

Long-acting reversible contraception: levonorgestrel 13.5 mg intrauterine delivery system

Evidence summary

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[nice.org.uk/guidance/esnm41](https://www.nice.org.uk/guidance/esnm41)

Key points from the evidence

The content of this evidence summary was up-to-date in June 2014. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

In a [randomised controlled trial](#) that compared 2 low-dose intrauterine delivery systems containing 13.5 mg and 19.5 mg levonorgestrel (n=2885), the failure rate of the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#): failure rate 0.4% in year 1 and 0.9% over 3 years) was similar to failure rates seen with correct and consistent use of other methods of long-acting reversible contraception. Serious adverse events were reported by 8 women (0.6%) using the levonorgestrel 13.5 mg intrauterine delivery system, including 3 ectopic pregnancies and 2 cases of pelvic inflammatory disease.

The levonorgestrel 19.5 mg intrauterine delivery system used as a comparator in the study is not licensed or available commercially, and there is insufficient evidence comparing the levonorgestrel 13.5 mg intrauterine delivery system with existing contraceptives, including the levonorgestrel 52 mg intrauterine system ([Mirena](#)). Two studies are underway comparing this device with a combined oral contraceptive containing drospirenone and ethinylestradiol ([Yasmin](#);

[NCT01254292](#)) and the progestogen-only subdermal implant ([Nexplanon](#); [NCT01397097](#)) respectively.

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| <p>Effectiveness</p> <p>In women using the levonorgestrel 13.5 mg intrauterine system in Nelson et al. (2013) (n=1432):</p> <ul style="list-style-type: none">• 10 pregnancies occurred over 3 years (0.33 pregnancies per 100 woman-years).• The contraceptive failure rate was 0.4% in year 1 and 0.9% over 3 years, which is similar to failure rates seen with correct and consistent use of other methods of long-acting reversible contraception. | <p>Safety</p> <ul style="list-style-type: none">• In women using the levonorgestrel 13.5 mg intrauterine system in the study:<ul style="list-style-type: none">- 8 serious adverse events were reported (0.6%) including 3 ectopic pregnancies and 2 cases of pelvic inflammatory disease.- Over 3 years, the discontinuation rate for adverse events was 21.9%.• According to the summary of product characteristics for Jaydess, the most common adverse effects are headache, abdominal or pelvic pain, acne or seborrhoea, bleeding changes, ovarian cysts and vulvovaginitis. |
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| User factors | Resource implications |
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| <ul style="list-style-type: none"> • NICE advises that women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception. • The levonorgestrel 13.5 mg device is smaller than the levonorgestrel 52 mg device but there is insufficient evidence comparing the 2 devices in terms of pain and ease of insertion. • The majority of women who used the levonorgestrel 13.5 mg intrauterine system were satisfied with their treatment and bleeding patterns but comparisons with levonorgestrel 52 mg and other contraceptives are lacking. | <ul style="list-style-type: none"> • The levonorgestrel 13.5 mg intrauterine system (Jaydess) costs £69.22 for up to 3 years' contraception • The levonorgestrel 52 mg intrauterine system (Mirena) costs £88.00 for up to 5 years' contraception. • Costs of other long-acting reversible contraceptives are listed in the costs of alternative contraceptives section of this evidence summary. |

Introduction and current guidance

The NICE guideline on [Long-acting reversible contraception](#) (NICE clinical guideline 30) advises that women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception. The NICE guideline offers best-practice advice for all women of reproductive age who may wish to use copper intrauterine devices, progestogen-only intrauterine systems and progestogen-only injectable contraceptives. The Faculty of Sexual and Reproductive Healthcare (FSRH) has produced [clinical guidelines](#) on various methods of contraception (processes used to produce FSRH guidance have been [accredited by NICE](#)).

This evidence summary considers the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#); initial release rate 14 micrograms/24 hours, average release rate 6 micrograms/24 hours for up to 3 years). This device contains a lower dose, and is smaller than the levonorgestrel 52 mg intrauterine delivery system ([Mirena](#); initial release rate 20 micrograms/24 hours), which has been available since March 1995.

Full text of [Introduction and current guidance](#).

Product overview

The levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#)) is licensed for up to 3 years' contraception. It received a marketing authorisation in January 2013 and was launched in the UK in March 2014.

Full text of [Product overview](#).

Evidence review

This evidence summary is based on a randomised controlled trial that compared 2 low-dose intrauterine delivery systems containing 13.5 mg and 19.5 mg levonorgestrel ([Nelson et al. 2013](#)). The higher dose levonorgestrel intrauterine delivery system used in this study is not licensed or available commercially and is only briefly discussed. The study included 2885 healthy nulliparous and parous women aged 18–35 years who had regular menstrual cycles (21–35 days) and requested contraception.

