

## 5.04 LEVONORGESTREL,

### Intrauterine drug delivery system, 19.5 mg, Kyleena<sup>®</sup>, Bayer

#### 1 Purpose of Application

- 1.1 The submission requested a Restricted Benefit listing for levonorgestrel, intrauterine drug delivery system 19.5 mg (Kyleena<sup>®</sup>) for contraception. Kyleena<sup>®</sup> is a long-acting reversible hormone-releasing contraceptive intrauterine system (LARC-IUS). Kyleena<sup>®</sup> has not previously been considered by the PBAC.
- 1.2 A listing for Kyleena<sup>®</sup> was requested on a cost-minimisation basis compared with levonorgestrel 52 mg (Mirena<sup>®</sup>) the only IUS currently listed on the PBS for contraception.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Women requesting contraception
Intervention	Kyleena <sup>®</sup> (LCS16) levonorgestrel 19.5 mg IUS (total content)
Comparator	Mirena <sup>®</sup> levonorgestrel 52 mg IUS (total content)
Outcomes	Pregnancy rate over 5 years, measured using the Pearl Index (number of pregnancies per 100 women-years of treatment exposure)
Clinical claim	<p>Kyleena<sup>®</sup> is non-inferior in terms of effectiveness (Pearl Index) as a contraceptive compared with Mirena<sup>®</sup>.</p> <p>Kyleena<sup>®</sup> is non-inferior in terms of safety compared with Mirena<sup>®</sup>.</p> <p>In addition to the main clinical claim, Kyleena<sup>®</sup> has other benefits over Mirena<sup>®</sup>:</p> <ul style="list-style-type: none"> <li>• Reduction in progestin-related side effects (e.g. ovarian cysts).</li> <li>• Reduction in pain and anxiety associated with insertion.</li> <li>• Reduction in amenorrhea.</li> </ul>

Source: Table 1.1.3, p13 of the submission

IUS = Intrauterine System; LCS = levonorgestrel contraceptive intrauterine system

## 2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LEVONORGESTREL Levonorgestrel 19.5 mg intrauterine drug delivery system, 1 system	1	0	\$ [REDACTED] <sup>a</sup>	Kyleena® Bayer Australia Ltd

Category/Program:	General Schedule
PBS indication:	Contraception
Treatment phase:	NA
Restriction:	Restricted Benefit
Treatment criteria:	NA
Clinical criteria:	NA
Population criteria:	NA
Prescriber criteria:	NA

<sup>a</sup> based on an AEMP of \$ [REDACTED] for Mirena prior to F1 anniversary statutory price reduction (this was calculated incorrectly in the submission as the indication specific AEMP for Mirena in contraception prior to F1 cuts was \$ [REDACTED]).

- 2.1 The requested PBS indication (contraception) is consistent with the approved TGA indication (contraception for up to 5 years) and one of the PBS indications of the main comparator Mirena®.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 3 Background

### Registration status

- 3.1 Kyleena® was TGA registered on 18 January 2017 for contraception for up to 5 years.

## 4 Population and disease

- 4.1 The population likely to use Kyleena® is women requesting contraception. The submission stated that most Australian women (81%) aged 16-49 years used some form of contraception. However, unintended pregnancies (UPs) occurred in up to 50% of women, which is associated with a substantial health, social, psychological, and economic burden. The ESC noted that any increased use of LARCs would reduce rates of unintended pregnancy.
- 4.2 The most common reason for UPs reported by women in Australia is contraception failure (21.2%), followed by forgetting to take/use contraception (20%) and not taking contraceptive pills consistently (10.4%).
- 4.3 The submission proposed that Kyleena® would have the same place in therapy as Mirena®, which is currently listed on the PBS. The ESC noted that due to easier insertion, there may be patients willing to access Kyleena® that do not currently use Mirena®.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated Mirena<sup>®</sup> as the main comparator. The ESC considered that this was appropriate as Mirena<sup>®</sup> is the only IUS currently listed on the PBS for contraception. Kyleena<sup>®</sup> is a new form of the listed drug, levonorgestrel, and the intended duration of use for both Kyleena<sup>®</sup> and Mirena<sup>®</sup> systems is up to five years.
- 5.2 The ESC considered that the smaller size of Kyleena<sup>®</sup> may be appealing to women who have previously chosen to have the etonogestrel 68 mg implant (Implanon<sup>®</sup>) rather than Mirena<sup>®</sup>, and therefore some substitution for Implanon may occur. The pre-PBAC response disagreed with ESC's view and argued that the population using sub-dermal implant or injection would likely have different preferences to the population with a preference for using intra-uterine contraceptive. The PSC response maintained that as Mirena<sup>®</sup> is the only IUS listed on the PBS, it is the only appropriate comparator.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals and organisations via the Consumer Comments facility on the PBS website. The comments described a range of benefits associated with the use of Kyleena<sup>®</sup> including its smaller size and lower dose compared to Mirena<sup>®</sup>. The comments also highlighted the value of these benefits for younger and nulliparous women, who may prefer a lower hormone dose, due to potential systemic hormonal side effects. The comments also noted the decreased risk of insertion complications such as pain, failed insertion, ovarian cysts and uterine perforation.
- 6.3 The PBAC noted the advice received from Royal Australian and New Zealand College of Obstetricians and Gynaecologists highlighting the likely uptake of Kyleena<sup>®</sup> in clinical practice. The PBAC specifically noted in the advice that the use of Kyleena<sup>®</sup> will potentially result in public health savings due to prevention of unplanned pregnancies.

