Australian Public Assessment Report for levonorgestrel

Proprietary Product Name: Jaydess (intrauterine delivery system)

Sponsor: Bayer Australia Ltd

February 2014
About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.

- The TGA administers the Therapeutic Goods Act 1989 (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

- AusPARs are prepared and published by the TGA.

- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.
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## I. Introduction to product submission

### Submission details

- **Type of submission:** Major variation: new strength, new indication, modified delivery system
- **Decision:** Approved
- **Date of decision:** 10 September 2013
- **Active ingredient:** Levonorgestrel
- **Product name:** Jaydess
- **Sponsor's name and address:** Bayer Australia Ltd
  875 Pacific Highway
  Pymble NSW 2073
- **Dose form:** Intrauterine drug delivery system
- **Strength:** 13.5 mg
- **Container:** Sachet
- **Pack size:** 1 x intrauterine drug delivery system and insertion device.
- **Approved therapeutic use:** Contraception for up to 3 years.
- **Route of administration:** Intrauterine
- **Dosage (abbreviated):** Jaydess is inserted into the uterine cavity and is effective for up to three years.
- **ARTG number:** 200456

### Product background

Levonorgestrel is a progestin from the 19-nortestosterone class and is used as the progestin component in oral contraceptives, in hormonal replacement therapy, subdermal implants and intrauterine delivery systems (IUS).

Mirena IUS containing 52 mg levonorgestrel has been registered by Bayer Australia Ltd (the sponsor) since July 2000 and is currently approved for: Contraception. Treatment of idiopathic menorrhagia. Prevention of endometrial hyperplasia during oestrogen replacement therapy. This AusPAR describes the application by Bayer Australia Ltd to register a lower dose form of Mirena, under the product name Jaydess, containing 13.5 mg of levonorgestrel in a delivery system that is smaller in size (smaller insertion tube...
diameter and T-frame) compared with the Mirena IUS. Jaydess is proposed for the following indication:

**Contraception**

Jaydess is proposed to provide contraceptive protection over a period of up to three years compared with up to 5 years with Mirena. The sponsor initially proposed to register Jaydess for *contraception for up to 3 years* but later amended the proposed indication to *contraception* for consistency with that approved for Mirena.

**Regulatory status**

Jaydess received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 18 September 2013. The higher strength product (Mirena, containing 52 mg levonorgestrel) was registered on the ARTG in July 2000.

At the time TGA considered this application, a similar application had been approved in the US (January 2013), Sweden (January 2013), UK (January 2013), Netherlands (March 2013) and Canada (June 2013).

**Product Information**

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

**II. Quality findings**

**Drug substance (active ingredient)**

Levonorgestrel (structure shown below) is a second generation synthetic progesterone containing 5 chiral centres that is produced as a single stereoisomer. It is a white to almost white crystalline powder that is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in ethanol. There is no evidence that the substance exists in different polymorphic forms.

![Figure 1. Structure of levonorgestrel](image)

It is manufactured at the same site as the drug substance used for the approved Mirena product and an assurance was provided that all aspects pertaining to the drug substance manufacture are unchanged from those approved for the Mirena product. The manufacture and quality control according to the relevant British Pharmacopoeia (BP) monograph (European Pharmacopoeia (Ph Eur) 0926) have been assessed by the European Directorate for the Quality of Medicines and a Certificate of Suitability has been issued.
Drug product

The IUS delivery system (illustrated below) comprises a whitish or pale yellow drug reservoir mounted on a vertical stem of a T-shaped low density polyethylene frame (T-body). The T-body has two arms at the upper end and a loop at the other end. A silver ring is attached to the upper part of the vertical stem of the T-body to facilitate ultrasound detection. A removal thread is attached to the loop at the end of the vertical stem of the T-body. The IUS is inserted into the uterus with a preloaded ready-to-use integrated inserter device. The drug reservoir consists of a core containing levonorgestrel.

Figure 2. Schematic illustration of the delivery system

![Image of delivery system]

Figure 3. Schematic illustration of the integrated inserter

![Image of inserter]

The finished product is terminally sterilised and is then packaged in a thermoformed blister. Sterility aspects of the product have been assessed and found to be acceptable. The quality of the product is controlled by a specification that includes appropriate limits for the identity, assay and uniformity of dosage of the drug substance as well as limits for drug substance related impurities. Adequate method details and validation data were provided for all of the proposed tests in the drug product specification.

Controls are also included for the quality of the intrauterine device, including its appearance, breaking force, recovery of the horizontal arms as well as sealed joint strength and packaging seal integrity tests. The Biomaterials and Engineering Section of the TGA has reviewed this application and concluded that a device evaluation is not required.

A key test in the drug product specification is the in-vitro release rate. The long term in-vitro release rate was also studied, over a period of 3 years in Phase III studies.

Stability data were provided to support the proposed shelf life of 24 months at 30°C, when the product is stored in the proposed packaging system and protected from light. At this stage, both the PI and the labels require the addition of a ‘protect from light’ statement prior to approval.
**Biopharmaceutics**

The company has justified not supplying biopharmaceutic data for the proposed product largely on the basis that it is mainly locally acting with a low (< 121 ng/mL) concentration of levonorgestrel in serum.