- [Nelson et al. \(2013\)](#) (n=2885) found that the levonorgestrel 13.5 mg intrauterine delivery system is an effective contraceptive device. The failure rate observed in the study in year 1 (0.4%) was similar to those seen with correct and consistent use of other methods of long-acting reversible contraception ([Trussell 2011](#)). Over 3 years, 10 pregnancies occurred in the levonorgestrel 13.5 mg group (0.33 pregnancies per 100 woman-years: cumulative failure rate 0.9%). Four of the pregnancies were associated with either complete or partial expulsion of the levonorgestrel intrauterine delivery system.
- In the study, over 3 years, serious adverse events were reported by 8 women (0.6%) using the levonorgestrel 13.5 mg intrauterine delivery system. Three ectopic pregnancies and 2 cases of pelvic inflammatory disease classed as serious adverse events occurred. There were no uterine perforations. Over 3 years, 21.9% of women using the levonorgestrel 13.5 mg intrauterine delivery system discontinued treatment because of adverse events (1.0% for serious adverse events and 4.7% for bleeding disturbances including amenorrhoea).
- According to the [summary of product characteristics](#), the most common adverse effects of the levonorgestrel 13.5 mg intrauterine delivery system are headache, abdominal or pelvic pain, acne or seborrhoea, bleeding changes (increased or decreased menstrual bleeding, spotting, infrequent bleeding and amenorrhoea), ovarian cysts and vulvovaginitis, with an incidence of 1 in 10 or more. Adverse effects with an incidence of between 1 in 100 and 1 in 10 are depressed mood or depression, migraine, nausea, alopecia, upper genital tract infection,

dysmenorrhoea, breast pain or discomfort, device expulsion (complete or partial) and genital discharge.

Full text of [Evidence review](#).

Context

The levonorgestrel 13.5 mg intrauterine system costs £69.22 for up to 3 years' contraception. The levonorgestrel 52 mg intrauterine system ([Mirena](#)) costs £88.00 for up to 5 years' contraception. See the costs of alternative contraceptives section for details of other contraceptives.

Full text of [Context](#).

Estimated impact for the NHS

The NICE guideline on [Long-acting reversible contraception](#) advises that women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception. The place in practice of the levonorgestrel 13.5 mg intrauterine delivery system is likely to be as an alternative to other methods of long-acting reversible contraception, including the levonorgestrel 52 mg intrauterine delivery system.

There is insufficient evidence comparing the levonorgestrel 13.5 mg and 52 mg intrauterine delivery systems. An open-label phase II study by [Gemzell-Danielsson et al. \(2012\)](#) (n=742) included a levonorgestrel 52 mg arm and found that levonorgestrel 13.5 mg provided good contraceptive efficacy compared with the established device. However, this study was not sufficiently [statistically powered](#) to determine whether the levonorgestrel 13.5 mg intrauterine delivery system is non-inferior to the levonorgestrel 52 mg intrauterine delivery system. It is unclear whether pain and ease of insertion were improved with the levonorgestrel 13.5 mg delivery system compared with the levonorgestrel 52 mg delivery system; the investigators were not [blinded](#) and their evaluations of ease of insertion were subjective (easy, slightly difficult or very difficult). In addition, at the time the study was carried out the levonorgestrel 52 mg device had a 4.75 mm diameter insertion tube, whereas the current tube measures 4.4 mm diameter, which limits the applicability of the results.

[Nelson et al. \(2013\)](#) suggest that the levonorgestrel 13.5 mg intrauterine delivery system might appeal to women seeking a lower exposure to synthetic hormones. They also state that this device might be suitable for women with a narrower cervical canal, a smaller uterine cavity, or both, because it is smaller than the levonorgestrel 52 mg intrauterine delivery system. However, there is insufficient evidence to support these claims. The majority of women who used the levonorgestrel

13.5 mg intrauterine delivery system in the study were satisfied with their treatment and bleeding patterns but comparisons with the levonorgestrel 52 mg intrauterine delivery system are lacking.

Although [Nelson et al. \(2013\)](#) suggest that the small size of the levonorgestrel 13.5 mg intrauterine delivery system might make it suitable for use in nulliparous women and women who have never delivered vaginally, the [summary of product characteristics](#) states that it is not first-choice for contraception in nulliparous women because clinical experience is limited. Safety and efficacy of the levonorgestrel 13.5 mg intrauterine delivery system has not been confirmed in girls and young women aged under 18 years. However, a clinical study in this population is underway ([NCT01434160](#)).

The [summary of product characteristics](#) states that the levonorgestrel 13.5 mg intrauterine delivery system is not recommended for treating heavy menstrual bleeding or protecting against endometrial hyperplasia during oestrogen replacement therapy. The levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)) is licensed for these indications in the UK.