### ***Clinical trials***

- 6.4 The clinical evidence provided in the submission was based on three comparisons:

- LCS Phase II study: a head-to-head phase II RCT comparing LCS16 [Kyleena®] vs Mirena® at three years;
- LCS Pearl Index study: a direct phase III RCT comparing LCS16 [Kyleena®] to non-PBS listed IUS levonorgestrel 13.5 mg (Jaydess®) at three years plus extension study data of LCS16 to five years; based on the PBAC's acceptance of the non-inferiority of Jaydess® to Mirena® (levonorgestrel 13.5 mg, July 2013 and March 2014 public summary documents); and
- a naïve comparison at five years of LCS16 [Kyleena®] (LCS Pearl index study open label extension) and a pooled analysis of three five-year Mirena® randomised control trials.

6.5 Details of the trials presented in the submission are provided in the table below.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Kyleena® Levonorgestrel 19.5 mg IUS RCTs</b>		
Direct head-to-head trial		
LCS Phase II Study	<p><b>Phase II Jaydess® vs. Kyleena® vs. Mirena® at 3 years</b> Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra-low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing in vitro 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception.</p>	14 September 2011
Publications	Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena.	Fertility and Sterility 2012; 97(3):616-622
Indirect comparison		
LCS Pearl Index Study	<p><b>Phase III Jaydess® vs. Kyleena® at 3 years with 2-year extension study for Kyleena®</b> A Randomised, multi-centre, open-label, study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra-low dose levonorgestrel contraceptive intrauterine system (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years.</p>	6 August 2015
Publications-full papers	<p>Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial.</p> <p>Gemzell-Danielsson K, Apter D, Dermout S, Faustmann T, Rosen K, Schmelter T, et al. Evaluation of a new, low-dose levonorgestrel intrauterine contraceptive system over 5 years of use.</p>	<p>Obstet Gynecol 2013; 122(6):1205-1213</p> <p>European Journal of Obstetrics Gynecology and Reproductive Biology 2017; 210:22-28</p>
Publications-conference abstracts	Drosman SR, Gemzell-Danielsson K, Lynen R, Rosen K, Nelson AL. A multicenter, randomized, Phase III study of two low-dose levonorgestrel intrauterine systems (LNG-IUS) for contraception: A subgroup analyses of efficacy and safety in nulliparous versus parous women.	Contraception 2013; 88(2):309
	Faustmann TA, Gemzell-Danielsson K, Apter D, Rosen KA, Schmelter T, Merz M, et al. Efficacy and safety of a low-dose levonorgestrel intrauterine system (LNG-IUS12) according to age, parity, and body mass index over 5 years of use.	Fertility and Sterility 2016; 106:e7-e8
	Gemzell-Danielsson K, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. The effect of age, parity and body mass index on the efficacy, safety, placement and user satisfaction associated with two low-dose levonorgestrel intrauterine contraceptive systems: Subgroup analyses of data from a phase III trial.	PLoS ONE 2015; 10(9)

