new product which includes a quick reference guide which will highlight the differences between the two products. At face value, this appears to be sufficient material for prescribers in order to ensure proper use of the product along with external training material. As these materials are considered to be promotional, rather than educational activities targeted to a specific safety concern, it is not considered necessary to include them in the ASA. The intentions around marketing Jaydess were unclear, due a submission having been received to change the PI for Jaydess. Therefore, further clarification was sought from the sponsor (see below).

During the post-second round evaluation, the RMP evaluator requested that the sponsor address the questions outlined below regarding Recommendation 9 and 10. The sponsor provided responses to the questions raised by the evaluator and these are discussed below.

Table 7. RMP evaluation of the sponsor's responses to RMP questions and clarification of facts following the second round evaluation

RMP evaluation of sponsor's responses and clarifications following the second round evaluation
Question 1: Is Jaydess currently marketed in Australia, and if not, does the sponsor intend to market if the current application to modify the Jaydess application is approved?
Sponsor's response: The sponsor wishes to re-affirm that Jaydess is not and will not be marketed in Australia. This application was submitted for compliance reasons; although Jaydess is not marketed in Australia, the sponsor is required to maintain the currency of the registration as per our parent company. Therefore, if this current application is approved, Jaydess will still not be marketed in Australia.
RMP Evaluator comment: The sponsor's response that Jaydess will not be marketed in Australia is noted.
Question 2: The sponsor is advised that there should be only one current ASA. It is recommended that a combined ASA (for Jaydess and Kyleena) should be resubmitted which includes all the activities included in the separate ASA version 3.6 (Jaydess) and 4.1 (Jaydess and Kyleena). The revised ASA can be submitted and considered for both the application [referenced in Question 1 (above)] and the present application for marketing authorisation of Kyleena.
Sponsor's response: As Kyleena is currently under review and is not yet approved in Australia, the combined ASA for Jaydess and Kyleena (Version 4.1) was not submitted in the application [referenced in Question 1 (above)]. Therefore, two ASAs were maintained. However, once Kyleena is approved, the Jaydess ASA (Version 3.6) will be superseded by the combined Jaydess/Kyleena ASA (Version 4.1).
RMP evaluator's comment: The sponsor should ensure that ASA version 3.6 for the Jaydess submission is replaced with the Jaydess/Kyleena ASA version 4.1 once Kyleena is approved for marketing. However, if Jaydess is not going to be marketed then there should be no need to evaluate the RMP (version 3.6) for this PI change Jaydess submission.
Question 3: The sponsor should clarify their response to Recommendations 9 and 10 from the second round RMP evaluation for Kyleena (see Table 6, above), particularly if the intention to market Jaydess in Australia has changed or is likely to change
Sponsor's response: In the EU, Jaydess is marketed with Mirena (Kyleena will also be marketed soon). As a result, additional risk minimisation activities for medication error were deemed necessary for healthcare professionals due to the different duration of use between Jaydess and Mirena. However, as Jaydess will not be marketed in Australia, the potential for medication error is not applicable as both Mirena and Kyleena have the same duration of use for contraceptive efficacy. Therefore, the sponsor believes that healthcare professional educational material and a physician questionnaire are not required for Mirena and Kyleena.
RMP evaluator's comment: The sponsor's response has reassured the evaluator that Jaydess will not be marketed in Australia therefore the healthcare professional material and physician questionnaire will not be required for Mirena and Kyleena.

Wording for conditions for registration

The suggested wording for registration is: The EU-RMP (version 3; 15 October 2015, data lock point 15 July 2015), with Australian Specific Annex (version 4.1; August 2016), must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission for the drug product Kyleena levonorgestrel 19.5 mg IUS was summarised in the following Delegate's overview and recommendations.

The Delegate noted that proposed trade name Sofitta was changed to Kyleena during the evaluation phase.

The requested indication is: *'Contraception for up to 5 years'.*

The proposed dosing regimen is: *'Kyleena is inserted into the uterine cavity and is effective for up to 5 years*'.

Background

Kyleena is a new drug delivery system that is proposed for registration. The currently registered intrauterine drug delivery systems are:

- Mirena levonorgestrel 52 mg intrauterine drug delivery system (AUST R 73027) inserted every 5 years
- Jaydess levonorgestrel 13.5 mg intrauterine drug delivery system (AUST R 200456) inserted every 3 years.

Both these products were considered by the Australian Drug Evaluation Committee (ADEC) or the Advisory Committee on Prescription Medicines (ACPM) and recommended for registration.[8] Jaydess is currently not marketed in Australia.