There is no published evidence comparing the levonorgestrel 13.5 mg intrauterine delivery system with other methods of contraception. However, 2 studies are underway comparing this device with a combined oral contraceptive containing drospirenone and ethinylestradiol ([Yasmin](#); [NCT01254292](#)) and the progestogen-only subdermal implant ([Nexplanon](#); [NCT01397097](#)) respectively.

Full text of [Estimated impact for the NHS](#).

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

According to the NICE guideline on [Long-acting reversible contraception](#) (NICE clinical guideline 30), it is estimated that about 30% of pregnancies are unplanned. NICE advises that women requiring contraception should be given information about and offered a choice of all methods,

including long-acting reversible contraception. Long-acting reversible contraception is defined as contraception that requires administration less than once per cycle or month and includes copper intrauterine devices, progestogen-only intrauterine systems, progestogen-only injectable contraceptives and progestogen-only subdermal implants.

In Great Britain, the uptake of long-acting reversible contraception in women aged 16–49 years has increased slowly since the NICE guideline was published in 2005, from around 8% in 2003/04 to around 12% in 2008–09. This figure is still low compared with the oral contraceptive pill (25%) and condoms for men (25%), which are the most popular methods of contraception ([Office for National Statistics, Contraception and sexual health 2008–09](#)). NICE states that increasing the uptake of long-acting reversible contraception could reduce the number of unintended pregnancies. The effectiveness of the barrier method and oral contraceptive pills depends on their correct and consistent use. By contrast, the effectiveness of long-acting reversible contraception does not depend on daily concordance.

The NICE guideline on [Long-acting reversible contraception](#) offers best-practice advice for all women of reproductive age who may wish to use copper intrauterine devices, progestogen-only intrauterine systems and progestogen-only injectable contraceptives. The Faculty of Sexual and Reproductive Healthcare (FSRH) has produced [clinical guidelines](#) on various methods of contraception (processes used to produce FSRH guidance have been [accredited by NICE](#)).

This evidence summary considers the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#); initial release rate 14 micrograms/24 hours, average release rate 6 micrograms/24 hours for up to 3 years). This device contains a lower dose, and is smaller than the levonorgestrel 52 mg intrauterine delivery system ([Mirena](#); initial release rate 20 micrograms/24 hours), which has been available since March 1995.

Product overview

Drug action

According to the [summary of product characteristics](#), the contraceptive effects of the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#)) are primarily due to its progestogenic effects on the endometrium. High intrauterine levels of levonorgestrel cause changes within the endometrium that prevent implantation. In addition, sperm penetration is decreased because the cervical mucus thickens, and fertilisation is prevented because sperm mobility and function is inhibited in the uterus and fallopian tubes. Most women continue to ovulate.

Licensed therapeutic indication

The levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#)) is licensed for up to 3 years' contraception. It received a marketing authorisation in January 2013 and was launched in the UK in March 2014.

The levonorgestrel 13.5 mg intrauterine delivery system is not licensed for use as a post-coital contraceptive. In addition, the [summary of product characteristics](#) states that it is not recommended for treating heavy menstrual bleeding or protecting against endometrial hyperplasia during oestrogen replacement therapy. The levonorgestrel 13.5 mg intrauterine delivery system is not first choice for contraception in nulliparous women because clinical experience is limited. Similarly, safety and efficacy has not been confirmed in girls and young women aged under 18 years.

Contraindications, special warnings and precautions for use are similar to those of the established levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)).

Course and cost

The levonorgestrel 13.5 mg intrauterine delivery system is a small T-shaped device, which after insertion into the uterine cavity releases, on average, 6 micrograms of levonorgestrel per day for up to 3 years.

The [summary of product characteristics](#) advises that the levonorgestrel 13.5 mg intrauterine delivery system should only be inserted by clinicians who are experienced in inserting intrauterine delivery systems and/or have undergone training on the insertion procedure for this device. It should be inserted into the uterine cavity within 7 days of the onset of menstruation and removed no later than the end of the third year.

The levonorgestrel 13.5 mg intrauterine delivery system costs £69.22.

Evidence review

This evidence summary is based on a [randomised controlled trial](#) that compared 2 low-dose intrauterine delivery systems containing 13.5 mg and 19.5 mg levonorgestrel ([Nelson et al. 2013](#)). The higher dose levonorgestrel intrauterine delivery system used in this study is not licensed or available commercially and is only briefly discussed.

There are no published phase III studies comparing the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#)) with the established levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)). The results of a phase II study that compared levonorgestrel 13.5 mg, 19.5 mg and 52 mg are discussed briefly in the evidence summary ([Gemzell-Danielsson et al. 2012](#)). However, this study was not sufficiently statistically powered to compare contraceptive efficacy.

