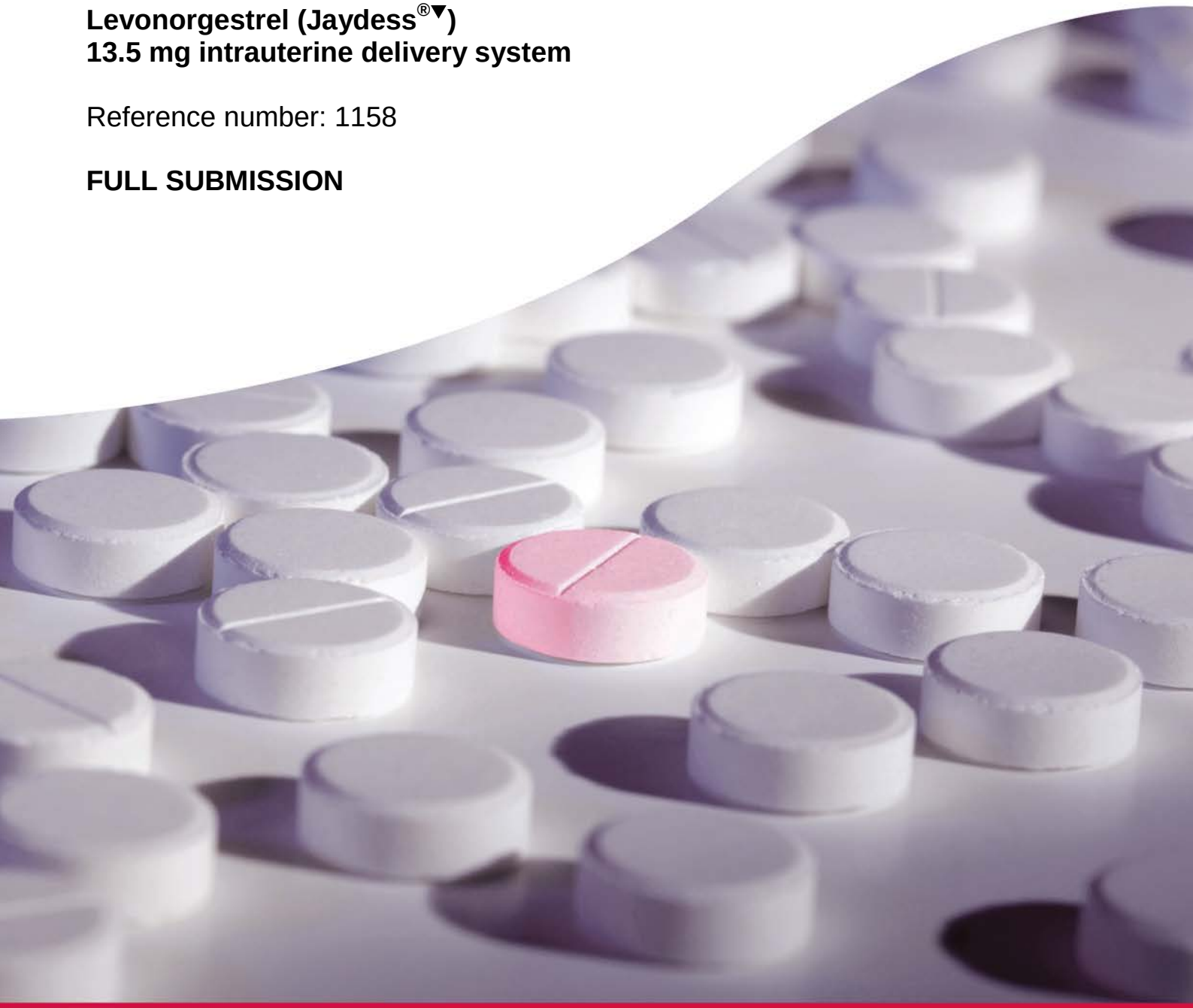
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Levonorgestrel (Jaydess®▼)
13.5 mg intrauterine delivery system