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Kaunitz AM, Dermout S, Tuppurainen M, Jensen J, Rosen K, Gemzell-Danielsson K. Efficacy and safety of two low-dose levonorgestrel intrauterine systems according to women's age: A global, multicentre, open-label, randomised 3-year Phase III Pearl Index study.</p> <p>Nelson A. New developments in LNG-IUS: The small five-year low-dose levonorgestrel device (LNG-IUS 12).</p> <p>Nelson A, Apter D, Hauck B, Rybowski S, Rosen K, Gemzell-Danielsson K. A global, randomized, phase III, pearl index study comparing the efficacy and safety of two low dose levonorgestrel-releasing intrauterine systems (LNG-IUS) in nulliparous and parous women.</p> <p>Nelson A, Rosen K, Faustmann T, Schmelter T, Gemzell-Danielsson K. A phase III study of a 19.5 mg total dose levonorgestrel intrauterine contraceptive system over 5 years of use.</p> <p>Nelson AL, Gemzell-Danielsson K, Drosman SR, Lynen R, Rosen K. A multicenter, randomized, phase 3 study of two low-dose levonorgestrel contraceptive intrauterine systems (LNG-IUS): A subgroup analysis in nulliparous women.</p>	<p>European Journal of Contraception and Reproductive Health Care 2013; 18:S191-S192</p> <p>European Journal of Contraception and Reproductive Health Care 2018; 23:16</p> <p>Fertility and Sterility 2012; 98(3):S5</p> <p>International Journal of Gynecology and Obstetrics 2015; 131:E144</p> <p>Fertility and Sterility 2012; 98(3):S196</p>
<b>Five-year Mirena® levonorgestrel 52 mg IUS RCTs</b>		
Andersson 1994	<p><b>Mirena® vs. Nova T at 5 years</b>  <u>Publications:</u>                      Andersson K, Odland V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: A randomized comparative trial.</p>	Contraception 1994; 49(1):56-72
Luukkainen 1986	<p><b>Mirena® vs. Nova T at 5 years</b>  <u>Publications:</u>                      Luukkainen T, Allonen H, Haukkamaa M. Five years' experience with levonorgestrel-releasing IUDs.</p>	Contraception 1986; 33(2):139-148
Sivin 1990	<p><b>Mirena® vs. Copper T 380 A (TCu380A) at 5 years</b>  <u>Publications:</u>                      Sivin I, El Mahgoub S, McCarthy T, Mishell Jr DR, Shoupe D, Alvarez F, et al. Long-term contraception with the levonorgestrel 20 mcg/day (LNg 20) and the Copper T 380Ag intrauterine devices: A five-year randomized study.</p>	Contraception 1990; 42(4):361-378

Source: Table 2.2.2, pp26-27 of the submission

IUD = intrauterine device; IUS = intrauterine system; LCS = levonorgestrel contraceptive intrauterine system; LNG = levonorgestrel; RCT = randomised controlled trials

6.6 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Study ID	N	Study design and duration	Risk of bias	Population	Outcomes
<b>Phase II Jaydess® vs. LCS16 vs. Mirena® at 3 years</b>					
LCS Phase II study	742	<ul style="list-style-type: none"> <li>Phase II, MC, OL, R, dose finding study</li> <li>3 years</li> </ul>	Low	Nulliparous and parous women aged 21-40	<ul style="list-style-type: none"> <li>Primary outcome: Pearl Index</li> <li>Secondary outcomes: expulsion and ease/pain assessment on IUS insertion</li> </ul>
<b>Phase III Jaydess® vs. LCS16 at 3 years with 2-year extension study for LCS16</b>					
LCS Pearl Index study	2885	<ul style="list-style-type: none"> <li>Phase III, MC, OL, R, parallel-group study</li> <li>3 years for Jaydess®, 5 years for LCS16 (including a 2-year extension study)</li> </ul>	Low	Nulliparous and parous women aged 18-35 years	<ul style="list-style-type: none"> <li>Primary outcome: Pearl Index</li> <li>Secondary outcomes: bleeding patterns and expulsion</li> </ul>
<b>Five-year Mirena® RCTs</b>					
Andersson 1994	2758	<ul style="list-style-type: none"> <li>MC, OL, R, parallel-group study</li> <li>5 years</li> </ul>	Low	Women aged 18-38 years with ≥ 1 previous pregnancy	<ul style="list-style-type: none"> <li>Primary outcome: Pearl Index</li> <li>Secondary outcomes: bleeding patterns and expulsion</li> </ul>
Luukkainen 1986	417	<ul style="list-style-type: none"> <li>OL, R, parallel-group study</li> <li>5 years</li> </ul>	Low	Women aged 18-38 years with ≥ 1 previous pregnancy	<ul style="list-style-type: none"> <li>Primary outcome: Pearl Index</li> <li>Secondary outcomes: bleeding patterns and expulsion</li> </ul>
Sivin 1990	2245	<ul style="list-style-type: none"> <li>MC, OL, R study</li> <li>5 years</li> </ul>	Low	Fertile, parous women aged 18-38 years	<ul style="list-style-type: none"> <li>Primary outcome: Pearl Index</li> <li>Secondary outcomes: bleeding patterns and expulsion</li> </ul>
<b>Naïve comparison of LCS16 vs. Mirena®</b>					
LCS Pearl Index study	1453	Used the cumulative Pearl Index at 5 years reported in the LCS Pearl Index extension study (LCS16 extension arm)			
Five-year Mirena® trials	3086	Used the pooled cumulative Pearl Index at 5 years reported in the Five-year Mirena® studies (Mirena® arm)			