Two randomised, open-label studies are underway comparing the levonorgestrel 13.5 mg intrauterine delivery system with a combined oral contraceptive containing drospirenone and ethinylestradiol ([Yasmin](#); [NCT01254292](#)) and the progestogen-only subdermal implant ([Nexplanon](#); [NCT01397097](#)) respectively.

Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial ([Nelson et al. 2013](#))

- **Design:** This randomised, open-label, parallel-group study was undertaken in 138 centres in 11 countries (Argentina, Canada, Chile, Finland, France, Hungary, Mexico, The Netherlands, Norway, Sweden and the USA). It is unclear whether allocation was concealed and although women were blinded to treatment allocation for the first 30 months, it was not possible to blind investigators because of the different sizes of the 2 intrauterine delivery systems.
- **Population:** The study included 2885 healthy nulliparous and parous women aged 18–35 years who had regular menstrual cycles (21–35 days) and requested contraception. Exclusions were consistent with the contraindications for the levonorgestrel 52 mg delivery system and included vaginal or caesarean delivery or abortion within 6 weeks; history of ectopic pregnancy; breast feeding; previous or current pelvic inflammatory disease; unexplained abnormal uterine bleeding; and genital infection (until successfully treated). The groups were similar in terms of mean age (27 years), weight (68.7 kg), body mass index (25.3 kg/m²), smoking status (24% smokers), number of births (1.1) and parity status (39% nulliparous, 12% had had a caesarean delivery only).
- **Intervention and comparison:** Women were randomised to receive either the levonorgestrel 13.5 mg uterine delivery system or the levonorgestrel 19.5 mg uterine delivery system for 3 years. Up to 2 attempts to place the intrauterine delivery system were permitted in each woman. All women in whom placement was attempted were included in analyses: women who had a failed placement were assumed to have an exposure time of 1 day. Women were assessed every 3 months in year 1 and every 6 months in years 2 and 3. They recorded their vaginal bleeding in diaries and completed a user satisfaction questionnaire after the final study assessment.

- **Outcomes:** The primary outcome was pregnancy rate, which was expressed as the Pearl Index (the number of pregnancies per 100 woman-years). Secondary outcomes included cumulative failure rates, bleeding patterns, ease and pain of placement, user satisfaction, adverse events and discontinuation rates.

Table 1 Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial (Nelson et al. 2013)

| | Levonorgestrel 13.5 mg | Levonorgestrel 19.5 mg ^a | Analysis |
|--|---|---|---|
| Randomised | n=1432 | n=1453 | |
| Efficacy^b | n=1432 | n=1452 ^c | |
| Primary outcome: cumulative contraceptive efficacy over 3 years (Pearl Index ^d) | PI 0.33, 95% CI 0.16 to 0.60 (10 pregnancies per 3059 woman-years ^{e,f}) | PI 0.31, 95% CI 0.15 to 0.57 (10 pregnancies per 3211 woman-years ^{e,f}) | No significant difference |
| Selected secondary outcomes: | | | |
| Cumulative contraceptive failure rate over 3 years | 0.9% | 1% | Statistical significance of difference not reported |
| Proportion of women 'very satisfied' or 'somewhat satisfied' with treatment ^g | 95% | 96% | Statistical significance of difference not reported |
| Proportion of women 'very satisfied' or 'somewhat satisfied' with their bleeding patterns ^g | 77% | 76% | Statistical significance of difference not reported |
| Proportion of women who would have liked to continue using their study treatment ^{g,h} | 77% | 82% | Statistical significance of difference not reported |

| Safety ^a | n=1432 | n=1452 | |
|---|---|---|---|
| Women reporting serious treatment-related adverse events | 0.6% (8/1432) | 1.0% (15/1452) | Statistical significance of difference not reported |
| Discontinuation for any adverse event | 21.9% | 19.1% | Statistical significance of difference not reported |
| Discontinuation for serious adverse events | 1.0% | 1.2% | Statistical significance of difference not reported |
| Discontinuation for disturbances in menstrual bleeding, including amenorrhoea | 4.7% | 4.9% | Statistical significance of difference not reported |
| Cumulative ectopic pregnancy rate per 100 woman-years over 3 years | 0.10, 95% CI 0.02 to 0.29 (3 pregnancies per 3059 woman-years ^e) | 0.22, 95% CI 0.09 to 0.45 (7 pregnancies per 3211 woman-years ^e) | Statistical significance of difference not reported |
| Cumulative risk of at least partial expulsion over 3 years | 4.56% | 3.58% | Statistical significance of difference not reported |

Abbreviations: CI, confidence interval; PI, Pearl Index^d.