The current submission proposes to register Kyleena (designated LCS16 during development), a low dose IUS containing 19.5 mg of levonorgestrel with initial in vitro release rate of 16 µg/24 hours. The sponsor's rationale is:

> *'the smaller size of LCS16 as compared with Mirena has been designed to facilitate successful insertion in a wide range of women. The treatment duration of up to five years with LCS16 is considered to be a suitable option for women who would prefer the smaller insertion tube diameter and lower dose (compared to Mirena) but are interested in a 5 year treatment option (compared to Jaydess- also known as LCS12).'*

The clinical evaluator mentions that:

> *'the LCS16 IUS consists of a hormone-elastomer reservoir mounted on a T-shaped polyethylene frame. The sponsor states LCS16 uses the same T-frame as LCS12, but with a longer duration of action. Like LCS12, the LCS16 IUS T-frame contains a silver ring in the upper part of the vertical stem to facilitate detection and differentiation of LCS16 and LCS12 from other intrauterine systems on ultrasound. To further aid differentiation of LCS16 from LCS12 once in situ, a polypropylene removal thread*

[8] The Australian Drug Evaluation Committee (ADEC) was formed in 1963 and given the role of providing independent, scientific advice on new drugs, within the policy framework of the time, to the Federal Government. ADEC was replaced in 2010 by the Australian Committee on Pharmaceutical Medicines (2010). More recently, the Australian Committee on Medicines (ACM) was established in January 2017, to encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the ACPM, the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM).

with a blue colorant will be used for the commercial LSC16 product, which differs from the brown polyethylene removal threads of the commercial LCS12 product'.

Similar submissions have been made in EU, US and Canada. Kyleena has been approved for use in the US.

Quality

The sponsor did not submit in vivo biopharmaceutical studies, including bioavailability and bioequivalence studies, for the proposed product. The evaluator accepts the justification by the sponsor for not submitting bioavailability studies from a pharmaceutical perspective.

In vivo release rates were calculated using a population pharmacokinetic model over the 5 year period which considered ex vivo residual content data and plasma concentration data obtained from women who prematurely discontinued or completed the study treatment in the pivotal Phase III LCS16 efficacy study. This is considered acceptable by the evaluator.

The shelf life proposed by the sponsor and considered acceptable is 24 months when stored below 30°C (unopened). Once inserted, the intrauterine system may remain in place for up to 5 years (that is, the in-use shelf life is 5 years).

The device has been evaluated and was considered acceptable.

The schematic representation of the device is shown in Figures 1 and 2 earlier in this document.

Quality conclusions and recommendation

All outstanding chemistry and quality control issues have been satisfactorily resolved and the evaluator recommends approval from a chemistry perspective.

Nonclinical

The toxicology evaluator states that the nonclinical data submitted contained a series of GLP compliant toxicity studies conducted with the new materials used in Kyleena as well as previously evaluated data pertaining to existing materials. Only the new data are evaluated in the main body of this report.

The evaluator mentions that these were blue coloured polypropylene removal threads (which are in long-term body contact) and a grey-coloured polyethylene flange used as a component of the inserter device (in short-term body contact).

Biocompatibility of the modified polypropylene removal threads was shown in tests for cytotoxicity, genotoxicity, contact sensitisation, local (intracutaneous) tolerance and systemic toxicity; and biocompatibility of the modified flange of the inserter device was demonstrated in tests for cytotoxicity, contact sensitisation and local (intra-cutaneous) tolerance. The suite of tests performed was as per ISO 10993 requirements for materials in long and short term body contact.[3]

Some PI amendments were recommended.

Nonclinical conclusions and recommendation

The nonclinical evaluator recommends approval from a nonclinical point of view.

Clinical

Pharmacokinetics

The majority of the pharmacokinetic data for LCS16 was provided the pivotal Phase III LCS16 efficacy Study Protocol 91665/310442 (CSRs A52238 and PH-37274) and the Phase II Study Protocol 308901 (CSR A46796). (These two studies are referred to as Study A52238 and Study A46796, in this report). Pharmacokinetic data from Study A46796 and the 3 year Study A52238 were evaluated in the previous Jaydess submission (see the Jaydess AusPAR/Attachment 2 for further details).[5] Thus, several aspects of the pharmacokinetics are drawn upon from the previous evaluation report.

Based on the population pharmacokinetic approach, the in vivo release rate of LCS16 and LCS12 are as follows in Table 8 below.