Reference number: 1158

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Levonorgestrel (Jaydess®▼) 13.5 mg intrauterine delivery system

This assessment report is based on evidence submitted by Bayer Healthcare Pharmaceuticals on 22 January 2015[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Levonorgestrel (Jaydess®▼) for contraception for up to three years[2].
Dosing	The delivery system contains 13.5 mg of levonorgestrel and is inserted into the uterine cavity, with an average release rate of 6 mcg/24 hours over three years. Refer to the SPC for further information regarding insertion and removal/replacement[2].
Marketing authorisation date	25 January 2013[2].
UK launch date	Levonorgestrel (Jaydess®▼) was launched on 11 April 2014[1].

2.0 DECISION CONTEXT

2.1 Background

It is estimated that about 30% of pregnancies are unplanned[3]. The effectiveness of the barrier method and oral contraceptive pills depends on their correct and consistent use[3]. By contrast, long-acting reversible contraceptive (LARC) methods (i.e. intrauterine devices [IUDs] and intrauterine systems [IUSs], injectable contraceptives and subdermal implants) do not depend on daily concordance[3]. The clinical guideline on LARCs developed by the National Institute for Health and Care Excellence (NICE) states that LARCs have a wider role in contraception and their increased uptake could help to reduce unintended pregnancy[1,3].

Jaydess®▼ is a levonorgestrel-containing IUS licensed for contraception for up to three years[2]. The company suggest in their submission that Jaydess®▼ provides a LARC option for all women, and may be an alternative for some women who have not yet found a product that suits them[1]. It has a smaller T-shaped intrauterine frame, a narrower insertion tube and contains less levonorgestrel released at a lower daily dose than the other available IUS in the UK which is Mirena®. The company claim that Jaydess®▼ may be less painful to insert, and better suited to the more rapidly changing plans of younger women or to women who wish to have some space between pregnancies[1].

2.2 Comparators

The applicant company claim to have included a mixed comparator consisting of all reversible Welsh contraceptive options (including prescribed, over the counter and other methods), weighted by current level of use (i.e. market share), however, no published data has been submitted to support this claim. The company have included

the following comparators (in abstract form) in the clinical effectiveness evidence as supportive data:

- Ethinylestradiol/drospirenone (Yasmin®) - film-coated oral tablet
- Etonogestrel (Nexplanon®) - implant for subdermal use

The alternative IUS currently available in the UK (i.e. Mirena®) was not considered by the company to be an appropriate comparator for this submission.

See section 3.4 for further information.

2.3 Guidance and related advice

- NICE. Long-acting reversible contraception (update). Clinical Guideline (CG) 30 (2014)[3].
- The Faculty of Sexual and Reproductive Healthcare (FSRH) of the Royal College of Obstetricians and Gynaecologists. Service standards for sexual and reproductive healthcare (2013)[4].
- The FSRH of the Royal College of Obstetricians and Gynaecologists. CG intrauterine contraception (2015)[5].
- The All Wales Medicines Strategy Group. All Wales Prescribing Guidelines: initiating contraception in primary care (2012)[6].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission includes details of one phase II clinical study and one phase III clinical study[1]. The aim of the former was to select an appropriate and effective dose for the phase III testing and was not powered to accurately characterise the primary endpoint: this study will therefore, not be discussed further. Details and results of the phase III pivotal study (A52238) are presented below. In the absence of any head to head trials, the company also include supportive data from three further studies provided in abstract form. Two of these studies are ongoing, and therefore since no definite conclusions can be drawn these will not be discussed further.

3.1. Phase III study: A52238

This was a multicentre, open-label, randomised, parallel-group study assessing the safety, efficacy and pharmacokinetics of two doses of a levonorgestrel IUS (13.5 mg [Jaydess®▼] and 19.5 mg total content) for up to three years[1,7]. The larger dose of 19.5 mg is not licensed in the UK and therefore will not be discussed further.