^a The levonorgestrel 19.5 mg intrauterine delivery system used as a comparator in the study is not licensed or available commercially.

^b Efficacy and safety analyses included all randomised women in whom placement of an intrauterine delivery system was attempted.

^c Placement was not attempted in 1 woman because the depth of her uterus was unclear.

^d The number of pregnancies per 100 woman-years.

^e Relevant exposure was calculated from the total exposure in woman-years minus the time in which back-up contraception was used or sex hormones were taken for other reasons.

^f Five of the 20 pregnancies were associated with either complete or partial expulsion of the levonorgestrel intrauterine delivery system (4 with 13.5 mg and 1 with 19.5 mg).

^g 73.4% of women completed a user satisfaction survey after 3 years (for women who completed the study) or at the final study visit (for women who discontinued treatment early).

^h At the time of the study neither of the intrauterine delivery systems was available for use outside clinical trials.

Gemzell-Danielsson et al. (2012) (n=742) aimed to identify an appropriate dose for a new levonorgestrel intrauterine delivery system. This study was a randomised open-label phase II study in 37 centres in 5 European countries. It studied levonorgestrel 13.5 mg (n=239) and 19.5 mg (n=245) alongside the established levonorgestrel 52 mg intrauterine delivery system (Mirena; n=254) in healthy women aged 21–40 years. Outcomes included contraceptive efficacy, bleeding patterns, ease or pain of placement, and adverse events. Efficacy and safety analyses included all randomised women who successfully received a levonorgestrel intrauterine system (n=738).

Clinical effectiveness

Nelson et al. (2013) found that both of the levonorgestrel intrauterine delivery systems were effective contraceptive devices. Details for the levonorgestrel 19.5 mg intrauterine delivery system are shown in table 1. Over 3 years, 10 pregnancies occurred in the levonorgestrel 13.5 mg group (0.33 pregnancies per 100 woman-years). Four of the pregnancies were associated with either complete or partial expulsion of the levonorgestrel intrauterine delivery system.

In year 1, the failure rate was 0.4% in women using the levonorgestrel 13.5 mg intrauterine delivery system. This rate is similar to those seen with correct and consistent use of other methods of long-acting reversible contraception (Trussell 2011). Over 3 years, the cumulative failure rate of the 13.5 mg levonorgestrel intrauterine delivery system was estimated to be 0.9%.

Both of the devices used in the study were smaller than the existing levonorgestrel 52 mg device (reservoir and T frame 28 mm by 30 mm compared with 32 mm by 32 mm) and allowed placement using a smaller tube (3.8 mm diameter compared with 4.4 mm diameter). Overall, a levonorgestrel intrauterine delivery system was successfully placed in 99.5% of women randomised: placement was successful at the first attempt in 96.0% of women. Investigators rated placement as 'easy' in 89.6% of women and 'very difficult' in 1.2% of women. Pain of placement was reported as 'severe' by 7.6% of women, 'moderate' by 27.4% of women and 'mild' by 45.5% of women. 19.5% of women reported no pain. Prophylactic local anaesthesia and analgesia were used by 8.6% and 32.2% of women respectively. It is not known how these affected the women's evaluation of pain.

The mean number of bleeding and spotting days decreased over time in both groups and there were more days with spotting only than with bleeding in all reference periods. Of the 73% of women who completed a user satisfaction survey, 77% of women in the levonorgestrel 13.5 mg group said they were 'very satisfied' or 'somewhat satisfied' with their bleeding patterns.

Of the women surveyed, 95% said they were 'very satisfied' or 'somewhat satisfied' with their levonorgestrel 13.5 mg intrauterine delivery system: 77% of women said they would have liked to continue using their study treatment if it was available.

In [Gemzell-Danielsson et al. \(2012\)](#), over 3 years, 1, 5, and 0 pregnancies occurred in the levonorgestrel 13.5 mg, 19.5 mg and 52 mg groups respectively (3-year Pearl Indices 0.17, 0.82, and 0 respectively: 3-year cumulative failure rates 0.5%, 2.5% and 0% respectively). The study was not statistically powered to detect a difference between the groups.

The mean number of bleeding and spotting days decreased similarly over time in the groups, although the total number of bleeding and spotting days decreased with an increasing dose of levonorgestrel. Placement of the levonorgestrel 13.5 mg and 19.5 mg intrauterine delivery systems was considered easy in 94% of women compared with 86% of women in the 52 mg levonorgestrel group ($p < 0.001$). Similarly 72% of women using levonorgestrel 13.5 mg or 19.5 mg reported either 'no pain' or only 'mild pain' during placement compared with 58% in the 52 mg group (statistical significance of difference not reported). Note that the diameter of the insertion tube for the levonorgestrel 52 mg device used at that time was larger than that of the current device (4.75 mm compared with 4.4 mm [Bayer: personal communication, March 2014]).