Table 8. In vivo release rate of LCS16 and LCS12 over time

Time point	Days after insertion	LCS16 *In vivo* release rate (µg/day)	LCS12 *In vivo* release rate (µg/day)
Day 25	24	17.5	14.0
2 months	60	15.3	9.6
1 year	365	9.8	6.0
3 years	1095	7.9	5.4
5 years	1825	7.4	--
Mean over 3 years	0-1095	--	6.4
Mean over 5 years	0-1825	9.0	

Based on these findings, the evaluator is of the opinion that *'the in vivo release rates calculated over the 5 year period demonstrate a reduction over the first 12 months, with rates remaining relatively stable thereafter to 5 years'.*

It is noted that, the estimated in vivo release rate 24 hours after insertion for the Jaydess levonorgestrel IUS 13.5 mg is 14 µg/24 hours and the average in vivo release rate over 3 years is 6 µg/24 hours. The release rates for Kyleena were greater than those for Jaydess.

Pharmacodynamics

Again, the data are obtained from the Phase II Study A46796 and the Phase III LCS16 efficacy Study A52238.

The actions of this product are primarily local on the uterine cavity and cervix.

Based on Study A46796, evidence of ovulation was observed in most women in all examinations in the LCS16 group (n = 15), except in the first year during which 2 women were anovulatory. There was a dose response seen in relation to LCS12 and Mirena.

In the Phase III LCS16 efficacy study, ovulation was based on serum progesterone values (threshold > 2.5 ng/mL). In the subset of women treated with LCS16, evidence of ovulation was shown for 11/12 women in Year 1, 9/10 in Year 2, 7/7 in Year 3 and 1/1 in Year 4. There were no subjects left in the subset in Year 5.

Cervical mucus thickening was also seen in the subsets in Studies A46796 and A52238 using LCS12, LCS16 and Mirena. The numbers included are small to be conclusive regarding dose effect (53 in Study A46796 and 39 in Study A52238). Endometrial biopsy results (taken on a yearly basis up to the end of the 3 year period) in subsets of 30 per treatment arm in both studies showed a strong progestin effect and secretory endometrium in the majority of cases, indicating a high degree of endometrial suppression during treatment.

Serum oestradiol concentrations were variable (measured twice weekly for 6 weeks in Study A52238). In the LCS16 arm the values were within those observed in the normal menstrual cycle. This was studied in the first three years only.

Efficacy

Efficacy studies

The efficacy information is obtained from the same 2 studies discussed above and in the previous submission. The pivotal study to support efficacy was for 3 years duration. The latter study was extended for a further two years to provide support for the indication of 'contraception for 5 years'. This was an open label single arm extension phase of the LCS16 group up to 5 years.

The study population comprised 2884 healthy nulliparous and parous women aged 18 to 35 years in need of contraception. Subjects were randomised in a 1:1 ratio to either the LCS12 (n = 1432) or LCS16 (n = 1452) treatment arms. At the end of the 3 years, there were 707 subjects in the LCS16 treatment arm who continued in to the single arm extension study. There was no control group.

All safety and efficacy assessments were conducted on the full analysis set (FAS), which included all randomised subjects who received treatment (at least one insertion attempt), using the treatment actually received.

In total, 2871 (99.5%) women had successful insertions:

- LCS12: 1426 women (n = 1380 successful at the first attempt and n = 46 successful at the second attempt
- LCS16: 1445 women (n = 1390 successful at the first attempt and n = 55 successful at the second attempt).

All women with an unsuccessful insertion were included in the FAS (n = 13; LCS12 = 6 and LSC16 = 7). The FAS comprised 2884 subjects for the 3 year study and 1452 subjects for the single arm LCS16 extension phase.

Statistical principles have been previously discussed, in the earlier submission. It is noted that the primary efficacy variable was the occurrence of pregnancy, calculated as the Pearl Index with 2-sided 95% confidence intervals.

The primary efficacy variable was pregnancy rate, calculated as the Pearl Index and life-table analysis. Secondary variables included bleeding pattern, return to fertility and user satisfaction.

It is noted that for the LCS16 single arm extension study, there were 4 study visits at 6 monthly intervals from 36 to 60 months. Serum pregnancy testing was performed at screening, and interim visits as needed. Urine pregnancy testing was performed at Baseline, Visit 10 (36 months), Visit 12 (48 months) and Visit 14 (60 months) (see Attachment 2 for further details).

The 4 year Pearl Index was obtained in the first 4 years of treatment (number of pregnancies that occurred during the first four years of treatment divided by time the women were at risk of getting pregnant in the first 4 years of treatment). Similarly, the 5 year Pearl Index was obtained in the first five years of treatment (number of pregnancies that occurred during the first five years of treatment divided by time the women were at risk of getting pregnant in the first five years of treatment).

Results

2885 were randomised. Of the 870 subjects completing the 3 year treatment in the LCS16 treatment group, 707 continued in the LCS16 extension phase, with 550 (77.8%) of these subjects completing the study at Year 5.

Of the 707 subjects continuing the 5 year extension, 82.5% were Caucasian, mean age was 27.6 years (35.9% ≤ 25 years; 64.1 % > 25 ≤ 35 years), with a mean BMI 25.1 kg/m^2 (note, the demographics was similar to the original study group). There were 37.1% of subjects who were nulliparous (see Attachment 2 for further details).

