South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Family planning

MEDICINE REVIEW:

1. Executive Summary

Date: 26 August 2020 (Update of August 2019 review)
Medicine (INN): Low dose levonorgestrel intra-uterine systems (total content 13.5mg or 19.5mg)
Medicine (ATC): G02BA03
Indication (ICD10 code): Contraception (Z30.0/Z30.4/Z30.8)
Patient population: Women of childbearing potential (WOCP)
Prevalence of condition: n/a - This is for prevention of pregnancy
Level of Care: Primary health care
Prescriber Level: Primary health care practition
Current standard of Care: Copper containing intra-uterine devices
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): GS Gebhardt, S Takuva
PTC affiliation: GS Gebhardt -Tygerberg Hospital, Western Cape

2. Name of author(s)/motivator(s): *Primary reviewer:* Prof GS Gebhardt
Secondary reviewer: Dr S Takuva
Support: Ms TD Leong (comparative costing analysis)

3. Author affiliation and conflict of interest details:

- *Prof GS Gebhardt:* Stellenbosch University and Tygerberg Hospital, Adult Hospital Level Committee (2017-2020); no conflicts of interest to declare.
- *Dr S Takuva:* Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand; Member of Adult Hospital Level Expert Review Committee (2017-2020); Medical monitor and safety physician for the NIH-funded HIV Vaccine Trials Network which conducts candidate HIV vaccine candidate trials of products developed by Novartis Vaccines, GSK Biologicals, Janssen Pharmaceuticals and Vaccines and Sanofi Pasteur.
- *Ms TD Leong:* Essential Drugs Programme, National Department of Health; Secretariat to the Primary Health Care and Adult Hospital Level Expert Review Committees; no conflicts of interest to declare.

4. Introduction/ Background:

There are two low-dose progesterone-releasing intra-uterine delivery systems (IUS) currently on the market- Kyleena® (Bayer) contains 19.5mg levonorgestrel (LNG) and Jaydess® (Bayer) contains 13.5mg LNG. Both have a similar T-frame with identical introducers. The only difference is the hormone content and the duration of action (5 years for the 19.5mg LNG-IUS and 3 years for the 13.5mg LNG-IUS). They are only registered for contraceptive use- unlike the 52mg LNG-IUS currently available in SA (marketed as Mirena®) which is also registered for used for heavy menstrual bleeding and endometrial protection. As the 52 mg LNG-IUS is not currently available as a contraceptive device on the Essential Medicines List (EML), the comparisons of the low-dose LNG-IUS will not be with the high dose system, but with other available contraceptive drugs and systems where available.

A comparison of the three devices is shown below:

Trade name of LNG-IUS	**Kyleena®**	**Mirena®**	**Jaydess®**
Total LNG content (mg)	19.5	52	13.5
LNG release rate (mcg/24h) Initial Final Average	 17.5 7.4 (after 5 year) 9 (over 5 years)	 20 10 (after 5 years) 14 (over 5 years)	 14 5 (after 3 years) 6 (over 3 years)
Frame size (W x H, mm)	28 x 30	32 x 32	28 x 30
Inserter	One handed EvoInserter™	One handed EvoInserter™	One handed EvoInserter™
Insertion tube diameter (mm)	3.8	4.4	3.8
Silver ring for improved visibility on ultrasound?	Yes	No	Yes
Licensed duration of use for contraception (years)	5	5	3
Licensed for endometrial protection?	No	Yes	No

PICO Question

Population	Individuals of reproductive age
Intervention	Low-dose LNG-IUS
Comparison	Other available methods (oral contraception, injectables, copper-containing intra-uterine devices)
Outcomes	Efficacy – prevention of pregnancy Safety – weight gain, bleeding patterns, endometriosis, HIV acquisition, other adverse events

6. Methods:

a. Data sources: PubMed, ScienceDirect. Key word search were done using combinations of Jaydess; Kyleena; Levonorgestrel; Levosert; Liletta; Mirena; Skyla; adverse event; benefit; bleeding; compliance; contraception; efficacy; intra-uterine system; long acting reversible contraceptive.

b. Search strategy The full search details were (("progestins"[Pharmacological Action] OR "progestins"[MeSH Terms] OR "progestins"[All Fields] OR "progestogen"[All Fields]) AND releasing[All Fields] AND intrauterine[All Fields] AND systems[All Fields]) AND ("equipment and supplies"[MeSH Terms] OR ("equipment"[All Fields] AND "supplies"[All Fields]) OR "equipment and supplies"[All Fields] OR "device"[All Fields]). Additionally, I hand-searched reference lists of identified articles for further citations of interest. For efficacy, only studies designed with efficacy as the outcome/primary outcome were included.

c. Evidence synthesis

i. There were no systematic reviews of randomised studies identified.

ii. Limited data from phase II and III studies (all conducted by Bayer Health Care, the manufacturer of all three systems) comparing Kyleena with Jaydess and Mirena are summarized below. Terminology in the literature is inconsistent; some studies describe the different LNG-IUS devices according to their LNG content, some according

to their in vitro release rates and others use the in vivo release rate. For consistency, the product names are used in this review.