Safety and tolerability

In [Nelson et al. \(2013\)](#), over 3 years, serious adverse events were reported by 8 women (0.6%) using the levonorgestrel 13.5 mg intrauterine delivery system. Three ectopic pregnancies and 2 cases of

pelvic inflammatory disease classed as serious adverse events occurred. There were no uterine perforations. The cumulative risk of at least partial expulsion of the levonorgestrel 13.5 mg intrauterine delivery system over 3 years was 4.56%.

Over 3 years, 21.9% of women using the levonorgestrel 13.5 mg intrauterine delivery system discontinued treatment because of adverse events: 1.0% discontinued treatment because of serious adverse events and 4.7% discontinued treatment for bleeding disturbances including amenorrhoea.

In [Gemzell-Danielsson et al. \(2012\)](#), over 3 years, 2 women in the levonorgestrel 13.5 mg group and 5 women in the levonorgestrel 52 mg group reported serious adverse events possibly related to study treatment. The only adverse event that occurred significantly more often in any treatment group was ovarian cysts (symptomatic and asymptomatic cysts more than 3 cm diameter: 5.9% in the 13.5 mg group compared with 22.0% in the 52 mg groups; $p < 0.0001$ for the 13.5 mg and 19.5 mg devices combined compared with the 52 mg device).

According to the [summary of product characteristics](#), the most common adverse effects of the levonorgestrel 13.5 mg intrauterine delivery system are headache, abdominal or pelvic pain, acne or seborrhoea, bleeding changes (increased or decreased menstrual bleeding, spotting, infrequent bleeding and amenorrhoea), ovarian cysts and vulvovaginitis with an incidence of 1 in 10 or more. Adverse effects with an incidence of between 1 in 100 and 1 in 10 are depressed mood or depression, migraine, nausea, alopecia, upper genital tract infection, dysmenorrhoea, breast pain or discomfort, device expulsion (complete or partial) and genital discharge.

Evidence strengths and limitations

The main limitation to the evidence for the levonorgestrel 13.5 mg intrauterine delivery system is the lack of comparisons with other contraceptives. [Nelson et al. \(2013\)](#) compared the levonorgestrel 13.5 mg intrauterine delivery system with a similar levonorgestrel 19.5 mg intrauterine delivery system that is not licensed or commercially available. There are no published phase III studies comparing the levonorgestrel 13.5 mg intrauterine delivery system with the established levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)).

The phase II study by [Gemzell-Danielsson et al. \(2012\)](#) included a levonorgestrel 52 mg arm and found that levonorgestrel 13.5 mg provided good contraceptive efficacy compared with the established device. However, this study was not sufficiently [statistically powered](#) to establish whether this device is non-inferior to the levonorgestrel 52 mg intrauterine delivery system.

There is no published evidence comparing the levonorgestrel 13.5 mg intrauterine delivery system with other methods of contraception. However, 2 studies are underway comparing this device with a combined oral contraceptive containing drospirenone and ethinylestradiol ([Yasmin](#); [NCT01254292](#)) and the progestogen-only subdermal implant ([Nexplanon](#); [NCT01397097](#)) respectively.

The phase III study by [Nelson et al. \(2013\)](#) was well designed, relatively large (n=2885) and analyses were by [intention-to-treat](#). The phase II study by [Gemzell-Danielsson et al. \(2012\)](#) was smaller (n=742) and analyses excluded 4 women in whom a levonorgestrel device could not be placed. It is unclear whether [allocation was concealed](#) in either study. Women were [blinded](#) to treatment allocation for the first 30 months in [Nelson et al. \(2013\)](#) and until the end of the study in [Gemzell-Danielsson et al. \(2012\)](#). However, it was not possible to blind investigators because of the different sizes of the intrauterine delivery systems. Lack of allocation concealment and blinding are potential sources of [bias](#). Bayer Healthcare provided funding for both of the studies.

In the 2 studies, as well as being unblinded, investigators' evaluations of ease of insertion were subjective (easy, slightly difficult or very difficult). In addition, administration of local anaesthetics or analgesics was at the clinicians' discretion and it is not known whether administration of these influenced the pain and ease of insertion. The inserter that was used for the levonorgestrel 52 mg intrauterine delivery system in [Gemzell-Danielsson et al. \(2012\)](#) was slightly wider than the inserter currently in use (4.75 mm compared with 4.4 mm [Bayer: personal communication, March 2014]), which limits the applicability of the results. It is unclear whether the pain scales used in the studies have been validated.