The primary efficacy analysis is follows:

- 3 year data: There were a total of 20 pregnancies over the 3 year study (n = 10 in each group). The unadjusted Pearl Index for the first year was 0.41 (95% CI: 0.13, 0.96) for the LCS12 group and 0.16 (95% CI: 0.02, 0.58) for the LCS16 group. The 3 year unadjusted Pearl Index was 0.33 (95% CI: 0.16, 0.60) for LCS12, and 0.31 (95% CI: 0.15, 0.57) for LCS16.
- The cumulative failure rate over 3 years for all women (18 to 35 years) was 0.009 (95% CI: 0.005, 0.017) in the LCS12 group and 0.010 (95% CI: 0.005, 0.018) in the LCS16 group. See the AusPAR/Attachment 2 for the previous Jaydess submission for details.[5]
- 5 year data: There were a total of 13 pregnancies observed on LCS16 treatment (n = 2 during the first year, n = 4 during the second year, n = 4 during the third year, n = 1 during the fourth year and n = 2 during the fifth year). Of the 13 pregnancies, n = 8 ectopic/suspected ectopic, n = 2 spontaneous abortion, n = 1 missed abortion and n = 2 normal pregnancies carried to term.
- The primary efficacy endpoint was the overall Pearl Index, which was 0.29 (95% CI: 0.16, 0.50). The unadjusted Pearl Index is all subjects treated with LCS16 as extracted from the clinical evaluation report (see Attachment 2), and is shown in Table 9 below.

Table 9. Overall (accumulative) Pearl Index and Pearl Index per study year

Time	Subjects N	Pregnancies n	Total exposure WY	Relevant exposure WY	Pearl index	Lower; Upper 95% CI
Overall	1452	13	4611.99	4437.31	**0.29**	0.16; 0.50
Year 1	1452	2	1316.41	1252.43	**0.16**	0.02; 0.58
Year 2	1206	4	1105.32	1066.87	**0.37**	0.10; 0.96
Year 3	1010	4	926.28	897.75	**0.45**	0.12; 1.14
Year 4	773	1	677.18	659.17	**0.15**	0.00; 0.85
Year 5	636	2	581.53	558.30	**0.36**	0.04; 1.29
2 years	1452	6	2421.73	2319.30	**0.26**	0.09; 0.56
3 years	1452	10	3348.01	3217.05	**0.31**	0.15; 0.57
4 years	1452	11	4025.18	3876.22	**0.28**	0.14; 0.51
5 years	1452	13	4606.71	4434.53	**0.29**	0.16; 0.50

CI = confidence interval; FAS = full analysis set; N = number of subjects; n = number of pregnancies; WY = women years (1WY = 365 days)
Note: the relevant exposure was calculated from the total exposure minus the time in which backup contraception was used or sex hormones were taken for other reasons

The evaluator mentions that *'the Year 4 and Year 5 Pearl indices were 0.15 (95% CI: 0.00, 0.85) and 0.36 (95% CI: 0.04, 1.29) respectively. The Kaplan-Meier estimate of the cumulative failure rate (unadjusted) over 5 years was 1.4 %. The cumulative failure rate over 3 years reported for subjects in the LCS16 treatment arm was 1.0%'.*

Efficacy by subgroup analysis is discussed in Attachment 2. Here, Pearl Indices were stratified by age, parity and BMI. The confidence intervals were wide, possibly reflected small sample size and hence, did not reveal conclusive results.

Other efficacy analysis: Results of other efficacy outcomes are included in Attachment 2. Of note, bleeding profile: 3 year data, for both treatment groups, there was an increase in the number of subjects with amenorrhoea, infrequent bleeding and normal bleeding, and a reduction in the number of subjects with frequent, irregular and prolonged bleeding (see the AusPAR/Attachment 2 for the previous Jaydess submission for further details).[5] It is also stated that, over the course of the study, there was a reduction in prolonged bleeding,

frequent bleeding and irregular bleeding whilst an increase in amenorrhoea and infrequent bleeding was observed.

Return to fertility: Follow-up information is provided for 163 of the 179 women in the LCS16 treatment arm who discontinued due to wish for pregnancy (n = 62 in the extension phase). Of these 163 women, 116 (71.2%) became pregnant within the 12 month follow-up period, with 61 (37.4%) conceiving within 3 months following LCS16 removal.

Other efficacy studies

- Study A46796 (see AusPAR/Attachment 2 for the previous Jaydess submission for further details).[5]

This was a Phase II, multicentre, open label, randomised, dose finding study to investigate LCS12 (n = 239) and LCS16 (n = 245) compared to Mirena (n = 254) in nulliparous and parous women in need of contraception for 3 years. There were some formulation differences also observed by the evaluator. This is considered supportive data. Details are provided in Attachment 2.