Gemzell-Danielson et al. (2012) reported on a multicentre, open-label, randomised three-arm phase II study, which included a total of 738 women successfully fitted with Kyleena (n=245), Jaydess (n=239) or Mirena (n=254). (1) The study period was 3 years. This study was not powered to determine whether there was a significant difference in contraceptive effectiveness between the devices in terms of pregnancy The bleeding profiles were similar in all groups as was the incidence of side effects.

A large multicentre, open-label, randomised two-arm phase III study which included a total of 2,884 women was published by Nelson et al. (2013). (2) They compared women fitted with Kyleena (n=1,452) or Jaydess (1,432) over a study period of 3 years. 870 women using Kyleena and 819 using Jaydess completed the 3 year study. 707 women in the trial who were using Kyleena then entered an optional 2 year trial extension period and the resulting 5 years of data for Kyleena were reported by Gemzell-Danielson et al. (2017) (3).

They reported an unadjusted Pearl Index of 0.29 (95% confidence interval [CI] 0.16-0.50) for Kyleena over the 5-year duration of use. The reported cumulative failure rate at 5 years was 1.45% (0.18% at 1 year, 0.97% at 3 years). A total of 5 intrauterine and 8 ectopic pregnancies were observed. The Pearl Index is the most common technique used in clinical trials for reporting the effectiveness of a birth control (4). This is comparable to the copper-containing IUD (Pearl failure rate of 0.6-0.8) and the OC pill (0.3).

Comparing Kyleena and Jaydess over 3 years of use, the study reported a 3 year Pearl Index of 0.31 for Kyleena and 0.33 for Jaydess and a cumulative failure rate at 3 years of 1% for Kyleena and 0.9% for Jaydess.

In a single-arm phase III study of Jaydess in adolescents <18 years, 83.9% of users were still satisfied after 1 year. (5) Although the conclusion of the authors were that the drug was safe and effective, 12% experienced dysmenorrhea and a further 14.8% had pelvic pain which was the main reason that 16.8% of participants prematurely discontinued the method. There were no pregnancies in that year.

iii. There is only one related systematic review in the Cochrane Fertility Regulation library that evaluated the different hormonal and intrauterine methods for contraception for women aged 25 years and younger (6). The review considered RCTs in any language that reported the contraceptive failure rates for hormonal or intrauterine contraceptive methods, when compared with another contraceptive method, for women aged 25 years and younger. The other contraceptive method could have been another intrauterine contraceptive, another hormonal contraceptive or different dose of the same method, or a non-hormonal contraceptive. All three strengths of LNG-IUS were included. The overall quality of the five included trials were considered to be moderate to low. The different doses of the LNG-IUS did not appear to influence efficacy over three years. The current evidence was considered insufficient to compare efficacy and continuation rates for hormonal and intrauterine contraceptive methods in women aged 25 years and younger. The only study reporting on the lower dose systems was one by Kaunitz et al (unpublished data and conference poster abstract only from 2013).

iv. A systematic review on the safety of intra-uterine devices in young women showed that the overall risk for adverse outcomes for any users of intra-uterine devices is low and not clinically meaningful. The authors included LNG-IUS in the review, but did not specify the strength. (7)

v. A multinational, prospective, non-interventional cohort study of new users of LNG IUS and copper IUDs was performed in 61 448 women in a large European study.(8) One hundred and eighteen contraceptive failures occurred (26 LNG, 92 copper). Both types of IUD were highly effective, with overall Pearl indices of 0.06 [95% confidence interval (CI): 0.04–0.09] and 0.52 (95% CI: 0.42–0.64) for LNG IUS and copper IUDs, respectively. The adjusted hazard ratio for LNG IUS vs. copper IUDs was 0.16 (95% CI:0.10–0.25). Twenty-one pregnancies (7 LNG

IUS, 14 copper IUD) were ectopic, yielding an adjusted hazard ratio for ectopic pregnancy of 0.26 (95% CI: 0.10–0.66). The strength of the LNG-IUD was not specified (study done 2006-2012).

Summary of evidence synthesis

1. The low-dose LNG-IUS is as effective in preventing pregnancy (Pearl Index 0.29) as the COC pill (PI of 0.3) and significantly better than the copper containing intra-uterine device (PI of 0.6-0.8).
2. The low dose LNG-IUS is an attractive alternative option for adolescents as it has a long duration of action, few side- effects, is more effective in preventing pregnancy than the copper device and is overall well tolerated (>80% satisfaction after one year of use).
3. There is a marked reduction in ectopic pregnancies in users of the low-dose LNG as compared to the copper device.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [x] Not confident: [ ] Uncertain: [ ]	RCT data (see above).
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [x] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [ ]	Benefits outweigh potential harms. Systematic review by Jatlaoui et al (2017) showed that the overall risk for adverse events associated with IUDs in young women is low and not clinically meaningful. Confidence and skill of healthcare workers to insert IUDs are factors for consideration and is dependent on adequate training.
THERAPEUTIC INTERCHANG	Therapeutic alternatives available: Yes: [X] No: [ ] All other *available* contraceptive modalities, as women's choice is a prerogative.	Rationale for therapeutic alternatives included: All other *available* contraceptive modalities, as women's choice is a prerogative.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: [ ] Major: [ ] Uncertain: [x] **Is the option acceptable to key stakeholders?** Yes: [ ] No: [ ] Uncertain: [x]	There is no survey data of acceptability of low-dose LNG-IUS amongst users and healthcare workers in South Africa. Acceptability is reported to be high in high-income countries[9]. In LMIC, knowledge of IUCDs and acceptability amongst healthcare workers was reported to be low[10, 11, 12].
RESOURCE USE	**How large are the resource requirements?** More intensive: [x] Less intensive: [ ] Uncertain: [ ]	**Price of family planning agents/ 5 years (1825 days):**