A level A in vitro-in-vivo correlation was developed using in vitro levonorgestrel release data and ex vivo residual content data from women in Phase II clinical trials who discontinued the trials prematurely (Study 57411). The IVIVC model was developed by plotting the calculated cumulative percentages of levonorgestrel released in vivo (obtained from the measured residual levonorgestrel content data from ex vivo IUSs in Phase II) against the measured cumulative percentages released from in vitro release rate samples at the same time points for the two dose variants.

A quantitative point-to-point relationship between the calculated in vivo and measured in vitro release data was obtained by least square regression analysis (Level A correlation). The regression analysis resulted in a linear relationship which fitted the data appropriately. Acceptable internal and external validation data were provided (Study 57262).

**Advisory committee considerations**

This submission was not required to go to Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

**Quality summary and conclusions**

A device evaluation was not required as advised by the Biomaterials and Engineering section of TGA upon reviewing the data for this application. In addition, the changes to the applicator (inserter) do not require a device evaluation because it meets the essential principles of a class 1 device.

All issues raised in the TGA request for further information relating to the quality aspects (chemistry and in vitro-in vivo correlation) of the proposed product have been adequately addressed, and approval can be recommended from chemistry and quality control perspective, once the following outstanding issues are adequately resolved:

- The PI and labels require the addition of a “protect from light” statement prior to approval, and
- The approach of not including the drug substance release rate on the sachet label (in contrast to Mirena which has this inclusion) is unresolved, due to the different release rate at different periods for this product, but this has been referred to the clinical unit for comment.

Approval of the proposed product is recommended from a sterility perspective.

The leachables aspect of the product was reviewed by the TGA toxicology section as a non-clinical evaluation.
III. Nonclinical findings

Toxicity

Levonorgestrel

The toxicological profile of levonorgestrel is well characterised and no additional nonclinical studies conducted with levonorgestrel alone were submitted. The average dose of levonorgestrel delivered by this product (6 μg/day over 3 years) is less than that with Mirena (14 μg/day over 5 years). In vitro experiments revealed an initial burst of drug release (mean, 25 μg/day; maximum, 55 μg/day) that is higher than that for Mirena (20 μg/day). This burst quickly declines, and it does not translate to a higher peak serum concentration of levonorgestrel in patients (maximum concentration (C_max) of 171 pg/mL with Jaydess in the Phase III clinical Study A52238 compared with a serum level of 206 pg/mL at 6 months reported in the PI for Mirena).

Device materials

The materials used in the composition of Jaydess differ slightly from those in Mirena: the new product incorporates a silver ring/profile (to facilitate detection in ultrasound examination) and the inserter device uses a new coloured flange (pink).

The biocompatibility of the silver ring/profile was assessed in vitro in assays for cytotoxicity, haemolysis and genotoxicity and in vivo in studies on acute toxicity, local tolerance and skin sensitisation that used extracts of the material. Additional studies involved assessment of local tolerance in rabbits following intramuscular implantation of silver rods used in the manufacture of the ring, and of local and systemic tolerance in monkeys following intrauterine implantation of an IUS with silver ring attached. All safety-related studies were compliant with Good Laboratory Principles (GLP).

Extracts of the silver ring were found not to be genotoxic in assays for bacterial and mammalian mutagenicity, induce haemolysis in human erythrocytes, exert acute toxicity following intraperitoneal (IP) or intravenous (IV) administration in mice, cause any notable local reaction following intracutaneous injection in rabbits, or have skin sensitisation potential in guinea pigs. The silver rods were found to be non-irritating following intramuscular implantation in rabbits. Slight cytotoxicity was observed with undiluted extract of silver plus polycarbonate-based thermoplastic polyurethane (PCU) using a 24 h extraction period (as recommended in ISO 10993-5); however, greater cytotoxicity was evident with PCU without silver. Clear cytotoxicity was seen with 70% or 100% dilutions using longer extraction times (72 h and 28 days). The highest strength of extract that was without cytotoxicity was a 30% dilution, found to contain 1186 μg/L silver; 70% and 100% dilutions contained 2695–4066 μg/L silver. Cumulative in vitro release of silver ions from the clinical device was found to be 1.65 μg after 28 days; as such, cytotoxic concentrations should not be reached in clinical use. In keeping with this, no adverse local or systemic effects attributable to the presence of the silver ring were observed in 13 week and 9 month studies in cynomolgus monkeys using implanted size-adapted IUS devices (with or without levonorgestrel). These studies did not use implants with the same polymer composition as to be used in Jaydess but the studies are adequate to address safety concerns with respect to the silver ring.

Like Mirena, the drug core of Jaydess is composed of a mixture of levonorgestrel and poly(dimethylsiloxane), although at a different ratio. Biocompatibility of this new strength of material was demonstrated in studies examining cytotoxicity, genotoxicity (bacterial mutagenicity), haemolysis, acute toxicity (IP and IV administration in mice), pyrogenicity
(rabbit), local tolerance (intracutaneous in rabbit) and skin sensitisation potential (guinea pig).

The flange used in the Jaydess inserter differs from that used in Mirena only in the colourant used. The duration of patient exposure to this material is minimal, and extracts of the material were not found to be cytotoxic or cause skin sensitisation, and to be well tolerated locally following intracutaneous injection in rabbits.

**Pregnancy classification**

The sponsor has proposed Pregnancy Category B3.¹ This is considered appropriate, and matches the category used for Mirena.

**Impurities**

Proposed impurity limits for Jaydess are considered to be acceptable from a nonclinical perspective.