Participants in the 13.5 mg arm were a mix of healthy, nulliparous and parous women desiring contraception, aged 18 to 35 years old (n = 1432)[1,7].

The primary endpoint was pregnancy rate, expressed as a Pearl Index (PI: see Glossary)[1,7]. Secondary endpoints included bleeding profile and discontinuation rate.

The year one PI was 0.41 and the three-year PI was 0.33[1,7]. The exposure times were similar, because there were few (partial) expulsions in the study. No pattern in the pregnancy rates over time was observed. Five, three and two pregnancies occurred in years one, two and three, respectively. The PI 95% confidence intervals (CIs) for individual years overlapped, indicating a consistent contraceptive effect for the whole treatment period of three years. The cumulative failure rate for Jaydess®▼ (i.e. the probability of getting pregnant) was 0.4% for year one and approximately 0.9% for three years. No difference in failure rate over time was observed[1,7]. See Table 1 for PI results and cumulative failure rates.

Table 1. PIs and cumulative failure rates for Jaydess®▼ in the phase III study[1,7].

Time	Total exposure (WY)	Relevant exposure* (WY)	Number of pregnancies	PI/Cumulative probability of getting pregnant	95% CI
Unadjusted PI					
Year 1	1,280	1,218	5	0.41	0.13–0.96
Year 2	1,057	1,016	3	0.30	0.06–0.86
Year 3	870	825	2	0.24	0.03–0.88
¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
3 Years	3,208	3,059	10	0.33	0.16–0.60
Unadjusted Kaplan-Meier estimated cumulative failure rates					
Year 1	¶¶	¶¶	¶¶	0.004	¶¶
Year 2	¶¶	¶¶	¶¶	0.003	¶¶
Year 3	¶¶	¶¶	¶¶	0.002	¶¶
¶¶	¶¶	¶¶	¶¶	¶¶	¶¶
3 Years	¶¶	¶¶	¶¶	0.009	¶¶

*Relevant exposure was calculated from the total exposure minus the time in which backup contraception was used or sex hormones were taken for other reasons.
¶¶Commercial in confidence data removed.
CI: confidence interval; PI: Pearl Index (see Glossary); WY: women-years (1 WY = 365 days).

Note: the requirement of the EMA guidance, that the difference between the point estimate for the PI and the upper limit of the 2-sided 95% CI should not exceed 1, is met for the PIs for all time intervals considered for Jaydess®▼[8].

The three year unadjusted PI was also presented by subgroup: parity, age-group and body mass index (BMI), as well as for ectopic pregnancies only[1,7]. No difference in PI between subgroups was observed. Similarly, cumulative failure rates calculated by subgroup were similar to those for the total population[1,7].

[Commercial in confidence data removed]. There were more spotting days than bleeding days in all reference periods. Based on a user satisfaction questionnaire to assess tolerability outcomes, more than 75% were very satisfied or somewhat satisfied with the bleeding changes experienced compared to pre-treatment. Discontinuation rates, owing to change in menstrual bleeding pattern (including amenorrhoea), was low (4.7%)[1,7].

3.2 Supportive data

Study NCT01254292 is a phase III, multicentre, open-label, randomised, two-arm, parallel-group study which has been completed, and involves 567 women. The study compares user satisfaction and tolerability with use of Jaydess®▼ and an ethinylestradiol/drospirenone combined oral contraceptive (Yasmin®) over 18 months[1,9]. Both treatment groups were associated with high user satisfaction and were well tolerated. In the Jaydess®▼ and Yasmin® groups, respectively, 91.3% and 92.8% of women rated administration of study treatment as ‘acceptable with or without some inconvenience/discomfort’; 63.1% and 70.0% reported that they were ‘very satisfied’ or ‘somewhat satisfied’ with their bleeding pattern; and 66.2% and 48.8% reported that, given the choice, they would continue with the study treatment after study completion[1,9].