The unadjusted Pearl Indices were: LSC16 = 0.82 (95% CI: 0.27, 1.92); LSC12 = 0.17 (95% CI: 0.00, 0.93); Mirena = 0.00 (95% CI: 0.00, 0.59).

For the pooled analysis: please see Attachment 2.

The sponsor has provided a pooled analysis for LCS16 and LCS12 from the Phase II Study A46796 and the Phase III LCS16 efficacy study to provide additional information regarding Pearl Index calculations, bleeding data and IUS location within the uterine cavity. The evaluator has not considered this analysis further as the Phase II study is essentially of different design and also used a formulation that differed from the pivotal study.

Clinical evaluator's overall conclusions on efficacy

The clinical evaluator *'considers the study population in the pivotal study to represent the target population. The Pearl Index ranged from 0.15 to 0.45 with time. The Pearl Indices met the EMA guidelines efficacy requirement that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1. The cumulative failure rate over the 5 years was 1.4%'.*

Thus, proof of efficacy was demonstrated.

Safety

There were 1432 subjects exposed to LCS12 and 1452 exposed to LCS16 at 3 years.

Successful insertion at first attempt was reported in 96% of study participants.

84% reported AEs, generally the incidence was similar between devices; the incidence reduced with time.

Though the incidence of adverse events was similar between groups, the exception was ovarian cysts, which were 13.0% versus 20.9% in the LCS12 and LCS16 groups respectively. Other AEs of special interests did not reveal any clinically significant increase in the LCS16 group. Report PH-37274 deals with the uncontrolled extension study of Study A52238 on 707 subjects using LCS16. Whilst these data have limited significance due to the nature of being uncontrolled in design, there were no untoward concerns identified in relation to safety.

The Phase II Study A46796, (Protocol 308901) where LCS 12 (n = 239), LCS 16 (n = 245) and Mirena (n = 254) subjects were studied for three years, supported the safety findings of the pivotal study.

No decrease was seen in mean bone mineral density measurements, taken in a subset of 205 subjects at lumbar spine and total hip at baseline and at 3 annual visits.

Silver ion in pharmacokinetic analysis: This was taken from the previous Jaydess submission (see the Jaydess AusPAR/Attachment 2 for details).[5] *'In Study A52238 a subset (n = 12) had serum silver concentrations determined prior to and during treatment; no increases were detected with all concentrations except one pre dose measurement below* [the lower limit of quantification] *(LLOQ) of the bioanalytical method, 1 g/mL; this LLOQ is within the range measured in populations not exposed to occupational silver, 0.072 to 1.4 g/mL'*. Similar results would be expected for LCS16.

Clinical evaluator's overall safety conclusions

Overall, the safety of the LCS16 appears acceptable.

The safety profile is similar to that observed with the registered Jaydess, except for ovarian cysts which were predictably higher.

Clinical evaluator's risk-benefit assessment

Overall benefits: The evaluator lists effective contraception over 5 years, daily lower release rates of levonorgestrel compared with Mirena, a trend towards infrequent bleeding over five years and a lower systemic exposure to progesterone compared to oral products as benefits.

Overall risks: The risk assessment is found in Attachment 2. The risks that are unknown are: efficacy in women with BMI ≥ 30 kg/m^2; and the safety in MRI. Known risks of levonorgestrel IUS are unplanned pregnancy; ectopic pregnancy, expulsion, uterine perforation; ovarian cyst; pelvic inflammatory disease; pain on insertion; changes in bleeding pattern and progesterone related effects. These risks are satisfactorily addressed in the draft PI document.

Overall risk benefit assessment: This was deemed favourable.

Risk management plan

A summary of the identified safety concerns along with pharmacovigilance and risk minimisation activities is shown below in Table 10.

Table 10. Summary of safety concerns and related pharmacovigilance/risk minimisation activities

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Pelvic inflammatory disease	✓	✓a	✓	
	Ectopic pregnancy	✓	✓a	✓	
	Uterine perforation	✓		✓	
	Unintended pregnancy with LCS	✓	✓a	✓	
	Ovarian cysts	✓		✓	
	Expulsion	✓		✓	

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
	Bleeding changes	✓		✓	
Important potential risks	Potential for medication error	✓		✓	✓
	Potential for off-label use in indications other than contraception	✓		✓	
Missing information	Not applicable	✓		✓	

a) Outcomes study including drug utilisation study (DUS) component (EURASLCS12) and an ongoing pharmacoepidemiological study (Sweden) are being conducted for Jaydess.

