



North Staffordshire Clinical Commissioning Group
Stoke-On-Trent Clinical Commissioning Group
University Hospitals of North Midlands NHS Trust
Midlands Partnership NHS Foundation Trust
North Staffordshire Combined Healthcare NHS Trust

New Medicines Committee Briefing

January 2019

Drug: Levosert® 20mcg/24hour intrauterine device

is to be reviewed for use within:

Primary care	X
Secondary care	X

Summary

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. Levosert® will be available, alongside Mirena® (the current levonorgestrel-releasing intrauterine system (IUS) available on the NSJF) as an option for secondary care, CASH (contraception and sexual health), GUM and GP services.

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.

Formulary application

Consultant submitting application: Miss Pragya Gupta (consultant in obstetrics and gynaecology)

Clinical Director supporting application: Mr Richard Todd (consultant gynaecologist)

Dr Gupta has requested adding Levosert® to the joint formulary as Levosert® contains the same total amount of levonorgestrel with the same release profile as the current levonorgestrel-containing IUS on the joint NSJF (Mirena®), at a lower unit cost.

Head to head studies have shown that Levosert® has a similar efficacy and safety profile to Mirena®.

Levosert® has a similar side effect profile to Mirena®.

Background

NG88 (Heavy menstrual bleeding: assessment and management – published March 2018, last updated November 2018) recommends considering use of a levonorgestrel-releasing intrauterine system for management of heavy menstrual bleeding if they 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®'s 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.

NICE Guidance CG30 (Long-acting reversible contraception - published date: October 2005, last updated: September 2014) states that 60% of IUS patients will stop using their IUS within 5 years. 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.

Current formulary status

Levosert® is currently not included in the North Staffordshire Joint Formulary

North Staffordshire Joint Formulary: Section 7

7.3.2 Progestogen-only contraceptives		
7.3.2.1 Oral progestogen-only contraceptives		
Norgeston® (Levonorgestrel)		Administration can be delayed for 3 hours without loss of contraceptive effect.
Micronor® (Norethisterone)		Administration can be delayed for 3 hours without loss of contraceptive effect.
Noriday® (Norethisterone)		Administration can be delayed for 3 hours without loss of contraceptive effect.
Cerazette® (Desogestrel)		Administration can be delayed for 12 hours without loss of contraceptive effect.
Femulen® (Etonodiol diacetate)		Administration can be delayed for 3 hours without loss of contraceptive effect.
7.3.2.2 Parenteral progestogen-only contraceptives		
Injectable preparations		
Depo-Provera® (Medroxyprogesterone)		
Implants		
Implanon® (Etonogestrel)		Manufacturer states that it can only be fitted after specialist training
7.3.2.3 Intra-uterine progestogen-only device		
Mirena® (Levonorgestrel)		<input checked="" type="checkbox"/> MTRAC

Levosert® is currently not included in the South Staffordshire Joint Formulary

net Formulary

NHS
 South Staffordshire Joint Formulary
 Cannock Chase Clinical Commissioning Group
 East Staffordshire Clinical Commissioning Group
 South East Staffordshire and Seisdon Peninsula Clinical Commissioning Group
 Stafford and Surrounds Clinical Commissioning Group

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Formulary Chapter 7: Obstetrics, Gynaecology, and urinary-tract disorders - Full Chapter

07.03.02.03 Intra-uterine progestogen-only contraceptive

Intra-uterine Progestogen	Formulary	Mirena_Intra-Uterine System
Only System (Mirena [®]) BNF SPC BNF C	Green	The Prescriber must also be able to fit the Mirena and Assess for STI before fitting the IUD. This is included in the service level agreement and should not be prescribed on FP10

NICE CG44: Heavy menstrual bleeding

Levosert[®] is currently not included in the Birmingham, Sandwell, Solihull and environs APC Formulary.

Levosert[®] is currently not included in the Derbyshire Joint Formulary.

Levosert[®] is currently not included in the Wolverhampton Joint Formulary.

Levosert[®] is currently not included in the Leicestershire Health Community Medicines Formulary.

Therapeutic class and mode of action

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.

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.

Dosage and administration

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 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 Evo inserter at 4.4mm.

Safety and adverse effects

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.

Warnings and precautions

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
- 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.

Contraindications

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.

Drug Interactions

The interaction profile of Levosert® is as for other progestogens.

The metabolism of progestagens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. griseofulvin, rifampicin, rifabutin, nevirapine, efavirenz). On the other hand, substances known to inhibit drug-metabolizing enzymes (e.g. itraconazole, ketoconazole) may increase serum concentrations of levonorgestrel. The influence of these drugs on the contraceptive efficacy of Levosert® is not known, but it is not believed to be of major importance due to the local mechanism of action.

