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Advising on new medicines for Scotland
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NHS SCOTLAND

levonorgestrel 19.5mg intrauterine delivery system (Kyleena®)

SMC No 1299/18

Bayer plc

12 January 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

levonorgestrel (Kyleena®) is accepted for use within NHS Scotland.

Indication under review: contraception for up to 5 years.

A phase III, open-label, randomised study confirmed the contraceptive efficacy of levonorgestrel 19.5mg intrauterine delivery system according to the Pearl Index.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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Indication

Contraception for up to 5 years.[1]

Dosing Information

Levonorgestrel 19.5mg intrauterine delivery system is inserted into the uterine cavity and is effective for up to 5 years.

See summary of product characteristics (SPC) for further details regarding insertion and removal / replacement.

To be inserted by a healthcare professional using aseptic technique.[1]

Product availability date

January 2018.

Summary of evidence on comparative efficacy

The levonorgestrel 19.5mg intra-uterine delivery system (IUS) (Kyleena®) is a progestogen-only long-acting reversible contraceptive (LARC). The system exerts local progestogenic effects in the uterine cavity to prevent egg implantation within the endometrium, thicken the cervical mucus to prevent the passage of sperm, and prevent fertilisation by inhibiting sperm mobility and function within the uterus and fallopian tubes.[1]

Evidence to support the use of levonorgestrel 19.5mg IUS (Kyleena®) comes from a randomised phase III study[2] (NCT00528112) with a single-arm extension study[3] and a randomised phase II dose-finding study (NCT00185380).[4]

NCT00528112 was a multicentre, international, open-label, phase III study intended to evaluate the safety and efficacy of two low-dose levonorgestrel IUS. Fertile, nulliparous and parous women aged 18 to 35 years with regular menstrual cycles who requested contraception were randomised equally to levonorgestrel IUS 19.5mg (Kyleena®, n=1,453) or levonorgestrel IUS 13.5mg (Jaydess®, n=1,432) for a duration of three years. After a protocol amendment, women allocated to treatment with the levonorgestrel IUS 19.5mg (Kyleena®) system were given the choice to continue with treatment for up to an additional two years as part of an extension study. Placement of the intrauterine system occurred during the first seven days of the woman's menstrual cycle, with a maximum of two placement attempts permitted; women were withdrawn from the study if placement failed following two attempts. Investigators could permit the use of a local anaesthetic, oral analgesics, or cervical dilation as deemed necessary.[2]

The primary outcome was the pregnancy rate expressed as the Pearl Index (number of pregnancies per 100 woman-years) in the full analysis set (FAS) at three years; all randomised women in whom placement of a levonorgestrel IUS was attempted (excludes one patient allocated to the Kyleena® group). Ten pregnancies occurred in the levonorgestrel IUS 19.5mg (Kyleena®) group, one of which was as a result of expulsion of the system; the calculated Pearl Index was 0.31 per 100 woman-years (95% confidence interval [CI]: 0.15 to 0.57). Ten pregnancies also occurred in the levonorgestrel IUS 13.5mg (Jaydess®) group over the three-year study, four of which were a result of expulsion of the system (Pearl Index 0.33 pregnancies per 100-woman

years; 95% confidence interval [CI]: 0.16 to 0.60). There were no statistically significant differences between the treatment groups for any of the calculated Pearl Indexes.

Failure rates for the 19.5mg (Kyleena®) and 13.5mg (Jaydess®) levonorgestrel IUS groups, respectively, were 0.2% and 0.4% in year 1; 0.4% and 0.3% in year 2; 0.4% and 0.2% in year 3; and 1.0% and 0.9% for the cumulative three-years.[2, 5]

Placement of the system was successful in 99.5% (n=2,871/2,884) of women overall, with 96% (n=2,770/2,884) having a successful placement at first attempt. In the combined levonorgestrel IUS 19.5mg (Kyleena®) and levonorgestrel IUS 13.5mg (Jaydess®) treatment groups, investigators rated placement as 'easy' in 90% (n=2,585/2,884) of women. Participants rated pain on placement, with 20% (n=563/2,884), 46% (n=1,312/2,884), 27% (n=790/2,884) and 7.6% (n=218/2,884) respectively rating pain as 'none', 'mild', 'moderate' or 'severe'. Use of cervical dilation was required in 5.5% of women (n=159/2,884). Prophylactic local anaesthesia was used in 8.6% (n=248/2,884) of women, and 32% (n=929/2,884) received prophylactic analgesia. These outcomes were not reported for levonorgestrel IUS 19.5mg (Kyleena®) separately.[2]

