FSRH
Clinical Effectiveness Unit

The Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologists

Faculty of Sexual and Reproductive Healthcare
New Product Review: Levosert® intrauterine delivery system
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Levosert® is a levonorgestrel-releasing intrauterine system (LNG-IUS) containing 52mg levonorgestrel (LNG) in a reservoir mounted on a T-shaped polyethylene frame[1]. Levosert is now licensed in the UK for 5 years of use for contraception and management of heavy menstrual bleeding, but not for endometrial protection during estrogen replacement therapy[1].

Key similarities with Mirena® 52mg LNG-IUS

- Levosert (like Mirena) is licensed for 5 years for contraception and management of heavy menstrual bleeding (HMB).
- Both Levosert and Mirena contain 52mg LNG. Release rates of LNG are almost identical for Levosert and Mirena; for both devices, the initial release of levonorgestrel is approximately 20 micrograms/day, falling to approximately 10 micrograms/day by 5 years[2].
- Contraceptive efficacy, reduction in menstrual blood loss, bleeding patterns and rates of adverse events are very similar for Levosert and Mirena.
- Levosert and Mirena both have T-shaped frames measuring 32mm (W) x 32mm (L).

Key Differences from Mirena LNG-IUS

- Unlike Mirena, Levosert is **not** licensed for endometrial protection during estrogen replacement.
- Levosert is inserted using a two-handed technique, with an introducer similar to those for copper IUDs such as the Nova-T® and UT380®. Mirena is inserted using a single-handed EvoInserter™.
- The diameter of the Levosert introducer is 4.8mm, compared with 4.4mm for Mirena.
- Levosert currently costs £66 plus VAT (NHS price for Mirena is £88 plus VAT). If used for 5 years, Levosert is currently the most cost effective LNG-IUS for contraception.

Contraceptive efficacy

In ACCESS IUS, a large, phase 3, multi centre cohort study in the USA[3], 1714 women aged 16-45 years had Levosert inserted. 495 women completed five years of use (an additional 224 women were still in year 5 of use at the time of reporting). Nine pregnancies (of which six were ectopic) occurred during the study; the Pearl Index for Levosert was 0.15 for year 1 (this compares to 0.2 for Mirena[4]) and 0.2 for year 5. Based on 59,399 28 day cycles of Levosert use, the life table pregnancy rate over 5 years was 0.92% (95% confidence interval 0.46-1.82%); this compares to the 5-year cumulative failure rate of 0.7% for Mirena[4].

The ACCESS study[3] is currently continuing to follow participants to assess contraceptive efficacy of Levosert beyond 5 years.

Bleeding patterns

In a randomised controlled trial[5], 280 women with HMB used either Levosert or Mirena for one year. Similar bleeding patterns and reduction in menstrual blood loss were seen in both groups with no statistically significant differences. There is no other study *directly* comparing bleeding patterns with Levosert and Mirena.

In the ACCESS IUS study[3], which excluded women without regular menstrual cycles, 37% and 42% of Levosert users reported amenorrhoea (no bleeding or spotting in the last 90 days) at 3 and 5 years respectively. Around 70% reported amenorrhoea or spotting only at 3-5 years. In comparison, a study of 254 new Mirena users (also excluding women without regular menstrual cycles) reported amenorrhoea in 24% at 3 years.[6] Only 2.2% of Levosert users in the ACCESS IUS study discontinued use because of unacceptable bleeding.[3]

Adverse events and side effects

Perforation In ACCESS IUS[3], which excluded breastfeeding women, the incidence of perforation with Levosert was 0.1% (of 1714 insertions). This is similar to the reported perforation rate of 0.09% for Mirena.

Expulsion ACCESS IUS reported a Levosert expulsion rate of 3.8%. Most expulsions occurred during the first year of use; expulsion was more common in parous than nulliparous women[3]. The reported risk of expulsion with Mirena is similar (around 5%).[4] The RCT comparing Levosert and Mirena for treatment of heavy menstrual bleeding[5] reported similar expulsion rates (4.2% Levosert vs 3.6% Mirena).

Ectopic Pregnancy In ACCESS IUS[3], the overall incidence of ectopic pregnancy with Levosert was approximately 0.13 per 100 woman-years. This is similar to the 0.1% absolute risk of ectopic pregnancy in clinical trials of Mirena.[4]

Ovarian cysts In ACCESS IUS, 4.5 % of Levosert users had symptomatic benign ovarian cysts[3]. However, only 0.3% of women requested Levosert removal because of an ovarian cyst. Ovarian cysts have been reported in approximately 7% of women using Mirena[4]. In most cases, the cysts disappear spontaneously during two to three months' observation[3,4].