**Comments on the safety specification of the risk management plan**

The nonclinical Safety Specification contained in the draft Risk Management Plan (RMP) is largely acceptable. While progestogen-dependent tumours are included as a contraindication for Jaydess, no information on potential growth stimulating effects on hormone-dependent tumours is contained in the proposed PI document. Relevant changes to the PI to address this are recommended.

**Nonclinical summary and conclusions**

- The nonclinical data included various GLP-compliant studies examining the safety of the novel materials.
- While the average dose of levonorgestrel provided by this product (6 μg/day over 3 years) is lower than that for Mirena (14 μg/day over 5 years), Jaydess does have a higher initial (burst) release (25 μg/day compared with 20 μg/day). This rapidly declines and peak serum levels of levonorgestrel in patients (attained some days after insertion) do not exceed that for Mirena.
- Jaydess is to include a silver ring to facilitate detection by ultrasound. The inclusion of a silver ring attached to an IUS (but of different polymer composition compared with the proposed product) was not seen to affect local or systemic tolerance following intrauterine implantation in monkeys. Biocompatibility of the silver ring was further demonstrated in a set of tests for cytotoxicity, haemolysis, genotoxicity, acute toxicity, local tolerance (intramuscular and intracutaneous) and skin sensitisation potential.
- Biocompatibility was also satisfactorily established for the modified drug reservoir used in Jaydess, which contains the same ingredients as in Mirena but at a different ratio.
- The modified flange used in the Jaydess inserter device was shown to be biocompatible in tests for cytotoxicity, skin sensitisation and local (intracutaneous) tolerance.

¹ Category B3 is defined as: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
There are no nonclinical objections to the registration of Jaydess.

Revisions were recommended to nonclinical statements in the draft PI. Details of these are beyond the scope of the AusPAR.

**IV. Clinical findings**

**Introduction**

This is an application to register a new strength (13.5 mg) of levonorgestrel for an intrauterine delivery system (Jaydess). There is a 52 mg levonorgestrel intrauterine delivery system already registered in Australia (Mirena 52 mg levonorgestrel). The approved indication for Mirena is *contraception*.

The proposed indication for Jaydess is for *contraception*, which is the same as the indication for Mirena. One Jaydess is inserted into the uterine cavity and is effective for up to three years. It is removed manually and can be removed at any time prior to 3 years.

In the clinical trials, Jaydess is also referred to as LCS12: ultra low dose levonorgestrel intrauterine contraceptive system (LCS) with initial *in vitro* release of 12 µg/day.

**Clinical rationale**

Levonorgestrel is one of the 19-nortestosterone progestins. It is used worldwide as the progestin component in oral contraceptives, in hormonal replacement therapy, subdermal implants and intrauterine systems (IUS). Jaydess is a levonorgestrel-releasing intrauterine system (IUS) to be used for long-term contraception (up to three years). The dose of levonorgestrel released daily from the IUS results in tissue concentrations that make conditions unfavourable for pregnancy by making the endometrium relatively insensitive to circulating oestradiol and thickening the cervical mucus preventing fertilisation. There is also an inhibitory effect on ovulation which is clinically relevant at higher concentrations than that achieved by Jaydess.

There is already a levonorgestrel intrauterine implant available for this indication (Mirena). However compared with the Mirena duration of five years, Jaydess was developed to provide contraceptive protection for a shorter period of time - up to three years, with both a lower daily release rate of levonorgestrel and a smaller size of the system (smaller insertion tube diameter and T-frame) than Mirena. This aims to ensure easier and more acceptable insertion for nulliparous women.

**Guidance**

The clinical development program of Jaydess was considered adequate to satisfy the requirements of the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) ‘*Guideline on Clinical Investigation of Steroid Contraceptives in Women*’ (EMEA/CPMP/EWP/519/98 Rev 1, July 2005).

**Scope of the clinical dossier**

The submission contained the following clinical information:

- 2 reports of biopharmaceutical studies: *in vitro–in vivo* correlation study reports
- 12 reports of biopharmaceutical studies: bioanalytical and analytical methods for human subjects
- 2 studies pertinent to pharmacokinetics (PK) using human biomaterials: plasma protein binding study report and hepatic metabolism and drug interaction study
- 2 reports of human PK studies: healthy subject PK and initial tolerability study and patient PK and initial tolerability study reports
- 3 reports of human PK studies: population PK study reports
- 2 report of efficacy and safety studies: controlled clinical studies pertinent to the indication and uncontrolled clinical studies pertinent to the indication
- 7 other study reports/protocols

A clinical overview, clinical summaries and literature references were also provided.

**Paediatric data**

Not relevant as the PI proposes use in age 18 years and over.

**Good clinical practice**

The pivotal and supporting clinical Studies A46796 and A52238 were in line with international guidelines on the development of steroid contraceptives in women (CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1 July 2005) and have been discussed with several health authorities in Europe and the US Food and Drug Administration (FDA).

The documentation provided in the submission shows that all clinical studies performed in the framework of this submission were or are being conducted in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed. The protocols and protocol amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards.

**Pharmacokinetics**

**Studies providing pharmacokinetics data**

In addition to the studies described in Table 1, the clinical data included PK modelling, simulation and \textit{in vitro-in vivo} correlation studies.

