North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Levosert® levonorgestrel 20mcg/24hour intrauterine device

Verdict:	
Formulary inclusion:	Levosert® is to be included in the North Staffordshire Joint Formulary
Formulary category:	Green
Restrictions:	
Reason for inclusion:	The Committee was satisfied with the evidence for efficacy and safety, dosing convenience, cost implications and intended place in therapy
Link to formulary:	Primary care: http://www.northstaffordshirejointformulary.nhs.uk/ Secondary care: http://uhns/clinicians/clinical-guidance/clinical-guidelines/prescribing-formularies/
Link to medicine review summary:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians→ Support services → Pharmacy → Joint Formulary Related Documentation → North Staffordshire & Stoke-on-Trent Area Prescribing Committee Medicine Review Summary Verdict Sheets
Link to full review:	Primary care: https://www.stokeccg.nhs.uk/stoke-governance/policies/medicines-optimisation/formulary-review-and-verdict-sheets Secondary care: Trust Intranet→ Clinicians → Support Services → Pharmacy → Joint Formulary Related Documentation → New Medicine Committee (NMC) Medicines Reviews

Review summary:

Formulary application:
Levosert® is proposed as an addition to the North Staffordshire Joint Formulary (NSJF) for the treatment of heavy menstrual bleeding (HMB) in women requiring reversible contraception.
Studies have shown Levosert® has non-inferiority in safety and efficacy compared to Mirena®.
Since January 2019, Levosert® has been licensed to provide reversible contraception and treatment for HMB for 5 years. This duration of action is the same as for Mirena® for these indications.
Levosert® has a lower NHS list price than Mirena®. Introduction of Levosert® to the NSJF would result in a cost saving for the health economy.
If the new medicines submission for Levosert® is successful, it is suggested that prescribing of IUSs should be by brand name, as per MHRA advice.

Miss Pragya Gupta (consultant in obstetrics and gynaecology) presented the formulary submission to the New Medicines Committee on 6th February 2019. The formulary application is supported by Mr Richard Todd (UHNM clinical director for obstetrics and gynaecology).

Licensed indications:

Levosert® is licensed for the treatment of heavy menstrual bleeding. Levosert® may be particularly useful in women with heavy menstrual bleeding requiring (reversible) contraception.
Levosert® has not been studied in patients below 16 years of age.

Dosing:

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: 27/02/2019

North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

Levosert® is an intrauterine delivery system (IUS) (also known as an intrauterine device (IUD)) containing 52mg levonorgestrol. The initial in vivo release rate of 19.5 micrograms/day levonorgestrel from Levosert® decreases to 17.0 micrograms/day during the first year and 9.8 micrograms /day during the fifth year.

Levonorgestrel is delivered directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 113 ± 50 pg/mL after 5 years) resulting in only minor systemic effects.

Levosert® is effective for five years in the indications for contraception and heavy menstrual bleeding. Therefore it should be removed after five years of use.

It is recommended that Levosert® should only be inserted by health care professionals who are experienced in intrauterine contraceptive insertions or who have undergone sufficient training for insertion, as per Faculty of Sexual and Reproductive Healthcare guidance for training on insertion of IUDs.
As the method for inserting Levosert® differs from the method of insertion for Mirena®, healthcare professionals should be trained to insert the devices available locally,
Levosert® should be inserted within the first seven days following menstruation. It may be inserted at other times in the cycle if it is reasonably certain pregnancy can be excluded.
Levosert® should not to be inserted within six weeks of childbirth. It can be used immediately after first-trimester abortion
The length and width of the Levosert® is identical to Mirena (32mmx32mm). The inserter diameter of Levosert® is 4.8mm, compared with the Mirena Evoinserter at 4.4mm.

In her NMC presentation, Miss Gupta mentioned that clinicians within the obstetrics and gynaecology department have received training to insert Levosert®. She stated that no concerns were raised regarding the insertion technique.

Related guidance:

NICE: NICE Guideline (NG88) Heavy menstrual bleeding; assessment and management – published March 2018, last updated November 2018)
A levonorgestrel-releasing intrauterine system such as Levosert® is recommended for management of heavy menstrual bleeding if patient has
- no identified pathology
-fibroids less than 3 cm in diameter
–or suspected or diagnosed adenomyosis

NICE Clinical guideline [CG30] Long-acting reversible contraception. Published date: October 2005. Last updated: September 2014
-Choice of IUS should be guided by patient choice, clinical parameters, licensing and local availability.
-Up to 60% of women stop using their interuterine system within 5 years (licensed duration of action of Mirena® - IUS available at time of publication). The most common reasons are unacceptable vaginal bleeding and pain; a less common reason is hormonal (non‑bleeding) problems.

Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit:

- New Product Review : Levosert® intrauterine delivery system April 2015 (updated 12 February 2018)
- Letter of Competence for Intrauterine Techniques.

SMC: Levonorgestrel (Levosert®) 20 micrograms/24 hours intrauterine delivery system SMC No. (1058/15). 8th May 2015: Levosert® was accepted for use within NHS Scotland for women with heavy menstrual bleeding requiring reversible contraception.

Author: Xin Wei Tan, Secondary/Primary Care Interface Pharmacist, UHNM Date approved by APC: 27/02/2019

North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

RDTC: N/A

MTRAC: N/A

Background information:

Levonorgestrel is a progestogen used in gynaecology in various ways: as the progestogen component in oral contraceptives, in hormonal replacement therapy or alone for contraception in minipills and subdermal implants. Levonorgestrel can also be administered directly into the uterine cavity as an IUS. This allows a very low daily dosage, as the hormone is released directly into the target organ.

The contraceptive mechanism of action of the levonorgestrel IUS is based mainly on hormonal effects producing the following changes:
- Prevention of proliferation of the endometrium
- Thickening of the cervical mucus thus inhibiting the passage of sperm
- Suppression of ovulation in some women.

The physical presence of the system in the uterus would also be expected to make a minor contribution to its contraceptive effect.

In idiopathic menorrhagia, prevention of proliferation of the endometrium is the probable mechanism of action of levonorgestrel IUS in reducing blood loss.

NG88 (Heavy menstrual bleeding: assessment and recommends considering use of a levonorgestrel-releasing intrauterine system for management of heavy menstrual bleeding if patients meet the following criteria
- no identified pathology
-fibroids less than 3 cm in diameter
–or suspected or diagnosed adenomyosis . Adenomyosis is a condition in which endometrium breaks through the muscle wall of the uterus (the myometrium). Adenomyosis can cause menstrual cramps, lower abdominal pressure, and bloating before menstrual periods and can result in heavy periods.

The only levonorgestrel-releasing IUS currently included in the NSJF is Mirena®. Mirena®'is licensed to provide reversible contraception and treatment for HMB for 5 years

Levosert® was launched in the UK in April 2015 with a 3 year license. In February 2018 Levosert® was granted a 4 year license in the UK. In January 2019, Levosert® was licensed in the UK to provide reversible contraception and HMB treatment for 5 years, matching the licensed duration of action of Mirena® for these indications.

As the safety and side effect profile of Levosert® is similar to Mirena®, and Levosert® now has a licensed duration of action matching Mirena®, it is expected that introduction of Levosert® to the joint formulary will have minimal impact on IUS removal and insertion workload within the health economy.

Efficacy:

Levosert® has a similar in vivo release rate to Mirena®.

Estimated *in vivo* release rates for Levosert®

Time	Estimated *in vivo* release rate

	[micrograms per day]
Initial	19.5
1 year after insertion	17
5 years after insertion	10

Estimated *in vivo* release rates for Mirena®:

Time	Estimated *in vivo* release rate [micrograms per day]
Initial	20
1 year after insertion	18
4 years after insertion	12
5 years after insertion	10

Mawet et al compared the efficacy of Levosert® in the treatment of HMB vs Mirena®. This was a multicentre, randomised, controlled trial, in non-menopausal women diagnosed with functional HMB (defined as menstrual blood loss [MBL] ≥ 80 mL) randomised to either Levosert ® or Mirena ® and followed for up to one year. A total of 280 women were randomised (141 to Levosert ® and 139 to Mirena ®).
During the one-year treatment period, both Levosert ® and Mirena ® dramatically decreased MBL and increased haemoglobin and ferritin levels. Levosert® achieved a significant reduction in menstrual blood loss within 3 to 6 months of treatment. The volume of menstrual bleeding was decreased by 88% in women with heavy menstrual bleeding by the end of three months of use and 82% reduction was sustained for the duration of the study (12 months), with 15% becoming amenorrheic at the end of the first year and 29% at the end of the third year. Heavy menstrual bleeding caused by submucosal fibroids may respond less favourably. Reduced bleeding promotes an increase of blood haemoglobin in patients with heavy menstrual bleeding. There were no statistically significant differences between Levosert ® and Mirena ® regarding any of the parameters evaluated during the study. Similar bleeding patterns were observed in both groups.
Levosert ® was inserted with the same ease as Mirena ®. Both treatments were associated with identical expulsion rates and no perforations occurred in either treatment group.