ACCESS IUS[3] reported that small numbers of women chose to discontinue Levosert use because of acne (1.4%), dysmenorrhoea (1%), weight gain (1%), mood swings (0.8%), pelvic pain (1.3%) and dyspareunia (0.6%). During use of Levosert in ACCESS IUS, 5% or more of women reported vaginal infection or discharge, nausea/vomiting, headache, anxiety, depression and back pain which could potentially be related to Levosert use (it is not established that they were *caused* by the LNG-IUS). These possible side effects are in line with those reported by Mirena users[4].

How should Levosert be used?

Levosert is currently licensed for 5 years for contraception or treatment of heavy menstrual bleeding only. It should not be used for endometrial protection during estrogen replacement.

UKMEC guidance for use of Levosert for contraception is the same as for other LNG-IUS. Of note, the manufacturer of Levosert recommends that the minimum uterine cavity length for Levosert is 5.5cm[1].

Levosert is inserted using a two-handed technique, with a similar introducer to copper IUDs such as the Nova-T and UT380. The Faculty of Sexual and Reproductive Healthcare (FSRH) recommends that intrauterine contraception should only be inserted by healthcare professionals who have undergone appropriate training in insertion of intrauterine contraception.[7] Guidance on training in intrauterine techniques can be found on the FSRH website here.

Levosert can be inserted within the first seven days following menstruation without requirement for additional contraceptive precautions.[1] FSRH guidance supports insertion of a LNG-IUS at any other time in the cycle if pregnancy can be reasonably excluded.[7] FSRH recommendations for insertion after pregnancy are as for other LNG-IUS devices.[8]

Conclusion

Levosert offers highly effective contraception for 5 years and can be an effective management option for heavy menstrual bleeding. Contraceptive effectiveness, bleeding, safety and adverse event/ side effect profile are similar for Levosert and Mirena. If used for 5 years, Levosert is currently the most cost effective LNG-IUS available in the UK. It is possible that, in the future, Levosert's licence for contraception could be extended beyond 5 years depending on the results of current ongoing studies.

Table 1: Product characteristics of Kyleena, Mirena, Levosert and Jaydess.

Type of LNG-IUS	Levosert[1]	Mirena[4]	Kyleena[9]	Jaydess[10]
Total LNG content (mg)	52	52	19.5	13.5
LNG release rate (mcg/24h) Initial Final Average	 19.5 9.8 (after 5 years) 14.7 (over 5 years)	 20 10 (after 5 years) 14 (over 5 years)	 17.5 7.4 (after 5 years) 9 (over 5 years)	 14 5 (after 3 years) 6 (over 3 years)
Frame size (W x H, mm)	32 x 32	32 x 32	28 x 30	28 x 30
Inserter	Two handed inserter	One handed EvoInserter™	One handed EvoInserter™	One handed EvoInserter™
Insertion tube diameter (mm)	4.8	4.4	3.8	3.8
Silver ring for improved visibility on USS?	No	No	Yes	Yes
Colour of threads	Blue	Brown	Blue	Brown
Licensed duration of use for contraception (years)	5	5	5	3
Licensed for endometrial protection?	No	Yes	No	No
Licensed for heavy menstrual bleeding?	Yes	Yes	No	No
Minimum uterine cavity length (cm)	5.5 cm	Not indicated in SPC	Not indicated in SPC	Not indicated in SPC
Unit cost (£)	66.00	88.00	76.00	69.22
Cost per year over period of licensed use (£/year)	13.2	17.6	15.2	23.07

LNG-IUS: Levonogestrel-releasing intrauterine system; USS: Ultrasound scan

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The Clinical Effectiveness Unit (CEU) was formed to support the Clinical Effectiveness Committee of the Faculty of Sexual and Reproductive Healthcare (FSRH), the largest UK professional membership organisation working at the heart of sexual and reproductive healthcare. The CEU promotes evidence based clinical practice and it is fully funded by the FSRH through membership fees. It is based in Edinburgh and it provides a member's enquiry service, evidence based guidance, new SRH product reviews and clinical audit/research. Find out more here.