Source: Table 2.3.1, pp30-31 of the submission

IUS = intrauterine system; LCS = levonorgestrel contraceptive intrauterine system; LNG = levonorgestrel; MC = multi-centre; OL = open label; R = randomised; RCT = randomised control trial

6.7 All included trials were randomised and unblinded. The overall risk of bias was low. However, attrition was high, especially for the three five-year Mirena® studies which reported discontinuation rates varying between 53% and 74% at three years. The most common reasons for discontinuation were adverse events or planning pregnancy.

6.8 The key differences between the trials that may impact on the results were:

- The proportion of nulliparous women was 21.4% in the LCS Phase II study, 39.2% in the LCS Pearl Index study, and a weighted average of 7.7% in the Mirena® arms of the two five-year Mirena® studies that reported this information; and
- Pearl Indices differed for LCS16 at three years between the LCS phase II study (0.83) and the LCS Pearl Index Phase III study at 3 years (0.31), indicating there may be differences in the trial populations. Given the Pearl Index at five years was from the extension study of the LCS trial with a lower Pearl Index reported at three years, the contraceptive efficacy of LCS16 may have been overestimated.

6.9 The actual average treatment durations reported in all trials (2.3 to 3.2 years) were substantially shorter than the intended PBS population duration of treatment (five years), but did not differ between the LCS16 and Mirena® arms. The pre-PBAC response argued that the treatment duration presented in the submission was comparable to the PBAC’s recommendation of Mirena® in 2003 which was based on trials with a mean duration of treatment of 2.91 years (range 2.59-3.25 years).

### **Comparative effectiveness**

6.10 The primary outcome presented in the submission was the cumulative Pearl Index (at three years or five years). The Pearl Index is the pregnancy rate per 100 woman-years of exposure (the number of pregnancies divided by the number of women-years of exposure × 100).

#### LCS Phase II study LCS16 versus Mirena® at three years

**Table 4: Results of direct head-to-head LCS Phase II study at three years**

Outcomes	LCS16 (Kyleena®)	Mirena®	Unadjusted Risk difference (95% CI)
Risk of pregnancy n/N (%)	5/246 (2%)	0/256 (0%)	0.02 (0, 0.04)
Pearl index (95% CI) <sup>a</sup>	0.83 (0.27, 1.93)	0 (0, 0.60)	-
Probability of pregnancy K-M estimate (95% CI)	0.025 (0.011, 0.060)	0.000 (NA)	-

Source: Tables 2.5.1-2.5.2, pp51-52 of the submission; and calculated during the evaluation

CI = confidence interval; K-M = Kaplan-Meier; LCS = levonorgestrel contraceptive intrauterine system; NA = not available

<sup>a</sup> Relevant exposure years used to calculate Pearl Index is 604.53 in LCS16 group and 619.71 in Mirena® group

6.11 The submission stated that since this was a Phase II clinical study, it was not powered to test non-inferiority, and no statistical analysis of the differences between the Pearl Indices was conducted. The 95% CIs for the Pearl Indices overlapped, suggesting the contraceptive efficacy of LCS16 did not differ to that of Mirena®. However, the EMA requirement for efficacy (the difference between the point estimate for the Pearl Index and the upper limit of the 95% CI should not exceed 1) was not met for LCS16.

6.12 Despite overall low pregnancy rates in both arms, there were more UPs in the LCS16 group in comparison to Mirena® (5 vs. 0), including ectopic pregnancies. The risk of pregnancy was 2% in the LCS16 group and 0% in the Mirena® group. The ESC considered that this may be considered clinically significant for women who

experience an UP while treated with LCS16. The pre-PBAC response stated that the Phase II clinical study was based on a small sample over 3 years and thus not powered to demonstrate non-inferiority.

**Naïve comparison**

6.13 Mirena® arms from the three five-year Mirena® studies were combined in a pooled analysis and used in a naïve comparison of five-year Pearl Indices to the Kyleena® extension arm of the LCS Pearl Index study.