3.3 Comparative Safety

Safety data is based on the population (n = 1432) from the phase III study (A52238)[1,7]. Ovarian cysts were the most common adverse events (AEs) reported (13.0%), followed by acne (11.4%), urinary tract infection (11.0%), headache (9.3%) and dysmenorrhoea (9.1%). A total of three pregnancies observed under treatment were ectopic: no pattern in the ectopic pregnancy rates over time was observed. Treatment-related AEs were similar to those that are known to occur with the use of other IUSs and did not raise

any new safety concerns. Results from subgroup analysis reflected findings in the study population taken as a whole[1,7].

3.4 AWTTC critique

- The applicant company suggest in their submission that Jaydess®▼ provides a LARC option for all women, and may be an alternative for some women who have not yet found a product that suits them[1]. It is not clear therefore why Mirena®, as the only other alternative IUS currently available in the UK, would not also be considered a comparator. The applicant company argue that they expect Jaydess®▼ to be used in a different set of women and consequently any displacement of Mirena® is expected to be the exception, and the reason why it is not considered as a relevant comparator.
- The applicant company considers the most appropriate comparator for Jaydess®▼ to be a mixed contraceptive comparator consisting of all Welsh reversible contraceptive options[1]. The company sought clinical expert opinion in Wales and Scotland on this approach. 75% of experts (n = 9) that responded, supported the approach to use the mixed contraceptive comparator[1]. However no evidence has been submitted to support this claim.
- Although the Committee For Medicinal Products For Human Use (CHMP) accept that studies including an active comparator are not generally requested for efficacy purposes, information on other adverse events (including vaginal bleeding events),normally require comparative evidence[8]. The company have included only a combined oral contraceptive (ethinylestradiol/drospirenone [Yasmin®]) and a subdermal progestogen implant etonogestrel (Nexplanon®) as supporting evidence in abstract form with some studies ongoing. There is therefore a limited amount of comparative clinical effectiveness data provided in the submission with regards to the use of other contraceptive methods.
- The clinical effectiveness evidence presented is therefore not clearly reflected in the health economic analyses below.
- Almost one third of women did not complete the user satisfaction questionnaire undertaken at the 'end of study' visit from the phase III trial and women who discontinued before the questionnaire was introduced were not included. As treatment allocation was disclosed to women at 30 months (visit 9), the introduction of bias regarding questionnaire responses cannot be excluded[10].
- The applicant company have highlighted an 'unmet' need in younger women aged 21-29 years with uptake of LARCs such as Mirena® being low (1.6%) over a 12-month period[1].
- A general disadvantage associated with using intrauterine contraception is the need for trained fitters. However, those already trained to fit Mirena® or copper coils are qualified to fit Jaydess®▼[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission includes a cost-effectiveness analysis (CEA) of the three-year acting contraceptive levonorgestrel (13.5 mg) IUS with an average release rate of 6 mcg/24 hours[1]. The applicant company claim the system is compared against a mixed contraceptive comparator consisting of all reversible Welsh contraceptive options (including prescribed short- and long-acting contraceptives, over the counter, barrier methods as well as no contraception) which were weighted by level of use (i.e. market share).

The Markov model used to estimate cost-effectiveness follows a cohort of 1,000 women of reproductive age (15-44 years) who are at risk of pregnancy and seek reversible methods of contraception over a time horizon of three years in one-year

cycles. Three health states are included in the model: initial contraceptive method, subsequent contraceptive method and unintended pregnancy.

Cost-effectiveness is measured in terms of incremental cost per unintended pregnancy avoided and incremental net monetary benefit (INMB).

The base case analysis of the CEA considers the costs of contraceptive method acquisition, administration and method failure. Acquisition costs were taken from the Monthly Index of Medical Specialities (MIMS; August 2014)[11]. Cost of contraceptive administration (where applicable) included initial consultation, insertion and removal for long-acting reversible contraceptives, and follow-up consultations for short-acting and long-acting reversible contraceptives. Unit costs were from published sources[12]. Cost of unintended pregnancy (method failure) was taken from NHS reference costs[13] and included the cost of births, induced and spontaneous abortion and ectopic pregnancy, weighted based on UK birth summary tables and abortion statistics[14–16]. The costs of managing AEs other than contraceptive failure were not included. All costs were weighted for the mixed comparator according to market share and costs and outcomes were discounted at 3.5% after year one.