The additional activities planned are similar to that proposed in the EU-RMP and include physician education materials and a patient reminder card to minimise the risk of premature removal of Kyleena (medication error). The sponsor will provide the physician education material to the TGA when available. The evaluator recommends that this material should include information on Mirena and Kyleena.

Risk-benefit analysis

Delegate's considerations

Efficacy:

- Efficacy is adequately established.

Safety:

- The potential for Kyleena to be confused with Jaydess is overcome with the assurance by the sponsor that Jaydess will not be marketed in Australia. In addition, the two IUDs have different colour strings.
- The safety concerns, that is, pelvic infection, expulsion, ectopic pregnancy, lost threads, ovarian cysts are adequately addressed in the 'Precautions' section of the draft PI.
- MRI:
  - No data for Kyleena.
  - Data for Jaydess with similar silver ring suggests MRI scanning is safe (see below). Mirena does not have a silver ring. Copper IUDs are safe but are a cause of artefact.
  - The PI states: *'Non-clinical testing of another LNG-IUS with the same size silver ring and T-body has demonstrated that a patient may be scanned conditional') under the following conditions:*
    - *Static magnetic field of 3-Tesla or less,*
    - *Spatial gradient field of 36,000 Gauss/cm (360 T/m) or less*
    - *Maximum whole body averaged specific absorption rate (SAR) of 4W/kg in the First Level Controlled mode for 15 minutes of continuous scanning*

    In non-clinical testing, the aforementioned LNG-IUS produced a temperature rise of equal or less than 1.8°C at a maximum whole body averaged specific absorption rate (SAR) of 2.9 W/kg, for 15 minutes of MR scanning at 3T using a transit/receive body

coil. A small amount of imaging artefact may occur if the area of interest is in the same area or relatively close to the position of Kyleena.

No clinical data are currently available in women using Kyleena undergoing MRI'.

- The sponsor was requested to include information on patient card but has not agreed. There is currently no information about MRI in the CMI. The sponsor will be requested to address this.

- Use in valvular heart disease:
  - The PI states: '*Kyleena should be used with caution in women who have congenital heart disease or valvular heart disease and who are at risk of infective endocarditis'.*
  - However the Australian Antibiotic Guidelines do not recommend antibiotic prophylaxis for routine insertion of IUD unless there is an established genitourinary or pelvic infection.

Proposed action

The Delegate had no reason to say, at the time, that the application for Kyleena should not be approved for registration.

Request for ACPM advice

The Delegate had the following questions for the Committee:

1. Is the information about MRI in the PI sufficient?
2. IUD batch number is on the patient card. GPs usually keep a record of IUDs inserted. Is this sufficient to track the device?
3. Is there a need for a precaution in heart disease if no antibiotic prophylaxis is needed? What is the best reference to include in the PI?

Questions/issues for the sponsor

The Delegate had the following questions or outstanding issues for the sponsor to address:

- Please update on the status of applications to register Kyleena overseas.
- Please include information about MRI in the CMI.
- Please address outstanding issues regarding the RMP including the inclusion of safety in MRI under missing information.

Response from sponsor

The sponsor provides the following comments in relation to questions submitted to the ACPM.

Following receipt of the Delegate's Request for ACPM advice, the sponsor provided a justification to the RMP evaluator whereby sufficient testing has been conducted in regards to the safety of Kyleena during a MRI. The RMP evaluator has accepted the sponsor's justification and the final RMP evaluation report received on 11 November 2016 was amended to include the RMP evaluator's acceptance.

Therefore, the sponsor considers the Delegate's request regarding outstanding issue of safety of Kyleena during a MRI to be addressed and the inclusion of 'Safety with MRI' in the Missing Information of the EU-RMP to be not required.

Product Information (PI)

Non-clinical MRI testing has been conducted with Jaydess which has a similar T-body (same material and overall dimensions) and an identical silver ring as Kyleena. The testing was conducted in accordance to the international standard, which is a well-established standard to determine safety of implants and devices, such as IUD/IUS during MRI.[9] The standard is also generally accepted by the US FDA and is in line with the current FDA guidance.[10] The guidance is commonly employed in the testing of medical devices which specifically evaluate magnetic field interactions, MRI related heating and artefact testing.

The testing demonstrated that Jaydess can be used in commercially available MRIs under specific conditions. Since both products, Jaydess and Kyleena, have similar T-bodies (the same material and overall dimensions) and an identical silver ring, the MRI testing done for Jaydess is considered applicable for Kyleena. Subsequently, Kyleena can also be considered as MR conditional and can be scanned with MRI under the conditions established for Jaydess.

Based on the non-clinical MRI testing, the sponsor believes that there is sufficient information in the PI for the clinical use of Kyleena within the MRI conditions described in the proposed PI.