**Table 5: Results of the naïve comparison of LCS16 versus Mirena® at five years**

Outcomes	LCS16 (Kyleena®)	Mirena®
	LCS Pearl Index study extension arm	Pooled 5-year Mirena® studies
Risk of pregnancy n/N (%)	13/1453 (0.9%)	12/3086 (0.4%)
Pearl index (95% CI) <sup>a</sup>	0.29 (0.16, 0.50)	0.13 (NR)

Source: Tables 2.6.3-2.6.4, pp66-67 of the submission; and calculated during the evaluation

CI = confidence interval; NR = not reported

<sup>a</sup> Relevant exposure years used to calculate Pearl Index is 4435 in LCS16 group and 8985 in Mirena® group

6.14 Results of the naïve comparison of LCS16 versus Mirena® showed an overall low pregnancy rate for both study arms, however a higher UP rate for LCS16 compared to the Mirena® was observed (0.9% vs. 0.4%).

6.15 The PSCR stated that the difference in the Pearl Index of 0.16 (95% CI: -0.02, 0.34) between LCS16 and Mirena® at 5 years from the naïve comparison was not statistically significant, thus not a true difference.

6.16 The secondary outcomes presented by the submission were bleeding patterns, expulsion and ease of insertion/pain.

6.17 Partial or complete expulsion could result in a loss of contraceptive efficacy. In the LCS Phase II study, there were 3 total expulsions of the IUS (all in the LCS16 group) and 7 partial expulsions (LCS16 = 2, Mirena® = 4).

6.18 Only the LCS Phase II study reported the outcomes of ease of insertion/pain. LCS16 was rated as significantly easier to insert compared with Mirena®. However, the ESC considered that the clinical meaningfulness of this was uncertain and noted that the study was unblinded. Subjects rated the placement of LCS16 as less painful compared with Mirena® (p < 0.01) with 72.2% of subjects in the LCS16 group reporting either ‘no pain’ or only ‘mild pain’ during placement compared with 57.9% of subjects in the Mirena® group.

### Comparative harms

6.19 In the LCS Phase II study, there were no statistically significant differences between the LCS16 and Mirena® groups in the proportions of women experiencing any AE, serious adverse event (SAE), or discontinuation due to an AE.

**Table 6: Overview of adverse events in the LCS Phase II study – FAS**

Subjects	LCS16 (Kyleena®) N=245	Mirena® N=254	LCS16 (Kyleena®) vs. Mirena®		
			OR (95% CI)	RR (95% CI)	RD (95% CI)
With at least 1 AE (total years 1-3), n (%)	220 (89.8)	232 (91.3)	0.83 (0.46, 1.52)	0.98 (0.93, 1.04)	-1.5% (-6.7%, 3.6%)
With any SAE, n (%)	12 (4.9)	16 (6.3)	0.77 (0.35, 1.65)	0.78 (0.38, 1.61)	-1.4% (-5.4%, 2.6%)
Who discontinued study drug due to AE, n (%)	46 (18.8)	48 (18.9)	0.99 (0.63, 1.55)	0.99 (0.69, 1.43)	-0.1% (-7.0%, 6.7%)

Source: Tables 2.5.11, p60 of the submission

AE = adverse event; CI = confidence interval; FAS = full analysis set; LCS = levonorgestrel contraceptive intrauterine system; OR = odds ratio; RD = risk difference; RR = relative risk; SAE = serious adverse event

6.20 For the most common AEs (occurring in ≥ 5.0% of women), no significant difference between the LCS16 and Mirena® groups was reported, with the exception of ovarian cysts, which were significantly less likely with LCS16 (risk difference -15.4%; 95% CI: - 21.9%, - 8.9%).

6.21 According to the Periodic Safety Update Report (PSUR, up to December 2017), the absolute risk of ectopic pregnancy during LCS16 use is low. However, in the case of contraceptive failure, the relative risk of the pregnancy being ectopic is increased. In the TGA Clinical Evaluation Report, TGA noted a slightly higher unadjusted 5-year Pearl Index for ectopic pregnancy for LCS16 in the LCS Pearl Index study (0.18 [95% CI: 0.08, 0.36]) compared with the overall incidence of ectopic pregnancy for Jaydess® (0.11 per 100 women-years), but considered it lower than the rates in women not using any contraception (0.3-0.5 per 100 women-years). However, no comparison to Mirena® was made.

6.22 No indirect comparisons of the safety outcomes for LCS16 and Mirena® were presented by the submission.

### Clinical claim

6.23 The submission claimed Kyleena® was non-inferior in terms of effectiveness in contraception and safety compared with Mirena® over 5 years.