In [Nelson et al. \(2013\)](#), 27% of women did not complete the user satisfaction questionnaire and opinions among women who discontinued the study before the survey was introduced were not captured, which limits the generalisability of the results. Unblinding of treatment after 30 months may have introduced bias in women's responses to the questionnaire.

According to the [summary of product characteristics](#), the levonorgestrel 13.5 mg intrauterine delivery system has not been studied in women with hepatic or renal impairment. Similarly, safety and efficacy has not been confirmed in girls and young women aged under 18 years. However, a clinical study in this population is underway ([NCT01434160](#)).

Context

Alternative contraceptives

A wide range of contraceptives is available, including barrier methods, combined hormonal contraceptives, progestogen-only contraceptives (tablets, injections and implants), intrauterine methods and sterilisation. The Faculty of Sexual and Reproductive Healthcare (FSRH) has produced [clinical guidelines](#) on various methods of contraception (processes used to produce FSRH guidance have been [accredited by NICE](#)).

The NICE guideline on [Long-acting reversible contraception](#) offers best-practice advice for all women of reproductive age who may wish to regulate their fertility by using copper intrauterine devices, progestogen-only intrauterine systems ([Mirena](#)) and progestogen-only injectable contraceptives (intramuscular depot medroxyprogesterone acetate, [Depo-Provera](#) and norethisterone enantate, [Noristerat](#)). The progestogen-only subdermal implant, Implanon, recommended in the guideline is no longer available: it was replaced by [Nexplanon](#). A new formulation of depot medroxyprogesterone acetate for subcutaneous administration ([Sayana Press](#)) was discussed in [Evidence summary: new medicine 31](#).

Costs of alternative contraceptives

Table 2 Costs of long-acting reversible hormonal contraception methods

| | Usual dose and duration of action | Unit cost excluding VAT |
|--|---|------------------------------|
| Levonorgestrel intrauterine system (Jaydess) | 13.5 mg T-shaped intrauterine system for up to 3 years | £69.22 ^a |
| Levonorgestrel intrauterine system (Mirena) ^b | 52 mg T-shaped intrauterine system for up to 5 years | £88.00 ^a |
| Copper intrauterine devices | A range of devices is available for up to 5 or 10 years. The NICE guideline on Long-acting reversible contraception advises that devices with at least 380 mm ² copper and banded copper on the arms should be considered first-line | £7.95 to £27.11 ^c |

| | | |
|---|--|---------------------|
| Etonogestrel implant (Nexplanon) | 68 mg subdermal implant for up to 3 years | £79.46 ^a |
| Intramuscular depot medroxyprogesterone acetate (Depo-Provera) | 150 mg/ml intramuscular injection every 12 weeks (± 5 days) | £6.01 ^c |
| Subcutaneous depot medroxyprogesterone acetate (Sayana Press) | 104 mg/0.65 ml subcutaneous injection every 13 weeks (± 7 days) | £6.90 ^a |
| Norethisterone enantate (Noristerat) | 200 mg in 1 ml oily solution for intramuscular injection: may be repeated once after 8 weeks | £4.05 ^a |
| <p>^a Costs taken from MIMS, May 2014.</p> <p>^b In January 2014, a marketing authorisation was granted for a levonorgestrel intrauterine system (Tresovelle) that is <u>therapeutically equivalent</u> to Mirena. However, it is currently licensed only for heavy menstrual bleeding. It is also unclear whether it will be marketed in the UK.</p> <p>^c Costs taken from Drug Tariff, May 2014.</p> | | |

Estimated impact for the NHS

Likely place in practice

The NICE guideline on [Long-acting reversible contraception](#) advises that women requiring contraception should be given information about and offered a choice of all methods, including long-acting reversible contraception. The place in practice of the levonorgestrel 13.5 mg intrauterine delivery system ([Jaydess](#)) is likely to be as an alternative to other methods of long-acting reversible contraception, including the levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)).

There is insufficient evidence comparing the levonorgestrel 13.5 mg and 52 mg intrauterine delivery systems. [Gemzell-Danielsson et al. \(2012\)](#) included a levonorgestrel 52 mg arm and found that levonorgestrel 13.5 mg provided good contraceptive efficacy compared with the established device. However, this study was not sufficiently statistically powered to determine whether the levonorgestrel 13.5 mg intrauterine delivery system is non-inferior to the levonorgestrel 52 mg intrauterine delivery system. Also, it is unclear whether pain and ease of insertion were improved

with the levonorgestrel 13.5 mg delivery system compared with the levonorgestrel 52 mg delivery system because, for example, the investigators were not [blinded](#) and their evaluations of ease of insertion were subjective (easy, slightly difficult or very difficult). In addition, at that time the levonorgestrel 52 mg device had a 4.75 mm diameter insertion tube, whereas the current tube measures 4.4 mm diameter, which limits the applicability of the results.