Consumer Medicines Information (CMI)

The sponsor believes information about MRI is sufficiently addressed in the CMI. The CMI currently advises patients that Kyleena contains a silver ring and that prior to undergoing a MRI, to tell their healthcare professional that they are using Kyleena. In addition, the CMI also advises patients that Kyleena can only be scanned under specific conditions. The information regarding MRI in the CMI is consistent with the PI.

Tracking of the IUS

Generally, healthcare professionals would record the batch number of the IUS inserted in the patient record as part of good clinical practice. The sponsor considers this to be sufficient to track the IUS.

Valvular heart disease

The sponsor agrees with the Delegate's comment that no antibiotic prophylaxis is needed for routine IUS insertion in women with congenital or valvular heart disease. The majority of guidelines on contraceptive use, such as the Medical Eligibility Criteria (MEC) published by national and international societies have adopted the recommendations from antibiotic prophylaxis guidelines and do not/no longer recommend prophylactic antibiotics to prevent endocarditis (see Table 11 below). As commented by the Delegate, this is consistent with the Australian Antibiotic Guidelines. The only exception is the World Health Organization (WHO) MEC, who advise to use antibiotic prophylaxis for insertion.[11] This recommendation has remained largely unchanged since the first edition of the WHO MEC dating back to 1996.[12] In line with these recommendations, the sponsor no longer recommends prophylactic use of antibiotics for insertion in the PIs of levonorgestrel IUS including Kyleena (the PI update for Mirena is planned for early next year). Nevertheless, the sponsor feels that a precaution maybe justified in some cases. Namely, complicated

[9] American Section of the International Association for Testing Materials (ASTM International) Standard F2503-08: Standard Practice for Marking Medical Devices and Other Items for Safety in the Magnetic Resonance Environment.
[10] FDA Guidance related to MR safety evaluation (2014): 'Guidance for Industry and FDA Staff: Establishing Safety and Compatibility of Passive Implants in the Magnetic Resonance (MR) Environment'.
[11] WHO: Medical Eligibility Criteria for Contraceptive Use. Geneva: World Health Organization, 2015. 5th Edition.
[12] WHO: Improving Access to Quality Care in Family Planning. Medical Eligibility Criteria for Initiating and Continuing Use of Contraceptive Methods. 1996, 1st Edition.

valvular and congenital heart disease is assigned Category 2 which translates to 'A condition where the advantages of using the method generally outweigh the theoretical or proven risks'. In addition, the Faculty of Sexual and Reproductive Healthcare (FSRH) guidance (Contraceptive choices for women with cardiac disease) gives the following advice for women with cardiac disease: '*For women with cardiac diseases the decision to use intrauterine contraception should involve cardiologist*…' (see Table 11 for details). Thus, the sponsor considers that the proposed (current) wording of the precaution adequately reflects the current recommendations on IUD use in women with valvular and congenital heart disease.

Table 11. Relevant guidelines on use of antibiotics in patients with valvular heart disease

MEC	Condition	Category for IUD use	Antibiotic prophylaxis addressed?	Other comments
US MEC (2016)[13]	Valvular HD: Uncomplicated Complicated	1 (Both complicated and uncomplicated	According to the American Heart Association, 'administration of prophylactic antibiotics solely to prevent endocarditis is not recommended for patients who undergo genitourinary tract procedures, including insertion or removal of IUDs'.	No direct evidence exists on the safety of IUDs among women with peripartum cardiomyopathy. Limited indirect evidence from noncomparative studies did not demonstrate any cases of arrhythmia or infective endocarditis in women with cardiac disease who used IUDs. Separate category for women with peripartum myocardiopathy (Category 2), comment: IUD insertion might induce cardiac arrhythmias in healthy women; women with peripartum cardiomyopathy have a high incidence of cardiac arrhythmias
UK MEC	Valvular and congenital	1 (Uncomplicated),	'Prophylaxis against	Congenital heart disease including

[13] CDC: US Medical Eligibility Criteria for Contraceptive Use (2016) MMWR Recomm Rep. 2016; 65 (RR-3):1-103

MEC	Condition	Category for IUD use	Antibiotic prophylaxis addressed?	Other comments
(2016)[14]	heart disease: Uncomplicated Complicated	2 (Complicated)	bacterial endocarditis is no longer indicated for women with artificial heart valves or previous endocarditis when inserting or removing IUS. However, this does not necessarily mean that there is no risk'.	Aortic stenosis; Atrial septal defects; Atrio-ventricular septal defect; Cardiomyopathy (hypertrophic or dilated); Coarctation of the Aorta; Complex Transposition of the Great Arteries; Ebstein's Anomaly; Eisenmenger Syndrome: Patent Ductus Arteriosus; Pulmonary Atresia; Pulmonary Stenosis; Tetralogy of Fallot; Total Anomalous Pulmonary Venous Connection; Tricuspid Atresia; Truncus Arteriosus; Ventricular Septal Defect
WHO MEC 2015[11]	Valvular heart disease: Uncomplicated Complicated	1 (Uncomplicated), 2 (Complicated)	'Clarification: Prophylactic antibiotics to prevent endocarditis are advised for insertion'.	
FSRH guidance/ women with cardiac	See UK MEC	See UK MEC	'Prophylactic antibiotics are not routinely	'Vasovagal reactions may occur as a result of cervical

[14] Faculty of Sexual & Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2016). 2016.