Presentation

Levosert® consists of an inserter and levonorgestrel IUS, which is loaded at the tip of the inserter. Inserter components are an insertion tube, plunger, flange, body and slider. The device consists of a white or almost white hormone-elastomer core, mounted on a T-body and covered in opaque tubing, which regulates the release of levonorgestrel. The T-body has a loop at the end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop.

List of excipients: Silicon base, tetra-n-propyl silicate, stannous octoate, polydimethylsiloxane elastomer, polydimethylsiloxane tubing, low density polyethylene T-frame with 20-24% barium sulphate polypropylene thread coloured with copper phthalocyanine blue

Patent Status

Date of first authorisation/renewal of the authorisation: First marketed in the UK April 2015 (3 year license)

Date of revision of the text: February 2018

Guidance and Evidence Summary

NICE Guidance

Y

NG88 (Heavy menstrual bleeding: assessment and management – published March 2018, last updated November 2018) recommends considering use of a levonorgestrel-releasing intrauterine system such as Levosert® for management of heavy menstrual bleeding if they meet the following criteria

- no identified pathology

-fibroids less than 3 cm in diameter –

or suspected or diagnosed adenomyosis

CG30 (Long-acting reversible contraception - published date: October 2005, last updated: September 2014) was published before Levosert® was launched in the UK. CG30 advises that choice of IUS should be guided by patient choice, clinical parameters, licensing and local availability.

The guidance states up to 60% of women stop using their interuterine system within 5 years (licensed duration of action of Mirena®). The most common reasons are unacceptable vaginal bleeding and pain; a less common reason is hormonal (non-bleeding) problems.

Scottish Medicines Consortium (SMC)	Y
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Levosert® was accepted for use by the SMC on 8th May 2015 within NHS Scotland for women with heavy menstrual bleeding requiring reversible contraception.

All Wales Medicines Strategy Group (AWMSG)	Y
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Levosert® was excluded from the AWMSG in October 2015

Levosert® met the AWMSG exclusion criteria in place for medications which fall outside the role and remit of AWMSG and where progression to formal appraisal is unlikely. In these circumstances health boards may consider whether individual products are appropriate for local formulary inclusion.

Regional Drug and Therapeutic Centre (RDTC)	N
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Midlands Therapeutics Review and Advisory Committee (MTRAC)	N
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Efficacy

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

Estimated *in vivo* release rates for Levosert®

Time	Estimated <i>in vivo</i> 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 <i>in vivo</i> 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] \geq 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 amenorrhic 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 assessing 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.

Cost Analysis

Predicted UHNM expenditure

Levosert® is available via the National Branded Framework at £ [REDACTED] excl VAT per unit (= £ [REDACTED] incl VAT).

Mirena® is available at £ [REDACTED] excl VAT (£ [REDACTED] incl VAT)

From November 2017 to October 2018, 508 Mirena units were dispensed at UHNM. This excludes sales to external organisations (eg CASH services).

Potential UHNM expenditure	
Mirena® price per unit incl VAT	£ [REDACTED]
Levosert® price per unit incl VAT	£ [REDACTED]
Saving per Levosert® compared to Mirena®	£44.87
Annual usage within UHNM (November 2017-October 2018; excluding sales to external customers) for all licensed indications	508 patients
Estimated annual number of UHNM patients prescribed Mirena® for endometrial hyperplasia (10-15 per month). <i>NB: Levosert® is not licensed for this indication. It is proposed Mirena® will still be prescribed for this cohort</i>	120-180 patients
Estimated number of UHNM patients per annum who could be prescribed Levosert® instead of Mirena®	328 -388 patients
Minimum annual saving for UHNM if Levosert® used instead of Mirena®	£14,717.36

Predicted primary care expenditure

CASH services which purchase Levosert® from UHNM can access the National Branded Framework price of £ [REDACTED] per unit excl. VAT.

CASH services purchasing Mirena® from UHNM as of January 2019	
[REDACTED]	[REDACTED]

The NHS list purchase price of Levosert® is £66 excluding VAT.

The NHS list purchase price of Mirena® is £88 excluding VAT

Potential primary care expenditure – presuming Levosert® purchased at list price	
Mirena® price per unit excl VAT	£88.00
Levosert® price per unit excl VAT (list price)	£66.00
Saving per Levosert® compared to Mirena®	£22.00

Annual usage within the 6 CCGs (October 2017-September 2018)	319
Potential annual saving in drug expenditure for primary care if Levosert® used instead of Mirena® (based on list price)	£7018 Savings in primary care likely to be greater as some providers are able to access the National Framework Price of £ [REDACTED]

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