An ongoing phase 3 randomized, open-label, multicentre trial is currently accessing the efficacy of Levosert® for up to 10 years (ClinicalTrials.gov Identifier: NCT00995150). 3 year data was published in 2015. At the time of publication, a total of 1600 women aged 16-35 years and 151 women aged 36-45 years agreed to LNG20 (Levosert®)placement, including 1011 (57.7%) nulliparous and 438 (25.1%) obese women. Data for contraceptive efficacy was based on the 272 women aged 16-35 years that had completed 3 years of Levosert use by July 2013. Successful placement occurred in 1714 (97.9%) women. Six pregnancies occurred, four of which were ectopic. The Pearl Index (which measures effectiveness of contraception) for LNG20 was 0.15 (95% CI 0.02-0.55) through Year 1, 0.26 (95% CI 0.10-0.57) through Year 2, and 0.22 (95% CI 0.08-0.49) through Year 3. The cumulative life-table pregnancy rate was 0.55 (95% CI 0.24-1.23) through 3 years.
(The contraceptive efficacy of Mirena has been studied in 5 major clinical studies with 3330 women using Mirena. The failure rate (Pearl Index) was approximately 0.2% at 1 year and the cumulative failure rate was approximately 0.7% at 5 years. The failure rate also includes pregnancies due to undetected expulsions and perforation. Similar contraceptive efficacy has been observed in a large post-marketing study with more than 17000 women using Mirena. Because the use of Mirena does not require daily intake compliance by the users, the pregnancy rates in “typical use” are similar to those observed in controlled clinical trials (“perfect use”)).
In NCT00995150, Levosert® expulsion was reported in 62 (3.5%) participants, most (50 [80.6%]) during the first year of use. This is a similar expulsion rate seen in phase 3 trials involving Mirena®. Of women who discontinued

LNG20 and desired pregnancy, 86.8% conceived spontaneously within 12 months. Pelvic infection was diagnosed in 10 (0.6%) women. Only 26 (1.5%) LNG20 users discontinued due to bleeding complaints.

4 year efficacy and safety data was published in 2017 by Thomas et al. The study refers to Liletta®, which is the name Levosert® is marketed under in the US. Successful IUS placement occurred in 1,568 (98%) women aged 16-35 years and 146 (97%) women aged 36-45 years, including 1,011 (57.7%) nulliparous and 438 (25.1%) obese women. Among women 16-35 years at enrolment, eight pregnancies occurred including one following perforation and one following expulsion. Six (75%) pregnancies were ectopic. The eight pregnancies included three nulliparous women and one obese woman. The Pearl Index in the first year was .15 (95% CI .02-.55). Cumulative life-table pregnancy rates through years two, three and four were .49 (95% CI .22-1.09), .60 (95% CI .28-1.26) and .78 (95% CI .37, 1.60). Perforation following IUS placement occurred in two (0.1%) women; both were diagnosed within the first year. Expulsion was reported in 63 (3.7%) participants, most (50 [80.6%]) during the first year of use. Pelvic infection was diagnosed in 12 (.7%) women. Only 38 (2.2%) women discontinued due to bleeding complaints. The study concluded Liletta® (Levosert®) is highly effective and safe over four years of use in nulliparous and parous women as well as non-obese and obese women.

Teal et al. published 5 year efficacy and safety data in October 2018. The study refers to Liletta®. Women aged 16-45 years were enrolled; those women aged 36-45 years received the IUS for safety evaluation only. The study involved 1,568 women aged 16-35 years and 146 women aged 36-45 years after successful IUS placement. The 16-35 year old subjects included 1,011 (57.7%) nulliparous and 438 (25.1%) obese women. Among these women, nine pregnancies occurred including four in nulliparous women and one in an obese woman. One pregnancy occurred following perforation and one following expulsion. Six (67%) pregnancies were ectopic. The Pearl Index in the first year was .15 (95% CI .02-.55). Cumulative life-table pregnancy rates through years three and five were .59 (95% CI .28-1.25) and .92 (95% CI .46-1.82), respectively. Perforation following IUS placement occurred in two (0.1%) women; both were diagnosed within the first year. Expulsion occurred in 63 (3.7%) participants, most (50 [80.6%]) during the first year of use. Pelvic infection was diagnosed in 11 (.6%) women. Only 39 (2.3%) women discontinued due to bleeding complaints, primarily (n=29 [74.3%]) in the first year. The study concluded that Liletta® (Levosert®) is highly effective and has an excellent safety profile over five years of use.