**Table 1. Submitted pharmacokinetic studies**

<table>
<thead>
<tr>
<th>PK topic</th>
<th>Subtopic</th>
<th>Study ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK in healthy adults</td>
<td>General PK-Single dose</td>
<td>A229 (with oral levonorgestrel)</td>
<td>Absolute bioavailability of levonorgestrel from Microlut and dose linearity of levonorgestrel PK in 18 healthy, young women</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A10982 (with Mirena)</td>
<td>A Multicenter, Open-Label, Non-Randomised Study of SHG 00650 Levonorgestrel Intrauterine System in Parous Women Seeking Contraception to Evaluate its Efficacy, Safety, and PK Profile when</td>
</tr>
<tr>
<td>PK topic</td>
<td>Subtopic</td>
<td>Study ID</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Multi-dose</td>
<td>N/A</td>
<td></td>
<td>Inserted for 12 months</td>
</tr>
<tr>
<td>Bioequivalence</td>
<td>Single dose</td>
<td>13362 13363</td>
<td>There was no PK bioequivalence data provided. These 2 studies were to show pharmacodynamic equivalence with other contraceptives and dose comparison with other levonorgestrel formulations.</td>
</tr>
<tr>
<td>Multi-dose</td>
<td>None provided</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food effect</td>
<td>Not provided</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PK in special populations**

<table>
<thead>
<tr>
<th>Target population</th>
<th>Single dose</th>
<th>Study ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>nulliparous and parous</td>
<td></td>
<td>A46796 (Phase II)</td>
<td>Multi-center, open, randomised, dose finding Phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems releasing <em>in vitro</em> 12 μg/24 h and 16 μg/24 h of levonorgestrel compared to Mirena in nulliparous and parous women in need of contraception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A52238 (Phase III)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>91775 – Phase IIIb extension study for A52238 in Asia-Pacific region (China, Korea, Australia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>A52238</td>
<td>A52238 Phase III Multi-center, open-label, randomised study to assess the safety and contraceptive efficacy of two doses (<em>in vitro</em> 12 μg/24 h and 16 μg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for maximum of 3 years in women 18 to 35 years of age and extension phase of the 16 μg/24 h dose group (LCS16) up to 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multi-center, open, single arm study to assess efficacy, safety, bleeding pattern and PK of the ultra low dose levonorgestrel intrauterine contraceptive system (LCS) for a maximum of 3 years in women 18 to 40 years of age</td>
</tr>
</tbody>
</table>

Multi-dose

| Nil studies

Hepatic impairment

| A02495 | *In vitro* study |

Renal impairment

<p>| |
|                              |</p>
<table>
<thead>
<tr>
<th>PK topic</th>
<th>Subtopic</th>
<th>Study ID</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates/infants/children/adolescents</td>
<td>14371 (paediatric clinical trial under way for women post menarche)</td>
<td>Not relevant currently for this application if &lt; 18 years</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td></td>
<td></td>
<td>Not relevant for this application</td>
</tr>
<tr>
<td>Paediatrics</td>
<td>A57120</td>
<td>PK population study-Paediatric Scaling levonorgestrel LCS IUD (population analysis)</td>
<td></td>
</tr>
<tr>
<td>Genetic/gender-related PK</td>
<td>Males versus females</td>
<td>Females only</td>
<td></td>
</tr>
<tr>
<td>PK interactions</td>
<td>Levonorgestrel</td>
<td>This information was not provided for evaluation. Discussions about potential CYP450 3A4 interactions were discussed</td>
<td></td>
</tr>
<tr>
<td>Population PK analyses</td>
<td>Healthy subjects</td>
<td>A57120</td>
<td>Population based PK study-Pediatric Scaling levonorgestrel LCS IUD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A57551 (308901)</td>
<td>Exploratory population PK analysis of levonorgestrel in the multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A57552 (310442)</td>
<td>Exploratory population PK analysis of levonorgestrel in the multi-center, open-label, randomised Phase III study to assess the safety and contraceptive efficacy of two doses</td>
</tr>
<tr>
<td>Target population</td>
<td></td>
<td>These are also the population in the 'healthy' study groups</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

None of the PK studies had deficiencies that excluded their results from consideration.

**Evaluator’s overall conclusions on pharmacokinetics**

Jaydess (LCS12) acts primarily via local effects on the endometrium and cervix, therefore systemic concentrations, drug interactions, pharmacogenetic factors and food are of less relevance than for oral administration of levonorgestrel such as in oral contraceptives. Further the systemic concentrations are > 30 fold more with oral contraceptive use than with the levonorgestrel IUS.
There appears to be no PK issues of concern in healthy fertile women as studied in the large trials and there are no further PK studies that need to be undertaken for the requested indication. However, clinical studies have not been undertaken in women in 'special groups', that is, with renal or hepatic impairment, in adolescence, obesity or after age 40 years. Specifically, and on examining the pharmacometric work on clearance in the obese, it suggests it is important that pharmacovigilance is undertaken in obese women with Jaydess. Although the clinical data did not show a higher pregnancy rate in this group, it is possible from the PK simulation data. Further, that numbers of obese women in the clinical studies are small (5 in the pivotal Study A52238 in the LCS12 arm). For use in other special groups clinical studies and/or monitoring in these groups also needs to be undertaken prior to being confident about the efficacy in these groups.