At the end of the study (or at the final study visit for patients who discontinued early), 73% (n=1,063/1,452) and 74% (n=1,053/1,432) of patients randomised to levonorgestrel IUS 19.5mg (Kyleena®) and levonorgestrel IUS 13.5mg (Jaydess®), respectively completed a user satisfaction questionnaire. Of those surveyed on the levonorgestrel IUS 19.5mg (Kyleena®), 96% of women were "very satisfied" or "somewhat satisfied" with treatment and 82% indicated they would have continued with treatment after the study. Similarly, 95% of the levonorgestrel IUS 13.5mg (Jaydess®) treatment group were "very satisfied" or "somewhat satisfied" with treatment, and 77% indicated they would have continued with treatment after the study.[2]

There were three additional pregnancies reported during the two-year extension study (n=707). The unadjusted five-year Pearl Index was reported as 0.29 (95% CI: 0.16 to 0.50). The five-year cumulative failure rate was reported as 1.45%.[3]

For the 13 pregnancies reported in the levonorgestrel IUS 19.5mg (Kyleena®) FAS over the five-year study period; five were intrauterine pregnancies (two resulted in healthy term births and three resulted in spontaneous abortion) and eight were ectopic pregnancies; the five-year ectopic pregnancy Pearl Index was 0.18 (95% CI: 0.08 to 0.36).[3]

Prior to the phase III study, a randomised, open-label, phase II study was conducted (NCT00185380) to establish a suitable dose for the levonorgestrel low-dose IUS. Parous and nulliparous women aged 21 to 40 years were randomised equally to three years treatment with levonorgestrel IUS 19.5mg (Kyleena®), levonorgestrel IUS 13.5mg (Jaydess®), or the levonorgestrel IUS 52mg (Mirena®). In the Kyleena®, Jaydess® and Mirena® treatment groups, the respective number of pregnancies (Pearl Index) over the three-year study were five (0.82 per 100 woman-years; 95% CI: 0.27 to 1.92), one (0.17 pregnancies per 100 woman-years; 95% CI: 0.00 to 0.93), and zero (0 pregnancies per 100 woman-years; 95% CI: 0.00 to 0.59). The study was not powered to detect a difference between the treatment groups.[4]

Summary of evidence on comparative safety

In the phase III study levonorgestrel IUS 19.5mg (Kyleena®) FAS group, over five years, 89% (1,286/1,452) of patients reported an adverse event (AE) and 55% reported a treatment-related AE, based on investigator assessment. The proportion of women randomised to this group who reported an AE decreased per year from 74% in year one to 45% in year five.[3]

The most frequently reported AEs (with an incidence of ≥5%) considered to be possibly treatment-related were ovarian cyst 16%, acne 10%, pelvic pain 6.3%, dysmenorrhea 5.4%, and vaginal haemorrhage 5.0%.[3]

With the exception of ovarian cysts, the incidences of serious AEs of special interest during the five years of follow up were low: uterine perforation (0.2%), pelvic inflammatory disease (0.6%), expulsion of device (3.7%, partial expulsion [2.4%], complete expulsion [1.3%]), ectopic pregnancy (0.6%) and ovarian cysts (23%).[3]

Over five years, 23% (328/1,452) of women randomised to the levonorgestrel IUS 19.5mg (Kyleena®) discontinued due to an AE. The most common AEs resulting in discontinuation of treatment were vaginal haemorrhage (3.5%), device expulsion (3%), and pelvic pain (3%). In the FAS 5.2% (76/1,452) of women discontinued treatment due to bleeding disturbances, including amenorrhea.[3]