Clinical data included in the model comprised contraceptive method failure rate and discontinuation rate which were taken from USA real-world effectiveness data published by Trussell et al (2011)[17] for the mixed contraceptive comparator and trial-based data for levonorgestrel IUS (Jaydess®▼)[7].

A range of one-way sensitivity analyses were conducted to address uncertainty in parameters, available data and assumptions. Furthermore, results of probabilistic sensitivity analyses were presented as cost-effectiveness acceptability curves and scatterplots and a scenario analysis to extend the model time horizon to six years.

4.1.2 Results

The results of the base case analysis are presented in Table 2. The company reports that the mixed comparator was £963,913 more costly and resulted in 377 more unintended pregnancies compared to levonorgestrel over the model horizon of three years, making levonorgestrel IUS the dominant treatment.

Table 2. Summary of base case results.

	Levonorgestrel IUS (Jaydess®▼)	Comparator	Increment
Total Cost (£)	£586,654	£1,550,567	−£963,913
Cost of treatment acquisition (initial method)	£69,220	£18,088	£51,132
Cost of med. resource (initial method)	£284,559	£128,607	£155,952
Cost of treatment acquisition and med. resource (subsequent method)	£20,317	£66,618	−£46,302
Cost of failure (initial method)	£25,172	£849,664	−£824,492
Cost of failure (subsequent method)	£187,387	£487,591	−£300,204
Total Event (n)	71	448	−377
Number of failure events (initial method)	8	285	−276
Number of failure events (subsequent method)	63	163	−101
ICER	Dominant		
INMB	£1,240		
The incremental net monetary benefit (INMB) was calculated by assigning a monetary value (willingness to pay of £732 which equals the cost of an abortion) to the units of effectiveness generated. A positive INMB indicates cost-effectiveness as the monetary value of the incremental effectiveness gained exceeds to incremental cost of achieving it. ICER: Incremental Cost-Effectiveness Ratio; INMB: Incremental Net Monetary Benefit; IUS: Intrauterine System.			

Changes in input parameters did not significantly change the results of the analysis in the one-way sensitivity analysis and cost-effectiveness was preserved when inputs were varied within plausible ranges. The results were most sensitive to the failure rates of the second largest weight within the mixed contraceptive comparator (barrier methods). Levonorgestrel IUS (Jaydess®▼) was found to be dominant throughout the probabilistic sensitivity analysis simulations and after doubling the time horizon, with a probability of being cost-effective of 100%.

4.1.3 AWTTC critique

The company's analysis states that levonorgestrel IUS (Jaydess®▼) dominates the mixed contraceptive comparator with a probability of being cost-effective of 100%. However, this dominance relies mainly on the choice of the comparator which is based on a UK opinion survey done by the Office of National Statistics during 2008/09[18] and the method failure data used to populate the model which is largely based on USA data from 1995 and 2002 surveys[17].

Strengths and limitations with the economic analysis are as follows:

- The composition and weighting of the mixed contraceptive comparator is based on 2008/09 UK data and the validity and applicability of this treatment mixture to Wales in 2015 is uncertain. The company argues that they would not expect contraception options to differ significantly between 2009 and 2015 as oral contraception was the most prescribed method in the UK in 2014.
- While the mixed comparator includes IUS options, the analysis does not include Mirena® or other long-acting contraception options as separate comparators. The company states that levonorgestrel IUS (Jaydess®▼) is targeted at women who would not otherwise use Mirena® as it is easier to insert and has a smaller T-shaped intrauterine frame and can be used regardless of age and parity. According to the applicant company, this will result in a different target population making Mirena® an inappropriate comparator. However, the comparison of a single treatment to a weighted mixture of treatments with different properties (such as failure rates) might introduce bias.