Pharmacodynamics

Studies providing pharmacodynamic data

The main pharmacodynamic (PD) parameters of interest are those of pregnancy rate and adverse effects. Menstrual cycles, bleeding patterns and return to fertility are other parameters measured. In both the pivotal Phase II (A46796) and Phase III (A52238) studies, parameters from a subset of 12 women per treatment arm (LCS12 and LCS with initial \textit{in vitro} release of 16 µg/day (LCS16)) were used to determine a non-compartmental population PK model.

Table 2. Submitted pharmacodynamic studies

<table>
<thead>
<tr>
<th>PD Topic</th>
<th>Subtopic</th>
<th>Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Pharmacology</td>
<td>Effect on safety and efficacy</td>
<td>A46796 Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing \textit{in vitro} 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to Mirena in nulliparous and parous women in need of contraception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A52238 Phase III Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (\textit{in vitro} 12µg/24 h and 16µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16µg/24 h dose group (LCS16 arm) up to 5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>91775 Multi-center, open label, single arm study to assess efficacy, safety, bleeding pattern and PK of the ultra low dose levonorgestrel intrauterine contraceptive system (LCS) for a maximum of 3 years in women 18 to 40 years of age</td>
</tr>
</tbody>
</table>

Secondary Effect on bone Examination of effects on bone mineral
### PD Topic

<table>
<thead>
<tr>
<th>Subtopic</th>
<th>Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology</td>
<td></td>
</tr>
<tr>
<td>mineral density</td>
<td>density is a substudy of A52238</td>
</tr>
<tr>
<td>Effect on oestradiol concentrations</td>
<td>The observed oestradiol concentrations seen in A52238 are within the typical range of normal menstrual cycles.</td>
</tr>
<tr>
<td>Effect on cervix</td>
<td>The three formulations investigated in the phase 2 study, A46796 showed an increase in the systemic exposure in the order LCS12 (this application) LCS16 and Mirena. There was no difference in the effect on the endometrium or on the cervix</td>
</tr>
<tr>
<td>Effect on endometrium</td>
<td>Endometrial safety was also substudy of A52238</td>
</tr>
<tr>
<td>Gender other genetic and Age-Related Differences in PD Response</td>
<td>Used only in women</td>
</tr>
<tr>
<td>Effect of gender</td>
<td>Used only in women</td>
</tr>
<tr>
<td>Effect of age</td>
<td>Physiology-based PK (PBPK) modelling via the software PK-Sim used to explore the expected PK properties of LCS in females of different ages</td>
</tr>
<tr>
<td>PD Interactions</td>
<td>Nil likely to be relevant</td>
</tr>
<tr>
<td>Population PD and PK-PD analyses</td>
<td>Healthy subjects A57262</td>
</tr>
<tr>
<td></td>
<td>External validation of an IVIVC for the low dose levonorgestrel contraceptive system</td>
</tr>
</tbody>
</table>

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

**Evaluator's overall conclusions on pharmacodynamics**

In summary, the pharmacodynamics parameters and the methods by which they are measured are appropriate for the indication. They include the target group, and studies to examine the lower dose of levonorgestrel as compared to the currently TGA registered levonorgestrel IUS product are appropriate. Including the Phase IIIb studies underway, no further studies on specific parameters are required from a pharmacodynamics perspective. However the 5 year arm of the LCS16 group and the data from Phase IIIb studies are important to corroborate the early pharmacodynamics data presented here.

**Dosage selection for the pivotal studies**

There is already a 52 mg levonorgestrel IUS available in Australia (Mirena). This IUS releases levonorgestrel over 5 years. LCS12 (Jaydess) was designed to release smaller amounts of levonorgestrel per day (12 µg/day for Jaydess) and to be removed after 3 years. As there is now many years of safety data for Mirena, the main 2 issues for the clinical use of Jaydess is whether the clinical effectiveness is maintained (in terms of pregnancy prevention) over the 3 years with a much lower levonorgestrel release, and
whether there are any safety concerns with the formulation or structure of the IUS. The 2 clinical studies (A52238 and A46796) investigate these issues with LCS 12 (Jaydess).

**Efficacy**

**Studies providing efficacy data**

Proof of the clinical efficacy of Jaydess (contraception) was based on the number of pregnancies in the clinical studies: one pivotal Phase III study (A52238) and a supporting Phase II study (A46796). Much of the study design was similar for both studies.

Study A52238 was a Phase III, multicentre, randomised, open-label, 2-arm (LCS12 and LCS16), parallel group, 3 year (up to 5 years for LCS16 only) study and recruited generally healthy 18 to 35 year old nulliparous or parous women in need of contraception. There were 1432 women in the LCS12 and 1452 in the LCS16 group. The primary efficacy variable was pregnancy rate (Pearl Index, defined as the number of pregnancies per 100 women years on treatment).

The Phase II Study A46796 was a multicentre, open-label, randomised, dose finding study to investigate LCS12 and LCS16 compared to Mirena for a maximum of 3 years. The study recruited parous or nulliparous women of 21 to 40 years of age (inclusive) with good general health and in need of contraception. There were 240 women in the LCS12, 245 in the LCS16 group and 256 in the Mirena group. The number of pregnancies was recorded and the pregnancy rate (Pearl Index) was calculated as the primary efficacy variable.

In addition, a pooled analysis was undertaken and relevant data from this were discussed as comparison in the discussion of clinical efficacy and safety endpoints when relevant.