Safety:

Levosert® delivers levonorgestrel directly into the uterine cavity with low plasma concentrations (252 ± 123 pg/mL 7 days after insertion and 113 ± 50 pg/mL after 5 years) resulting in only minor systemic effects.

The adverse effect profile of Levosert® is similar to the adverse event profile of Mirena®.
Undesirable effects are more common during the first months after the insertion, and subside during prolonged use.
Very common undesirable effects (occurring in more than 10% of users) include uterine/vaginal bleeding including spotting, oligomenorrhoea, amenorrhoea (and benign ovarian cysts)

Levosert® may be used with caution after specialist consultation, or removal of the system should be considered, if any of the following conditions exist or arise for the first time during treatment:
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Unusually severe or unusually frequent headache
- Jaundice
- Marked increase of blood pressure
- Malignancies affecting the blood or leukaemias in remission
- Use of chronic corticosteroid therapy
- Past history of symptomatic functional ovarian cysts

North Staffordshire and Stoke-on-Trent Area Prescribing Committee

Medicine Review Summary

- Active or previous severe arterial disease, such as stroke or myocardial infarction
- Severe or multiple risk factors for arterial disease
- Thrombotic arterial or any current embolic disease
- Acute venous thromboembolism.

The above cautions are similar to those for Mirena®.

Levosert® may be used with caution in women who have congenital heart disease or valvular heart disease at risk of infective endocarditis.

In general, women using Levosert® should be encouraged to stop smoking, which is guidance provided to all women prescribed contraceptives.

The contraindications are identical to those for Mirena®.
In addition, the manufacturers recommend that if the uterine depth is sounded to less than 5.5 cm, the procedure to insert Levosert® should be discontinued

Place in therapy:
It is proposed that Levosert® will become 1st choice levonorgestrol IUS for treatment of HMB in patients requiring reversible contraception. Mirena® will remain as a 2nd line IUS option for HMB and as 1st line IUS for protection from endometrial hyperplasia during oestrogen replacement therapy.

During her NMC presentation, Miss Gupta stated that prescribing of IUSs is already per brand name, in accordance with MHRA advice.

Cost comparison:

Device	Secondary care price per unit (incl. VAT)	Primary care price per unit (if accessing National Branded Framework price)	Primary care price per unit (list price)
Levosert®	[redacted]	[redacted]	£66
Mirena®	[redacted]	[redacted]	£88

References:

1. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. New Product Review : Levosert® intrauterine delivery system April 2015 (updated 12 February 2018)
2. Medicines and Healthcare Products regulatory Agency (MHRA). Levonorgestrel-releasing intrauterine systems: prescribe by brand name. Published January 21st 2016.
3. NICE Clinical guideline [CG30] Long-acting reversible contraception. Published date: October 2005. Last updated: September 2014
4. NICE Guideline (NG88) Heavy menstrual bleeding; assessment and management – published March 2018, last updated November 2018)
5. Faculty of Sexual and Reproductive Health. Letter of Competence for Intrauterine Techniques. https://www.fsrh.org/education-and-training/letter-of-competence-intrauterine-techniques-loc-iut/
6. eMC. Summary of Product Characteristics. Levosert® 20 micrograms/24 hours IDS. Last updated 2rd January 2019. Accessed 17th January 2019
7. eMC. Summary of Product Characteristics. Mirena. Last updated 12th April 2018. Accessed 17th January 2019

8. Mawet et. al. Impact of a new levonorgestrel intrauterine system, Levosert ®, on heavy menstrual bleeding: results of a one-year randomised controlled trial. The European Journal of Contraception and Reproductive Health Care, 2014; 19: 169–179
9. Eisenberg et. al. Three-year efficacy and safety of a new 52-mg levonorgestrel-releasing intrauterine system. Contraception Journal. July 2015. Volume 92, Issue 1, Pages 10–16
10. Thomas, Michael et al. Four-Year Efficacy and Safety of the Liletta® Levonorgestrel Intrauterine System [11A]. Obstetrics & Gynecology: May 2017 - Volume 129 - Issue 5 - p 11S–12S
11. Teal, Stephanie B et. A. Five-Year Efficacy and Safety of the Liletta® Levonorgestrel Intrauterine System [13F]. Obstetrics & Gynecology: May 2018 - Volume 131 - Issue - p 66S–67S