- The mixed comparator includes “no contraception method” to reflect all choices available to women. This could overestimate the number of unintended pregnancies for the comparator. However, the company states that after re-weighting the mixed comparator without the “no contraception” option and re-calculating the results, levonorgestrel remained dominant in all analyses.
- Most of the key parameters are informed by the Trussell et al (2011)[17] study. Data reported in this study are based on real-world data collected during 1995 and 2002 surveys done in the USA. While the company states that no real-world UK or Wales data was available and the Trussell study provided the most complete and robust data identified in a systematic review of the literature, it is questionable how transferable this data is to the 2015 Welsh population which could introduce considerable uncertainty or potential bias to the results. The analysis directly compares real-life failure and discontinuation data for the mixed comparator to trial-based data for levonorgestrel IUS (Jaydess®▼). This is justified by the company on the basis that for Mirena®, trial-based and real-world reported data were found to be identical[17,19]. However, there is no comparable supportive evidence for levonorgestrel IUS (Jaydess®▼) which limits the confidence in this assumption.
- The model calculates cost-effectiveness over a three year time horizon with one-year cycles. It is not clear why the company has chosen such a long cycle length considering the short time horizon. Especially, since the duration of an unintended pregnancy was estimated to be around eight months on average, it appears that the one-year cycle length could introduce bias. The company argues that the cost applied in the unintended pregnancy state is reflective of the actual cost associated with pregnancy irrespective of the length of time.
- The company presents results as incremental cost per unintended pregnancy avoided instead of using quality adjusted life years (QALYs). They argue that a QALY might not be the most appropriate measure for contraception and use a willingness to pay threshold of £732 (cost of induced abortion) to establish cost-effectiveness. In the absence of QALYs, it would be more problematic to interpret the results if levonorgestrel IUS (Jaydess®▼) were more effective and more costly compared to the mixed contraceptives. While the company’s analysis states that levonorgestrel IUS (Jaydess®▼) dominates the comparator, the large uncertainty in the applicability of the data could shift the results to a different quadrant of the cost-effectiveness plane (e.g. levonorgestrel IUS (Jaydess®▼) more effective and more costly). The company states that quality of life might not be an appropriate outcome measure for contraception and could be controversial. However, the same might apply to measuring cost-effectiveness as number of unintended pregnancies avoided with a cost-effectiveness threshold of the cost of an abortion considering that not every unintended pregnancy will result in an abortion.
- The CEA does not take into account any adverse reactions which may be higher for intrauterine systems or devices compared to oral or barrier methods. While the company argues the adverse events (such as modified bleeding patterns) are insubstantial compared to pregnancy events, the analysis may overstate the cost-effectiveness of levonorgestrel IUS (Jaydess®▼), particularly as the outcome does not capture any impacts on women’s health-related quality of life (HRQoL).

Overall, while levonorgestrel IUS (Jaydess®▼) remains dominant in all sensitivity analyses with a 100% probability of being cost-effective compared to mixed contraceptives, there are considerable limitations of the economic model and choice of comparator and uncertainty surrounding the appropriateness of the data inputs.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Prevalence was defined according to women being of reproductive age (ages 16 to 45 years) at risk of pregnancy and requiring contraception. Based on the 2014 Welsh population size[20] and an estimation of women requiring contraception based on 2008/09 UK data[18], prevalence was estimated to be 334,526 women. The percentage of population at risk was kept constant throughout the modelling, hence, incidence was not considered. The company estimates that uptake will be 0.3% in year one, increasing to 2.34% in year five. This translates into 1,004 women receiving levonorgestrel IUS (Jaydess®▼) in year one increasing to 7,828 women by year five. The year five uptake rate is based on the current market share of Mirena®. The budget impact analysis takes into account discontinuation rate and the cost of subsequent contraceptive method.

Deterministic one-way sensitivity analyses and scenario analyses were conducted by varying the discontinuation rate, uptake, mixed comparator composition and excluding cost of subsequent contraceptives.