**Evaluator’s conclusions on clinical efficacy**

**Pregnancy**

Although for obvious reasons a placebo group was not studied, contraceptive efficacy of LCS12 (Jaydess) when inserted according to the insertion instructions has been met. In the pivotal Study A52238 for 18 to 35 year old women, the unadjusted Pearl Index for LCS12 for the first year was 0.41 with the upper limit (UL) of the two sided 95% confidence interval (CI) of 0.96, and 0.33 for the total three years of use, with the UL of the two sided 95% CI of 0.60. The CHMP recommend that the difference between the point estimate and the UL of the 95% CI of the Pearl Index is < 1.

Further, in the supporting Study A46976, the highest Pearl Index (unadjusted: 1.52; adjusted: 1.53) was observed in Year 2 for the LCS16 arm. With the exception of this group and time, all Pearl Indices were below 1 and the UL of the 95% CI never exceeded 4.5.

The evaluator noted the requirement of the EMA/CHMP Guideline on Clinical Investigation of Steroid Contraceptives in Women (EMEA/CPMP/EWP/519/98 Rev 1 July 2005), that the difference between the point estimate for the Pearl Index and the upper 95% CI limit should not exceed 1, which although being met for the three year Pearl index with Mirena and LCS12, was missed for LCS16.

Using a life table analysis, and using the pivotal Study A52238, LCS12 has a failure rate of approximately 0.4% at 1 year and a cumulative failure rate of approximately 0.9% at 3 years.

In terms of the 95% CI of the Pearl Index for the supporting Study A46796 not being met in the LCS16 arm, it was noted that this is a Phase II study only, that it occurred in the LCS16 and not the LCS12 (Jaydess) arm and that the failure rate also includes pregnancies due to undetected expulsions.
Demographic and baseline characteristics of the pivotal Study A53328 and Study A46796 were representative of the target population, with a large group of both ≤ 25 year olds and nulliparous women (approximately 600 women in each of these categories in the total LCS12 population). Further information on follow-up in those who wished to conceive but hadn’t at the completion of the study, and vigilance in special groups was required and was subsequently provided by the sponsor in response to a TGA request for further information (see below).

**Bleeding**

Jaydess had a favourable effect on bleeding as is seen with higher high dose levonorgestrel preparations. Specifically, the proportion of women with amenorrhea gradually increased over the course of the 3 year treatment period although the number was relatively small compared to the effect with Mirena. Additionally, the proportion of women with prolonged and frequent bleeding decreased. This effect appeared to be dose related, with increasing levonorgestrel, as in LCS16 and Mirena, having greater effects.

**Compliance**

Overall compliance (as defined via IUS location with ultrasound) was high in both studies in all treatment groups. Importantly no difference in correct position of the IUS was seen between parous and nulliparous women.

**Early safety signals**

An analysis of the available return-to-fertility, although early, was reassuring with 25 out of 29 women who discontinued Study A46796 because of wish for conception becoming pregnant during the 12 month follow-up. Unintended pregnancy due to expulsion was uncommon although monitoring post registration would be important.

More than three quarters of women who completed the user satisfaction questionnaire were ‘very satisfied’ with study treatment.

Of note, almost all women are of Caucasian origin, and thus a generalisation to other ethnic groups cannot be made. The LCS12 has met the CHMP criteria for effective contraception, although this was not met for LCS16 in the Phase II study.

**Safety**

**Studies providing evaluable safety data**

Analysis of the safety of LCS12 is based on the same clinical studies as for analysis of contraceptive efficacy, that is, the pivotal Phase III Study A52238 and the comparative Phase II Study A46796.

The same analysis set (full analysis set (FAS), defined as including all women for whom the IUS was inserted (in A46796) or the insertion of an IUS was attempted (in A52238), according to the treatment actually received) was used for the safety (and efficacy) assessment. Safety data were examined for each individual study and also for the pooled analysis.

A summary of patient exposure is given in Table 3.
Table 3. Mean exposure to levonorgestrel and comparators in clinical studies.

<table>
<thead>
<tr>
<th>Study type/Indication</th>
<th>Uncontrolled studies</th>
<th>Total levonorgestrel (all doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LCS12</td>
<td>LCS16</td>
</tr>
<tr>
<td>Clinical pharmacology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>821</td>
<td>843</td>
</tr>
<tr>
<td>Treatment duration (Women Years (wy))</td>
<td>2.25</td>
<td>2.31</td>
</tr>
<tr>
<td>Study A46796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td>915</td>
<td>912</td>
</tr>
<tr>
<td>Treatment duration (Women Years)</td>
<td>2.51</td>
<td>2.50</td>
</tr>
<tr>
<td>TOTAL wy (days)</td>
<td>4.76 (1736)</td>
<td>4.81 (1755)</td>
</tr>
</tbody>
</table>

On average, the mean exposure for women on LCS12 in the youngest age group or nulliparous group was approximately 60 or 40 days shorter when compared to the overall population.

No post-marketing data are available for LCS12 because this product has not yet been marketed. However post-marketing safety data for Mirena, that has an initial release rate of approximately 20 μg/day and a 5 year period of use, are available, and a large active post-marketing surveillance and research (Phase IIIb) program is ongoing. In the latest Periodic Safety Update Report (PSUR) for Mirena, there was no evidence of any new safety concerns.

Evaluator’s overall conclusions on clinical safety

The safety of the LCS12 IUS was evaluated in 1672 women in good general health seeking contraception over a three year time point. An additional 1697 women were studied with the slightly higher release LCS16, and 256 with the higher dose Mirena.