Family planning agent	Pack size Price (ZAR)	Price/ 1825 days (ZAR)
LNG-IUS, 19.5 mg (100% of SEP)	3139.35*	3139.35
LNG-IUS, 19.5 mg (60% of SEP)	1883.61*	1883.61
Copper IUCD	159,99**	159,99
Levonorgestrel/ethinyl estradiol, triphasic tablets	6,28**	409,32
Levonorgestrel tablets	3,03**	197,49
Levonorgestrel/ethinyl estradiol, monophasic tablets	2,90**	189,02
Norethisterone enanthate injectionl	24,01**	782,47
Etonogestrel implant	224,58**	374,30
DMPA injection	15.40**	334,58

* SEP database, March 2020, https://mpr.code4sa.org/
**Contract circulars RT283-2017, HP03-2017CHM/01

Additional resources: n/a

EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	n/a
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [ ] No [X] Uncertain [ ]	Cost prohibits consideration for inclusion to the EML.

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	**We suggest using either the option or the alternative**	We suggest using the option	We recommend the option
	[X]	☐	☐	☐	☐

Recommendation: Based on the evidence reviewed, the Adult Hospital Level Committee reccomends that this agent may be considered as an alternative to the Copper IUCD, if the latter is unavailable. The Committee acknowledges that low dose LNG-IUS is smaller and may possibly be more acceptable by adolescents.
Rationale: Low dose LNG-IUS is comparable in efficacy and safety to copper IUD. However, this agent is currently cost prohibitive for inclusion on the EML.
Level of Evidence: II Moderate RCTs, Systematic Review (for safety), Observational studies

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[ ]	[X]

VEN status: n/a

Vital	Essential	Necessary
[ ]	[ ]	[ ]

NEMLC MEETING OF 5 DECEMBER 2019:
NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, noting that low dose LNG-IUS is currently unaffordable.

NEMLC MEETING OF 17 SEPTEMBER 2020:
NEMLC accepted the updated medicine review that now includes comparative pricing.

Monitoring and evaluation considerations: n/a

Research priorities: Local acceptability studies

References

1. 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. Fertil Steril. 2012 Mar 1;97(3):616-622.e3.
2. 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. Obstet Gynecol. 2013 Dec;122(6):1205–13.
3. 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. Eur J Obstet Gynecol Reprod Biol. 2017 Mar;210:22–8.
4. Shelton JD, Taylor RN. The Pearl Pregnancy Index reexamined: Still useful for clinical trials of contraceptives. Am J Obstet Gynecol. 1981 Mar 1;139(5):592–6.
5. Gemzell-Danielsson K, Buhling KJ, Dermout SM, Lukkari-Lax E, Montegriffo E, Apter D. A Phase III, single-arm study of LNG-IUS 8, a low-dose levonorgestrel intrauterine contraceptive system (total content 13.5mg) in postmenarcheal adolescents. Contraception. 2016 Jun;93(6):507–12.
6. Krashin J, Tang JH, Mody S, Lopez LM. Hormonal and intrauterine methods for contraception for women aged 25 years and younger. Cochrane Database Syst Rev [Internet]. 2015 [cited 2019 Aug 15];(8). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009805.pub3/full?highlightAbstract=withdrawn%7Cintrauterine%7Csystem%7Cintrauterin
7. Jatlaoui TC, Riley HEM, Curtis KM. The safety of intrauterine devices among young women: a systematic review. Contraception. 2017 Jan;95(1):17–39.
8. Heinemann K, Reed S, Moehner S, Do Minh T. Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. Contraception. 2015 Apr;91(4):280–3.
9. Bednarek PH, Jensen JT. Safety, efficacy and patient acceptability of the contraceptive and non-contraceptive uses of the LNG-IUS. Int J Womens Health. 2010 Aug 9;1:45-58.
10. Agha S, Fareed A, Keating J. Clinical training alone is not sufficient for reducing barriers to IUD provision among private providers in Pakistan. Reprod Health. 2011 Dec 30;8:40.
11. Chakraborty NM, Murphy C, Paudel M, Sharma S. Knowledge and perceptions of the intrauterine device among family planning providers in Nepal: a cross-sectional analysis by cadre and sector. BMC Health Serv Res. 2015 Jan 28;15:39.
12. Cleland J, Ali M, Benova L, Daniele M. The promotion of intrauterine contraception in low- and middle-income countries: a narrative review. Contraception. 2017 Jun;95(6):519-528.