6.24 The claim that Kyleena® was non-inferior in terms of contraception efficacy over 5 years to Mirena® was uncertain as:

- despite an overall low pregnancy rate, the results showed more unintended pregnancies in the Kyleena® group in comparison to Mirena® from both the direct

head to head trial (LSC Phase II study) at three years and the naïve comparison at five years;

- in the LCS Phase II study, Pearl Indices of Kyleena® and Mirena® showed overlapping 95% CI, however the EMA requirement for efficacy was not met for Kyleena®; and
- there were transitivity issues associated with the indirect comparisons.

6.25 The PBAC considered that the claim that Kyleena® was non-inferior in terms of effectiveness in contraception over 5 years to Mirena® to be reasonable, although the efficacy of Kyleena® may have been overestimated.

6.26 The PBAC considered the claim of non-inferior safety of Kyleena® versus Mirena® to be reasonable.

### **Economic analysis**

6.27 Based on the non-inferiority claim, the submission presented a cost-minimisation analysis with the equi-effectiveness dose being 9 µg/day over 5 years (Kyleena®) = 14 µg/day over 5 years (Mirena®). This is based on the mean daily in vivo levonorgestrel release rate from product information. The ESC considered that this is reasonable.

6.28 The proposed DPMQ for Kyleena® was \$ [REDACTED], which was incorrectly calculated by the submission because incorrect prices and indication-based weighting for Mirena® were used. The submission stated that the current weighted AEMP of Mirena® was \$182.67 (post 1 June 2018 SPR), derived from the AEMP for contraception (\$ [REDACTED] weighted at [REDACTED]%) and idiopathic menorrhagia (\$ [REDACTED] weighted at [REDACTED]%). The evaluation noted the indication-based weightings were not the current weightings applied to Mirena®, and did not total 100%. The correct indication-based weightings, as recommended at the March 2012 meeting of the PBAC, are [REDACTED]% for contraception and [REDACTED]% for menorrhagia. The PSCR disagreed that the proposed AEMP and DPMQ for LCS16 were calculated incorrectly in the submission, stating that the relative reimbursed cost effective AEMP for contraception is \$ [REDACTED], as presented in its submission to the November 2006 PBAC.

6.29 The indication-specific weightings of [REDACTED]% for contraception and [REDACTED]% for idiopathic menorrhagia were first proposed by the sponsor in its submission to the March 2012 meeting of the PBAC. The PBAC rejected these proposed weightings and instead recommended indication-specific weights of [REDACTED]% for contraception and [REDACTED]% for idiopathic menorrhagia.

6.30 At its April 2012 meeting, the Pharmaceutical Benefits Pricing Authority (PBPA) accepted the PBAC's recommendation of the indication-specific weights of Mirena® as above. The PBPA used the recommended weighting to calculate the revised price

of Mirena® which was applied on 1 October 2012 and was agreed at the Price to Pharmacist (PtP) level, rather than the AEMP. Therefore, the prices of Mirena® at 1 October 2012 were:

- the weighted PtP price was \$241.71
- the weighted AEMP was \$224.89 (calculated by removing the wholesale mark-up of 7.52% from the PtP price)
- the indication specific AEMPs for contraception was \$ [REDACTED] and idiopathic menorrhagia was \$ [REDACTED].

6.31 Statutory Price Reductions were applied to Mirena® on 1 April 2016 (5%) and 1 June 2018 (10%). Following the 1 June 2018 SPR, the current prices of Mirena® are:

- the weighted AEMP is \$182.67.
- indication-specific AEMP for contraception is \$ [REDACTED] (weighted at [REDACTED]%) and idiopathic menorrhagia is \$ [REDACTED] (weighted at [REDACTED]%)

6.32 Therefore, the DPMQ for LCS16 is \$ [REDACTED], based on the current contraception-specific AEMP for Mirena® (\$ [REDACTED]). Table 7 presents the cost minimisation analysis of LCS16 on the basis of the price of Mirena® in contraception.