The overall clinical safety profile of LCS observed (from the A46796 and A52238 studies) gave no new safety concerns that are not already known from the surveillance and clinical trial data from other IUSs and other levonorgestrel preparations. Specifically, many of the common adverse events (AEs) were similar to those that are known to occur with other levonorgestrel preparations (acne, ovarian cyst, dysmenorrhoea) were seen. The short-term presented data do not indicate an increased risk of venous thromboembolism, cardiovascular events nor cancer incidence.

In the pooled analysis, serious AEs (SAEs) were reported for 4.7% of women in the LCS12 (Jaydess) treatment group, 4.9% of women in the LCS16 group, and 6.3% of women in the Mirena group. Overall the most frequent SAEs in descending order were: appendicitis, ectopic pregnancy, ovarian cysts, abdominal pain and pelvic inflammatory disease (PID). The pooled incidence of PID in the LCS12 and 16 arms across Studies A46976 and A52238...
was approximately 0.4% with an incidence of 0.11 per 100 women years. The incidence of endometritis was 0.8% in pooled LCS12 and LCS16 data from Study A52238.

In terms of ectopic pregnancy the absolute risk with LCS12 is less than in non-contraceptive users (estimated ectopic rate of approximately 0.3 to 0.5 per 100 women years compared with 0.11 per 100 women years with LCS12, similar to the rate in the Mirena clinical studies).

Approximately 50% women had any drug related AE, with 8-26% in A46976 complaining of one or more ‘progestogenic’ side effects. There were a large number of discontinuations with approximately 20% of all women using LCS12 discontinuing use due to AEs. The most common ones were vaginal haemorrhage, device expulsion (3.2% at 36 months with Jaydess) and acne. There was a trend toward more partial and total expulsions in parous as compared to nulliparous women in subgroups analysis in both studies. In subgroups of women evaluated there were no clear safety issues although some (including the body mass index (BMI) > 30 kg/m² and some ethnic groups) were small.

There have been 2 perforations, one in the LCS16 (not Jaydess) group and 1 in the LCS12 group during sounding, in the Asia-Pacific study. Also, psychiatric SAEs were reported in 0.2% women, which included depression (< 0.1% overall) and anxiety (< 0.1% overall). Depression as an AE was reported in 5.4% (LCS12), 2.4% (LCS16) 3.9% (Mirena) and 3.9% (total in A46976). The most frequent psychiatric AE (incidence of 12%) reported in Study A52238 was depression (3.5%).

Further, although over 98% of the ovarian cysts reported in the LCS treatment groups were not serious and did not result in study drug discontinuation, study treatment was withdrawn in 8 women (three in the LCS12 group, and five in the LCS16 group) in A52238, and ovarian cysts were reported as SAE in 7 women (4 in the LCS12 group, and 3 in the LCS16 group). Five of these women underwent laparoscopic procedures and 2 were treated medically.

Lastly, removal was assessed as ‘very difficult’ in approximately 2% of all women.

The evaluator’s recommended safety concerns to be addressed were:

- Highlighting that many women get progestogenic side effects.
- Whilst the rate of ectopic pregnancy is less than in the general population, the likelihood of a pregnancy, if it occurs, being ectopic is higher. The sponsor is considering the feasibility of a prospective database study to address this risk of ectopic pregnancy in LCS12 users in the market and this is supported. The proposed label for LCS12 is to include a warning on the risk, and signs and symptoms of ectopic pregnancy although this is not evidence in the labelling submitted in the dossier. The company further proposes to explore options to make the patient information accessible through additional channels, such as the internet, as a means of further risk minimisation and this is supported although evidence that this is underway is needed.
- Although the incidence of PID and endometritis is uncommon (< 1/100), it did occur in the clinical trials and it was important to note that Jaydess does not protect against STDs. It was noted that the sponsor has stated that it is evaluating additional pharmacovigilance activities and educational programmes to reduce the incidence.
- Partial or complete IUS expulsion is a risk with Jaydess, which may be higher in the non-trial setting where IUS position is not checked routinely after insertion – between 1-10%.
- Perforation is rare, has not been seen with Jaydess but has occurred with a similar IUS. The sponsor has a planned educational program for LCS12 to emphasise correct insertion technique to reduce the risk of incorrect placement or perforation.
• Ovarian cysts whilst common in this population may cause complications.
• Depression and anxiety are common in this age group but there was a prevalence of 3% of these conditions in this study and awareness of this by the woman and the prescriber is important.

There were no safety concerns in laboratory variables, vital signs, and other safety parameters observed. The overall incidence of new abnormal endometrial or cervical findings was low. There was no negative effect on bone mineral density.

In summary, there appears to be no new safety concerns with LCS 12, compared to Mirena and other IUSs. However, the rate of ectopic pregnancies, PID and expulsions needs to be observed. Ongoing observational data in a subgroup of obese women (BMI > 35) should also be provided in the PSUR.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Jaydess in the proposed usage are:
• Effective long-term contraception with the unadjusted Pearl Index for LCS12 for the first year was 0.41, and the UL of the 2 sided CI was 0.96
• Reduced menorrhagia (prolonged and heavy bleeding) and intracyclic bleeding
• Less daily release rate of levonorgestrel than comparator IUS levonorgestrel product
• ‘Easy’ to insert for most nulliparous women, but no comparison data with other intrauterine devices or standard
• Theoretically LCS12 efficacy is unlikely to be impacted by the use of co-medications that induce cytochrome P450 enzymes although evidence is lacking.