Over the three-year comparative phase of the phase III study, the adverse event profile between levonorgestrel IUS 19.5mg (Kyleena®) and levonorgestrel IUS 13.5mg (Jaydess®) were similar with the exception of ovarian cysts (14% versus 7.7%, in the Kyleena® and Jaydess® groups, respectively). Discontinuation of treatment due to any AE over the three years occurred in 19% and 22% of women in the levonorgestrel IUS 19.5mg (Kyleena®) and levonorgestrel IUS 13.5mg (Jaydess®) groups, respectively.[2]

In total 78% (550/707) of patients completed the extension study; 22% (157/707) discontinued the study early of which 7.6% (12/157) were lost to follow-up. Treatment discontinuation during the two year extension study due to an AE was reported by 5% (36/707) of patients. [3]

Summary of clinical effectiveness issues

A number of factors influence the method of contraception an individual selects to use, and continued and effective contraceptive use is directly related to user-acceptability. Women should be provided with the relevant information about all the available methods of contraception for which they are medically suitable, in order for them to select a method best suited to their requirements.[6] Available contraceptive methods include the combined hormonal contraceptives (oral, transdermal and vaginal preparations), the progestogen-only contraceptives (oral, injection, implant and intrauterine system preparations), and other intrauterine devices (e.g. copper devices).[7] Clinical experts consulted by SMC advised that the higher dose levonorgestrel IUS 52mg (Mirena®) is the predominant LARC, with the lower dose levonorgestrel IUS 13.5mg (Jaydess®) also used. Levonorgestrel IUS 19.5mg (Kyleena®) would offer an alternative smaller device with 5 years contraceptive duration.

The Pearl Index (number of pregnancies per 100 woman-years), is used as a measure of hormonal contraceptive efficacy in line with guidance issued by the European Medicines Agency.[8] In the phase III randomised study, the three-year Pearl Index for levonorgestrel 19.5mg IUS (Kyleena®) was 0.31 pregnancies per 100-woman years (95% CI: 0.15 to 0.57), with a three-year cumulative failure rate of 1.0%. At the end of the two-year extension study, the five-year Pearl Index was 0.29 (95% CI: 0.16 to 0.50) with a five-year cumulative failure rate of 1.45%.

The studies were open-label and the two-year extension study was uncontrolled. There was a high drop-out rate from the three-year part of the phase III study (study completion 60% and 57% in the levonorgestrel IUS 19.5mg [Kyleena®] and levonorgestrel IUS 13.5mg [Jaydess®] groups, respectively). The most common reasons for study discontinuation were AEs.[2] The proportion of nulliparous women included in each of the treatment groups in the phase III study was 39%.[2] Of the thirteen pregnancies reported in the FAS at five years, eight were ectopic pregnancies.[3] Although the overall risk of ectopic pregnancy is reduced with the use of IUS when compared to no contraception, if a pregnancy does occur with an IUS in situ then the risk of ectopic pregnancy is increased.[9] Women considering Kyleena® should be counselled on the signs, symptoms and risks of ectopic pregnancy and for those who become pregnant, the possibility of an ectopic pregnancy must be considered and evaluated.[1]

The phase III study provides three-year comparative information versus Jaydess®. The phase II study provides some comparative information versus Mirena®, the most commonly used levonorgestrel IUS in Scotland, although this study was not powered to determine non-inferiority of Kyleena® to Mirena® and only followed patients for three years.

Summary of comparative health economic evidence

The submitting company presented a cost-effectiveness analysis comparing levonorgestrel IUS 19.5mg (Kyleena®) system to a 'mixed market' comparator comprising all possible reversible contraceptive options (and including 'no contraception' in 8.5% of women). A Markov model with a one year cycle length was used in which women started on their initial contraception and then could either discontinue or experience contraceptive failure (unintended pregnancy). Women would then move into the unintended pregnancy state or move on to a subsequent contraceptive method. For women in both arms of the model, the subsequent contraceptive method was the mixed market comparator i.e. for women who started on the mixed market comparator, their second contraceptive method would be the same mixed market option. A five year time horizon was used in the base case. The submitting company also presented the results in terms of Net Monetary Benefit (NMB) based on an estimate of the willingness to pay (WTP) to avoid an unintended pregnancy (assumed to be equivalent to the weighted average NHS cost of a pregnancy).