5.1.2 Results

The estimated net budget impact is presented in Table 3. The company's analysis estimates the net cost implications to be £154,005 in year one increasing to £527,479 in year five.

Table 3. Company-reported costs associated with use of levonorgestrel intrauterine system.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication[s] covered in this submission)	334,526	334,526	334,526	334,526	334,526
Uptake (%)	0.30%	0.81%	1.32%	1.83%	2.34%
Treated patients	1,004	2,710	4,416	6,122	7,828
Net costs*					
Acquisition costs	£51,946	£81,096	£72,410	£106,375	£133,982
Medical Resource use (primary care)	£102,060	£188,743	£221,140	£310,075	£393,497
Overall net cost	£154,005	£269,839	£293,550	£416,450	£527,479
* Overlap among items will mean that overall net costs may not necessarily equal their sum.					

Sensitivity analyses suggest that there is relatively little variation in net budget impact when key parameters are changed within reasonable limits. Year five net costs range from £475,073 to £685,723 and decrease to £335,202 if subsequent contraception method costs are not included.

5.1.3 AWTTC critique

There are a few limitations to this analysis:

- The estimates of net costs are dependent on the estimates of patient uptake rates. The company bases the uptake rate in year five on the current uptake of Mirena®. Considering that the company states in its cost-effectiveness analysis that levonorgestrel IUS (Jaydess®▼) is expected to be used in an entirely different set of women compared to Mirena®, it is unclear why this uptake rate was chosen and how appropriate and realistic this uptake rate is. The company argues that uptake rates are estimates and that the market share of Mirena® is likely to be the most realistic estimate available.

- The percentage of the population at risk is kept constant and population growth is not considered which might underestimate the net budget impact of levonorgestrel IUS (Jaydess®▼).

5.2 Comparative unit costs

Approximate acquisition costs for comparator long-acting reversible contraceptives (hormone and non-hormonal contraception) is given in Table 4.

Table 4. Examples of medicine acquisition costs for long-acting reversible contraceptives.

Regimens	Doses and treatment schedules	Approximate annual costs per patient
Hormonal long-acting reversible contraceptives (parental progestogen-only contraceptives)		
Medroxyprogesterone acetate (Depo-Provera®)	Regimen administered within five days of a normal menstrual cycle and at 12 weekly intervals. • 150 mg/ml intra-muscular injection	£26.04 (£6.01 per injection)
Medroxyprogesterone acetate (Sayana-Press®)	Regimen administered within five days of a normal menstrual cycle and at 13 weekly intervals • 104 mg/0.65 ml subcutaneous injection	£27.60 (£6.90 per injection)
Etonogestrel-releasing implant (Nexplanon®)	Subdermal implant effective for three years as a contraceptive • 68 mg implant for subdermal use	£27.81 (£83.43 per implant)
Hormonal long-acting reversible contraceptives (intrauterine progestogen system)		
Levonorgestrel (Jaydess®▼)	Effective for three years as a contraceptive • 13.5 mg intrauterine delivery system	£23.07 (£69.22 per system)
Levonorgestrel (Mirena®)	Effective for five years as a contraceptive • Levonorgestrel 52 mg releasing 20 mcg/24 hours intrauterine delivery system	£17.06 (£88 per system)
Non-Hormonal long-acting reversible contraceptives (intrauterine contraceptives)		
Cu-Safe T300®	Intrauterine device Replacement every five years	£1.82 (£9.11 per device)
Flexi-T® 300	Intrauterine device Replacement every five years	£1.89 (£9.47 per device)
GyneFix®	Intrauterine device Replacement every five years	£5.42 (£27.11 per device)
Load® 375	Intrauterine device Replacement every five years	£1.70 (£8.52 per device)
Multi-Safe® 375	Intrauterine device Replacement every five years	£1.79 (£8.96 per device)
Neo-Safe® T380	Intrauterine device Replacement every five years	£2.66 (£13.31 per device)
T-Safe® Quickload	Intrauterine device – quick loading system Replacement every 10 years	£1.03 (£10.29 per quick loading device)
T-Safe® 380A	Intrauterine device with a capsule loading device Replacement every 10 years	£1.05 (£10.47 per capsule loading device)
TT 380® Slimline	Intrauterine device Replacement every 10 years	£1.25 (£12.46 per device)
UT 380 Standard®	Intrauterine device Replacement every 5 years	£2.24 (£11.22 per device)