MEC	Condition	Category for IUD use	Antibiotic prophylaxis addressed?	Other comments
disease 2014.[15]			required for the insertion or removal of intrauterine contraception in women with an increased risk of infective endocarditis'.	stimulation during insertion or removal of intrauterine methods…the decision to use intrauterine contraception should involve a cardiologist...The intrauterine method should be fitted in a hospital setting if a vasovagal reaction presents a particularly high risk…'

Overseas regulatory status

Kyleena is currently approved in the US and the decentralised procedure in the EU has been finalised (national phase is still ongoing). The current overseas regulatory status of Kyleena was provided.

Other comments in relation to the Delegate's Overview

Potential for medication errors

The sponsor wishes to highlight that, in Australia, no additional risk minimisation activities for healthcare professionals are planned for the safety concern potential for 'medication error'. In the EU, Jaydess is marketed with Mirena (Kyleena will also be marketed soon). Therefore, additional risk minimisation activities for medication error were deemed necessary for healthcare professionals due to the different duration of use between Jaydess and Mirena. However, as Jaydess will not be marketed in Australia, the potential for medication error is not applicable as both Mirena and Kyleena have the same duration of use for contraceptive efficacy.

Furthermore, as per the final RMP evaluation report received on 11 November 2016, the RMP Evaluator has also accepted that no additional risk minimisation activity for 'medication error' is required for healthcare professionals.

Advisory Committee on Prescription Medicines considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Kyleena intrauterine drug delivery system containing a new strength of levonorgestrel, 19.5 mg, to have an overall positive benefit-risk profile for the following indication:

> *'Kyleena is indicated for contraception for up to 5 years'.*

[15] FSRH, Faculty of Sexual and Reproductive Healthcare. Contraceptive Choices for Women with Cardiac Disease (2014)

Proposed conditions of registration

In making this recommendation the ACPM agreed with the Delegate on the proposed conditions of registration and advised the above on the inclusion of the following:

- Subject to satisfactory implementation of the EU-RMP most recently negotiated by the TGA.
- Negotiation of PI and CMI to the satisfaction of the TGA.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Is the information about MRI in the PI sufficient?*

The ACPM was of the view that the information about MRI included in the PI was adequate but agreed there needed to be a statement in the CMI.

2. *IUD batch number is on the patient card. GPs usually keep a record of IUDs inserted. Is this sufficient to track the device?*

The ACPM considered that detailing the IUD batch number is on the patient card and it should be routine practice for clinicians to keep a record of all medical devices including IUDs and this is sufficient to track the device.

3. *Is there a need for a Precaution in heart disease if no antibiotic prophylaxis is needed? What is the best reference to include in the PI?*

The ACPM advised that most jurisdictions do not recommend antibiotic cover for routine insertion. These include the Australian Therapeutic Guidelines.

There is a known potential for vasovagal response and this can be problematic in cardiomyopathy or other cardiac disease. This is not mentioned in PI but clinicians should be well aware of risk of these effects and if significant risk, the procedure should be done in a facility with adequate resources to manage this. A routine observation period after any insertion would be prudent.

4. *Is there a safety concern with the potential for confusion of the device inserted?*

The ACPM noted that there are similarities between Jaydess and Kyleena in that both have a silver ring at the neck of the devices. The differentiating feature is the colour of the attached string. In addition, although registered in Australia, Jaydess has not been marketed here and the sponsor has given an assurance it will not be. However a device may be inserted overseas. The committee advised that reliance on the colour of the string would be problematic for clinicians as colour is not easily appreciated during per vaginal examination. It was however considered adequate for devices before insertion.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Kyleena levonorgestrel 19.5 mg intrauterine drug delivery system sachet. The approved indication for this therapeutic good is:

'Contraception for up to 5 years'.

Specific conditions of registration applying to these goods

- The Kyleena (levonorgestrel) EU Risk Management Plan (RMP), version 3, dated 15 October 2015 (DLP 15 July 2015), with Australian Specific Annex, version 4.1, dated August 2016, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Kyleena approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au