**Table 7: Cost minimisation analysis using cost of Mirena® in contraception**

Component	Kyleena®	Mirena®
Cost per device (AEMP)	\$ [REDACTED]	\$ [REDACTED] <sup>a</sup> (\$ [REDACTED] <sup>b</sup> )
Cost per device (DPMQ)	\$ [REDACTED]	\$ [REDACTED] <sup>a</sup> (\$ [REDACTED] <sup>b</sup> )
Dose duration	5 years	
Costs of administration	Equivalent	
Net difference in AEMP	\$ [REDACTED] <sup>a</sup> (\$ [REDACTED] <sup>b</sup> )	

Source: Section 3.3.1, p75 of the submission; and calculated during the evaluation

AEMP = approved ex-manufacturer price; DPMQ = dispensed price maximum quantity

<sup>a</sup> based on weighted AEMP for Mirena® contraception prior to F1 cuts (from 1 October 2012)

<sup>b</sup> based on current weighted AEMP for Mirena® contraception (post 1 June 2018 SPC)

**Drug cost/patient/system = \$ [REDACTED]**

6.33 The cost per patient per IUS was based on the proposed DPMQ of \$ [REDACTED]. Based on a cost minimisation to the current contraception price of Mirena®, the DPMQ per patient per IUS would be \$ [REDACTED].

**Estimated PBS usage & financial implications**

6.34 This submission was not considered by DUSC.

6.35 The submission used a market share approach to estimate the utilisation and financial implications associated with listing Kyleena®.

6.36 Table 8 presents financial estimates for listing Kyleena® in the base case analysis using the corrected weighting (█% for contraception use in Mirena®) and current Mirena® pricing (AEMP \$█ and DPMQ \$█).

**Table 8: Estimated use and financial implications to the PBS/RPBS of listing Kyleena®**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Utilisation of Kyleena®	█	█	█	█	█	█
<b>Estimated financial implications of Kyleena®</b>						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Estimated cost offsets of Mirena®</b>						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Co-payments	\$█	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS less co-payments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Net financial implications</b>						
Net cost to PBS/RPBS	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
<b>Submission estimates (Kyleena® at DPMQ of \$203.24 for the full six-years)</b>						
Total net cost to PBS/RPBS	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█

Source: Table 4.2.2, pp86-87; Table 4.3.1, p87; Table 4.4.1, p88 of the submission; and calculated during the evaluation  
 AEMP = approved ex-manufacturer price; DPMQ = dispensed price maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits

The redacted table shows that at Year 6, the estimated number of prescriptions was 10,000 to 50,000 and the net cost saving to the PBS/RPBS would be less than \$10 million.

6.37 The submission estimated that the net financial implications of the proposed PBS listing of Kyleena® would result in net cost saving to the PBS of approximately less than \$10 million over 6 years, based on Kyleena® DPMQ of \$█. The evaluation noted that this is likely to be an underestimation of the net cost saving to PBS/RPBS, where the financial estimates were most sensitive to Kyleena® DPMQ. During evaluation it was estimated that the proposed PBS listing of Kyleena® would result in net cost savings to the PBS of approximately \$10 to \$20 million over 6 years if the current Mirena® price for contraception (\$█) was applied to Kyleena®. However, there was uncertainty in the estimates because the displacement of Mirena® and other contraceptives due to Kyleena® is unknown.

6.38 The PSCR acknowledged the uncertainty in the utilisation estimates but maintained that the financial risk to the Australian Government is low since the proposed cost minimised Kyleena® price for contraception is lower than the weighted Mirena® price, resulting in a net cost saving. The ESC noted that the listing of Kyleena® on the PBS would confer a cost saving to the Government, regardless of the extent of use.

- 6.39 The ESC noted that, in clinical practice, Mirena<sup>®</sup> is often replaced early (before 5 years) as bleeding can eventually occur as the levonorgestrel dose decreases over time. An analysis of PBS data prescription data from 2006 to 2018 inclusive showed 673,216 patients received one supply of Mirena<sup>®</sup>, 190,537 received two supplies, and 53,183 patients received three or more supplies. Of the 243,720 patients who were supplied more than one Mirena<sup>®</sup> prescription, 45% of replacement prescriptions were supplied less than 4.5 years after initiation, and 39% were replaced between 4.5 and 5.5 years after initiation. Given that Kyleena<sup>®</sup> has a significantly lower dose of levonorgestrel than Mirena<sup>®</sup>, the ESC considered that bleeding and subsequent removal could occur earlier than with Mirena<sup>®</sup>, which would result in a higher usage of Kyleena<sup>®</sup> than Mirena<sup>®</sup>, and an associated higher cost to the Government. The pre-PBAC response argued there was no data available to support the ESC's view that Mirena<sup>®</sup> is replaced early due to the incidence of bleeding caused by dose decline over time.
- 6.40 The ESC noted that the PBS listing of Kyleena<sup>®</sup> may have the potential to grow the overall LARC market, as Kyleena<sup>®</sup> may appeal to some women who have not wanted to use Mirena<sup>®</sup>. The ESC considered that overall growth in the LARC market would be positive, given the effectiveness of LARCs in preventing unintended pregnancies and controlling bleeding.