Clinical data on the effectiveness of treatments were taken from the Pearl Index (PI) results from the phase III study for levonorgestrel IUS 19.5mg (Kyleena®) system and for the weighted average comparators, taken from a published paper which reported 'typical use' year 1 failure rates from women in the USA.[3, 10] As such, the comparative data driving the model were essentially taken from a naive indirect comparison. Discontinuation rates were taken from the same sources. Where unintended pregnancies occurred, the outcomes of those pregnancies (full term birth, terminations, miscarriage, ectopic pregnancy) were estimated from NHS Scotland statistics.

Costs in the model related to the cost of the contraception method, any associated costs of insertion/ removal, annual follow up costs and the costs associated with unintended pregnancy (based on a weighted average of the pregnancy outcomes as noted above).

The results showed that in the base case, levonorgestrel IUS 19.5mg (Kyleena®) system was dominant i.e. more effective at avoiding unintended pregnancies and less expensive. The company estimated that for a population of 1000 women, levonorgestrel IUS 19.5mg (Kyleena®) would cost £1,845,158 less and result in 566 fewer unintended pregnancies. In terms of the NMB results, this was reported as £3,828 and a positive NMB would be an indicator of a cost-effective treatment as the monetary value of the incremental effectiveness (in terms of pregnancies averted) exceeds the incremental cost of achieving the outcome.

One-way, scenario and probabilistic sensitivity analysis were provided and all showed that levonorgestrel IUS 19.5mg (Kyleena®) was a cost-effective treatment option (dominant, or positive NMB). The results were most sensitive to the failure rate assumed for oral contraceptives and barrier methods (the 2 predominant options in the mixed market comparator), the weighted average cost of a birth and the uptake rate of 'no method' within the mixed market comparator.

There were a number of issues with the analysis:

- The weighted average comparator includes 'no contraception' and this may not be appropriate and will have biased the results. The company provided additional analysis removing 'no contraception' from the weighted average comparator; the results indicated levonorgestrel IUS 19.5mg (Kyleena®) would cost £1,195,152 less and result in 371 fewer unintended pregnancies with an NMB of £2,495.
- The method used to estimate the overall cost of an unintended pregnancy may over-represent the costs (and thus bias in favour of Kyleena®) given that the rate of induced abortion may be higher than the rate reflected in the general population birth statistics which were used to estimate costs. The company provided revised analysis to account for this issue and also removal of 'no contraception' as noted above. The results indicated levonorgestrel IUS 19.5mg (Kyleena®) would cost £842,847 less and result in 371 fewer unintended pregnancies with an NMB of £1,748. This would appear to represent a more appropriate base case than that presented by the company.
- Additionally, the use of a weighted average is likely to mask widely differing cost effectiveness ratios if levonorgestrel 19.5mg IUS (Kyleena®) was compared to individual methods e.g. other LARCs like IUS, IUD and implants, which SMC clinical experts indicate are likely to be the main comparators. The company provided additional analysis against only LARCs and using the revised cost of an unintended pregnancy. The results indicated levonorgestrel IUS 19.5mg (Kyleena®) would cost £185,299 less and result in 119 fewer unintended pregnancies with an NMB of £486.
- As there is a lack of direct data against the range of other contraception products, the analysis is based on a naive indirect comparison using 'imperfect use' data from a review paper presenting USA data from 1995 to 2002. As such, there are uncertainties associated with the estimates of incremental effectiveness for levonorgestrel IUS 19.5mg (Kyleena®).
- The model assumes that women who experience failure on or discontinue on the mixed market comparator will move to the 'subsequent contraception' state and that this will be the 'mixed market' comparator. This will mean that the women in this arm of the model will continue for the duration of the model to be subject to the comparatively higher risks of failure/ discontinuation and this may bias the results in favour of levonorgestrel IUS 19.5mg (Kyleena®) by keeping women on less effective methods of contraception given the 'lumping

together' of the mixed market comparator. While more complex, a model which compared against different individual therapies rather than a weighted average may have been an advantage in being able vary the effectiveness of subsequent contraceptive choices

- In terms of the NMB approach used, the cost of an unintended pregnancy has been used as a proxy for the willingness to pay to avoid an unintended pregnancy. The company provided limited justification to support this financial cost being an appropriate measure for WTP among women, and this estimate is higher than that used in the previous Jaydess® submission. Using a lower WTP estimate consistent with the levonorgestrel IUS 13.5mg (Jaydess®) submission around the preferred base case noted above resulted in a lower overall NMB of £1,254.