[Nelson et al. \(2013\)](#) suggest that the levonorgestrel 13.5 mg intrauterine delivery system might appeal to women seeking a lower exposure to synthetic hormones (initially 14 micrograms per day compared with 20 micrograms per day with the levonorgestrel 52 mg intrauterine delivery system). They also state that this new device might be suitable for women with a narrower cervical canal, a smaller uterine cavity, or both, because it has a smaller reservoir and T frame (28 mm by 30 mm) and allows placement using a smaller tube (3.8 mm diameter) than the levonorgestrel 52 mg intrauterine delivery system (T frame 32 mm by 32 mm; tube 4.4 mm diameter). However, there is insufficient evidence to support these claims. The majority of women who used the levonorgestrel 13.5 mg intrauterine delivery system in the study were satisfied with their treatment and bleeding patterns but comparisons with the levonorgestrel 52 mg intrauterine delivery system are lacking.

Although [Nelson et al. \(2013\)](#) suggest that the small size of the levonorgestrel 13.5 mg intrauterine delivery system might make it suitable for use in nulliparous women and women who have never delivered vaginally, the [summary of product characteristics](#) states that it is not first-choice for contraception in nulliparous women because clinical experience is limited. Safety and efficacy of the levonorgestrel 13.5 mg intrauterine delivery system has not been confirmed in children and young women aged under 18 years. However, a clinical study in this population is underway ([NCT01434160](#)).

The [summary of product characteristics](#) states that the levonorgestrel 13.5 mg intrauterine delivery system is not recommended for treating heavy menstrual bleeding or protecting against endometrial hyperplasia during oestrogen replacement therapy. The levonorgestrel 52 mg intrauterine delivery system ([Mirena](#)) is licensed for these indications in the UK.

The levonorgestrel 13.5 mg intrauterine system costs £69.22 for up to 3 years' contraception compared with £88.00 for up to 5 years' contraception with the levonorgestrel 52 mg intrauterine system. See the [costs of alternative contraceptives section](#) for details of other long-acting reversible contraceptives.

There is no published evidence comparing the levonorgestrel 13.5 mg intrauterine delivery system with other methods of contraception. However, 2 studies are underway comparing this device with a combined oral contraceptive containing drospirenone and ethinylestradiol ([Yasmin](#);

[NCT01254292](#)) and the progestogen-only subdermal implant ([Nexplanon](#); [NCT01397097](#)) respectively.

Estimated usage

The manufacturer of the levonorgestrel 13.5 mg intrauterine delivery system estimates that the device will be used in approximately 1.5% of women seeking a prescription contraceptive after 1 year of availability (Bayer Healthcare: personal communication, February 2014).

Based on around 9.4 million women aged under 50 years using at least 1 method of contraception in 2008/09, this suggests that around 140,000 women may use the levonorgestrel 13.5 mg intrauterine delivery system after 1 year ([Office for National Statistics, Contraception and sexual health 2008–09](#)).

Relevance to NICE guidance programmes

The levonorgestrel 13.5 mg intrauterine delivery system was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

The NICE guideline on [Long-acting reversible contraception](#) (NICE clinical guideline 30) was published in 2005 and offers best-practice guidance on the use of copper intrauterine devices, progestogen-only intrauterine systems and progestogen-only injectable contraceptives. The progestogen-only subdermal implant, Implanon, recommended in the guideline is no longer available: it was replaced by Nexplanon. In the light of this change, NICE intends to review the evidence and update the appropriate section of the guideline.

References

Bayer plc (2014) [Jaydess summary of product characteristics](#) [online; accessed 2 April 2014]

Bayer plc (2013) [Mirena summary of product characteristics](#) [online; accessed 2 April 2014]

Gemzell-Danielsson K, Schellschmidt I, Apter D. (2012) [A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena](#). *Fertility & Sterility* 97: 616–22

Nelson A, Apter D, Hauck B et al. (2013) [Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial](#). *Obstetrics & Gynecology* 122: 1205–14

National Institute for Health and Clinical Excellence (2005) [Long-acting reversible contraception](#). NICE clinical guideline 30

Office for National Statistics (2009) [Opinions Survey Report No. 41 Contraception and Sexual Health, 2008-09](#) [online; accessed 5 March 2014]

Trussell J (2011) [Contraceptive failure in the United States](#). *Contraception* 83: 397–404

Development of this evidence summary

The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

Expert advisers

The [Clinical Effectiveness Unit](#) of the [Faculty of Sexual & Reproductive Healthcare](#).

Declarations of interest

No relevant interests declared.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

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