Note: not all regimens may be licensed for use in this patient population. See relevant Summaries of Product Characteristics for full licensed indications and dosing details[2,19,21–23].
Costs are based on Drug Tariff[24] and British National Formulary (BNF) prices as of February 2015[25].
Costs of administration are not included.
This table does not imply therapeutic equivalence of drug regimens or the stated doses.
Costs of failure or serious adverse events/adverse events are not included.
The licensed duration of long-acting reversible contraceptives were taken from the BNF from either the note on removal, effectiveness or replacement.
For Depo-Provera® the benefits of using beyond two years should be evaluated against risks.
Data on the recommended duration for Sayana-Press® could not be found.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, levonorgestrel (Jaydess®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration. There is no special Jaydess®▼ training, all those trained to Faculty of Sexual and Reproductive Healthcare (FSRH) standards can fit Jaydess®▼[1,2].

6.2 Ongoing studies

The company submission highlighted ongoing studies from which data will likely be available within 6–12 months:

- NCT00884260: an Asia-Pacific, phase III study assessing the efficacy, safety and bleeding pattern of Jaydess®▼ for a maximum of 3 years in women aged 18 to 40 years. Study completed June 2013[26].
- NCT01254292: a phase III study evaluating user satisfaction with and tolerability of the Jaydess®▼ in comparison to a combined oral contraceptive containing 30 mcg ethinylestradiol and 3 mg drospirenone (Yasmin®) over 18 months in women aged 18 to 29 years. Study completed May 2014[9]. See section 3.2 for details.
- NCT01397097: a phase III study evaluating the discontinuation rates, bleeding patterns, user satisfaction and adverse event profile of Jaydess®▼ in comparison to etonogestrel subdermal implant (Nexplanon®) over 12 months in women aged 18 to 35 years. Estimated completion, May 2015[27]. See section 3.2 for details.
- NCT01434160: a phase III study assessing the safety, efficacy, discontinuation rate and pharmacokinetics of Jaydess®▼ in post-menarcheal female adolescents under 18 years of age for one year, and an optional two year extension phase. Estimated completion date, June 2015[28].

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 23 and 26 January 2015.
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Pearl Index (PI)[1]

The primary outcome was the pregnancy rate, expressed as a pearl index (PI), the number of pregnancies per 100 woman-years e.g. 'first year PI' = number of pregnancies that occurred during the first year of treatment divided by time the women were at risk of getting pregnant in the first year of treatment; 'second year PI' = number of pregnancies that occurred during the second year of treatment divided by time the women were at risk of getting pregnant in the second year of treatment; 'Two year PI' = number of pregnancies that occurred during the first two years of treatment divided by time the women were at risk of getting pregnant in the first two years of treatment.

Vaginal bleeding[1]

Bleeding patterns were analysed in days and in episodes, using 90-day (over the three years) and 30-day (over the first year) reference periods, with the first reference period starting on the day of insertion. Bleeding was assessed from patients' daily records of bleeding patterns according to World Health Organisation (WHO) criteria (i.e. no bleeding, spotting, light, normal, or heavy). Amenorrhoea was defined as no bleeding/spotting throughout the reference period. Infrequent bleeding was defined as one or two bleeding/spotting episodes. Frequent bleeding was defined as more than five bleeding/spotting episodes. Prolonged bleeding was defined as bleeding/spotting episodes lasting more than 14 days. Women with prolonged bleeding may also be included in one of the other categories (excluding amenorrhoea).

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