While there remains uncertainty associated with the comparative effectiveness data, given the additional analyses provided by the company to address some of the weaknesses, the economic case has been demonstrated.

Summary of patient and carer involvement

No patient group submission was made.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) Clinical Guideline 30[11] on long-acting reversible contraception (September 2014 update) advises that women who require contraception should be provided with information about, and offered a choice of, all available methods including LARC; women should receive the method of contraception that is most suitable for them, ensuring there are no contraindications. Women considering a LARC should receive detailed verbal and written information to enable them to select a method and use it effectively. This information should take into consideration of their individual needs and should include: contraceptive efficacy, duration of use, risks and possible side-effects, non-contraceptive benefits, the procedure for initiation and removal/discontinuation and when to seek help when using the method.[11]

The UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) (2016), published by the Faculty of Sexual and Reproductive Healthcare (FSRH), notes that the method of contraception an individual selects is dependent on a number of factors. Individuals should be free to select the most acceptable method available to them, providing that they are medically eligible. Contraception must be used correctly and consistently in order to be effective. Continuation rates must be high for the long-acting contraceptives (e.g. intrauterine devices) to be cost-effective. Continued and effective use of a particular contraceptive method is directly related to its user-acceptability.[6]

FSRH guidance on intrauterine contraception (2015) provides evidence-based recommendations on the use of intrauterine methods, including copper-bearing intrauterine devices and the levonorgestrel releasing intrauterine system (levonorgestrel IUS) available in the UK. The guidance includes recommendations on the use of the Mirena® and Jaydess® levonorgestrel IUS but the guidance predates the availability of Kyleena®.[9]

Additional information: comparators

The most relevant comparators are the other LARC.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per unit (£)
Levonorgestrel 19.5mg IUS (Kyleena®)#	**Inserted into the uterine cavity within seven days of menstruation to provide contraception for up to five years.**	**76**
Levonorgestrel 52mg IUS# (Mirena®)	Inserted into the uterine cavity within seven days of menstruation to provide contraception for up to five years.	88
Etonogestrel implant*	By subdermal implantation, one implant inserted during the first five days of the menstrual cycle; remove implant within three years of insertion.	83
Levonorgestrel 13.5mg IUS (Jaydess®)*	Inserted into the uterine cavity within seven days of menstruation to provide contraception for up to three years.	69
Copper intrauterine device¥	Insert the copper intrauterine device at any time during the menstrual cycle if it is reasonably certain that the woman is not pregnant.	8 to 27
Medroxyprogesterone acetate 104mg injection	By subcutaneous injection, 104mg within the first five days of the menstrual cycle, repeated every 12 weeks.	7
Medroxyprogesterone acetate 150mg injection	By deep intramuscular injection, 150mg within the first five days of the menstrual cycle, repeated every 12 weeks.	6

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 27/10/2017 for all medicines except levonorgestrel 19.5mg IUS from company submission. Copper intrauterine devices from eMIMS 27/10/2017. Cost for up to 3 years. # Cost for up to 5 years. ¥ A range of devices are available for use for up to 5 or 10 years. This list is not exhaustive.*

Additional information: budget impact

The submitting company estimated there would be 690,092 patients eligible for treatment with levonogestrel 19.5mg IUS (Kyleena®) in all years. The estimated uptake rate was 1% in year 1 (6,136 patients) and 4% in year 5 (20,989 patients) with a discontinuation rate of 17% applied.

The gross impact on the medicines budget was estimated to be £466k in year 1 reducing to £266k in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £371k in year 1 reducing to £91k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 14 December 2017.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical

judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.