### ***Financial Management – pricing arrangements***

- 6.41 The submission requested that Kyleena<sup>®</sup> be considered under the pricing arrangements outlined in Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth of Australia (the Strategic Agreement), specifically that Kyleena<sup>®</sup> not be subject to statutory price reductions that have been applied to the comparator, Mirena<sup>®</sup>. The PBAC noted that the application of Clause 5.7 of the Strategic Agreement is determined by the Minister (or Delegate), and is not a matter for PBAC.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of a new form of the currently listed drug levonorgestrel, intrauterine drug delivery system 19.5 mg (Kyleena<sup>®</sup>) for contraception on the General Schedule as a restricted benefit.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of Kyleena<sup>®</sup> would be acceptable on the basis that it is cost-minimised to Mirena<sup>®</sup> based on the current indication-specific approved ex-manufacturer price (AEMP) for contraception, factoring in any statutory price reductions.

- 7.3 The PBAC welcomed the input from health care professionals and organisations for this submission that described the benefits of having an alternative LARC, particularly for younger and nulliparous women.
- 7.4 The PBAC accepted Mirena® as the appropriate comparator for Kyleena®. The PBAC noted that a small proportion of nulliparous women who have a preference for alternative methods of contraception (Implanon® and oral contraception) due to the perceived or actual discomfort associated with Mirena® may instead choose to use Kyleena®. However, overall the PBAC considered the patient population for Kyleena® and Mirena® to be the same and any differences in uptake between the two would be primarily driven by patient preference.
- 7.5 The PBAC considered the claim that Kyleena® is non-inferior in efficacy to Mirena® to be reasonable, noting that the efficacy of Kyleena® may have been overestimated. The PBAC noted the trial results from the LCS16 Phase II study and the naïve comparison demonstrated a numerically higher risk of unplanned pregnancies in the Kyleena® group (2%) compared to the Mirena® group (0%). The PBAC noted the differences in the results were not statistically significant but agreed with the ESC that this was a clinically significant outcome for women. However, on balance, the PBAC considered that the lower dose was of benefit and the results indicated that Kyleena® was comparable in terms of contraceptive effectiveness to Mirena®.
- 7.6 The PBAC accepted the claim that Kyleena® is non-inferior in safety to Mirena®. The PBAC noted that patients treated with Kyleena® were significantly less likely to have ovarian cysts than patients treated with Mirena® (risk difference -15.4%; 95% CI: - 21.9%, - 8.9%). However, the PBAC also noted there was very low risk of ectopic pregnancies resulting from contraceptive failure with Kyleena®.
- 7.7 The PBAC noted the equi-effective dose based on the mean daily dosing are:
- 9 micrograms/day over 5 years (Kyleena®); and
  - 14 micrograms/day over 5 years (Mirena®).
- 7.8 The PBAC considered the uptake of Kyleena® to be highly uncertain as it depended on displacement of Mirena® and other contraceptives. The PBAC noted advice from ESC which suggested the rate of displacement may be driven by a proportion of women seeking earlier replacement of Mirena®. The PBAC considered the extent to which this may occur to be uncertain and less probable amongst older women. Overall, the PBAC considered growth in the LARC market would be positive, given the effectiveness of LARCs in preventing unintended pregnancies and controlling bleeding.
- 7.9 The PBAC agreed that a restricted benefit listing for contraception was appropriate as this aligned with the current listing for Mirena® for contraception.

- 7.10 The PBAC advised that Kyleena® is suitable for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that the Early Supply Rule should apply.
- 7.12 The PBAC advised that under subsection 101(3BA) of the *National Health Act, 1953* levonorgestrel should not be treated as interchangeable on an individual patient basis with any other drugs.
- 7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
LEVONORGESTREL Levonorgestrel 19.5 mg intrauterine drug delivery system, 1 system	1	0	Kyleena® Bayer Australia Ltd
<b>Category/Program</b>	Section 85 (General Schedule)		
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners		
<b>PBS Indication:</b>	Contraception		
<b>Restriction:</b>	<input checked="" type="checkbox"/> Restricted benefit		

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 10 Sponsor's Comment

Bayer welcomes the PBAC decision to recommend the PBS listing of levonorgestrel 19.5mg (Kyleena) for contraception. Bayer will intend to work with the Department to seek the discretion of the Health Minister to determine the applicability of clause 5.7 of the pricing arrangements outlined in Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth of Australia.