First round assessment of risks

The risks of Jaydess in the proposed usage are:
• Possible long-term fertility issues due to ectopic pregnancy, PID, endometritis, expulsions
• Possible unintended pregnancy due to partial or total expulsion
• Progestogenic side effects

First round assessment of benefit-risk balance

The benefit-risk balance of Jaydess given the proposed usage is favourable for women aged 18-41 years requesting long-term contraception with an intrauterine device. The sponsor’s proposed pharmacovigilance and education programs around this product are recommended to be mandatory.

First round recommendation regarding authorisation

The evaluator recommended registration with an ongoing pharmacovigilance report, particularly on the risk of expulsions, ectopic (and normal) pregnancy, and rate of pelvic inflammatory disease.
In relation to the Indications (proposed PI 120813 version): the evaluator noted the sponsor had amended the proposed indication from ‘Contraception for up to three years’ to ‘Contraception’. The evaluator recommended that the approved indication be ‘Contraception for up to 3 years’ so it is clear this is not a temporary form of contraception that could be stopped and started. It also serves to remind women that after three years the IUS should be removed and a new method is required.

**List of questions**

**Efficacy**
Are there any additional relevant data from long term follow-up or extension of the pivotal studies?

**Safety**
Up to date information on the other (non-TGA) jurisdictions for Jaydess registration was not provided at the time of the submission. Is there up to date registration information?

Are there any additional relevant data from long term follow-up or extension of the pivotal studies? Other studies mentioned in the dossier included:

- Study 91775
- Study 13362
- A Phase IIIb study (protocol 13363)

Are there additional safety data from these studies, particularly with respect to ectopic pregnancy, expulsion, and infection, available for evaluation?

**Second round evaluation of clinical data submitted in response to questions**
A summary of the TGA evaluation of the sponsor’s responses to the list of clinical efficacy and safety questions is below. Full details can be found in Attachment 2 (Extract from the Clinical Evaluation Report) of this AusPAR.

The second round clinical evaluation also included evaluation of pharmacovigilance information provided in the sponsor’s response. Details of pharmacovigilance aspects of the application are included under Pharmacovigilance findings, below.

**Efficacy question**
The sponsor advised that the ongoing extension phase of the pivotal Phase III study (A52238) includes only subjects in the LCS16 group.

There had been one addendum to the Phase III study relating to the follow-up of return to fertility information gathered after completion of the 3 year phase of the study. In this extension study, 204 women who wished to become pregnant were followed up; 76.7% of these became pregnant in 1 year. This is comparable with return to fertility data for users of IUSs with higher dose levonorgestrel.

There was no long-term follow-up from the completed Phase II study (A46796). There had been one amendment to the Phase II study which was reviewed in the initial evaluation (analysis of bleeding patterns, return to fertility and PD, collected after the study was completed).
The sponsor advises that there are currently 4 studies ongoing with Jaydess and the estimated reporting timelines for these are in the latter half of 2013 and early 2014.

Safety questions

Up to date information on the other (non-TGA) jurisdictions for Jaydess registration was provided. Recent approvals in the USA and Sweden were noted.

Additional safety data

The sponsor’s response included a tabular listing of pregnancies, expulsions, PID reported and SAEs (up to a cut-off date of 23 December 2012) in the ongoing Jaydess studies. Information was also provided on 2 deaths (both judged as unrelated to LCS12) and perforations.

Overall, the rates are similar to the pivotal Study A52238 and there were no new events reported.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Jaydess in the proposed usage are unchanged from those identified under First round assessment of benefits, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of Jaydess in the proposed usage are unchanged from those identified under First round assessment of risks, above. The risks of Jaydess in the proposed usage are:

- Ectopic and intra uterine pregnancy
- Expulsion of IUD
- Infection

Second round assessment of benefit-risk balance

The benefit-risk balance of Jaydess given the proposed usage is favourable on a population basis. However there is a risk to future fertility particularly in nulliparous women due to the rate of ectopic pregnancies and PID, and the pharmacovigilance plans as assured by the sponsor needs to be mandated for this product. Further, information about long-term outcomes and real world practice needs to be communicated to prescribers and regularly updated. Specific data on obese women, parous and nulliparous needs to be provided, particularly around expulsions, PID, and pregnancies (both ectopic and intrauterine).

In relation to proposed post-marketing activities:

- Post-authorisation Safety Study (PASS) protocol needs to be included in Annex 5 of the EU-RMP as assured by the sponsor
- Pharmacovigilance activities as discussed in the response are mandated to occur and are communicated to the TGA.
- If the results from the insertion survey are not directly applicable to Jaydess then the sponsor needs to have considered an alternative education and training plan.
Bayer provides the assurance that the printed materials associated with these risk minimisation activities will be provided to TGA, once available.

Second round recommendation regarding authorisation
This was unchanged from that identified under First round recommendation regarding authorisation, with pharmacovigilance and education strategies as assured by the sponsor.

V. Pharmacovigilance findings

Risk management plan
The sponsor submitted a Risk Management Plan (EU-RMP Version: 1.0, dated 9 November 2011, with an Australian Specific Annex (ASA), Version: 1, dated 10 August 2012) which was reviewed by the TGA’s Office of Product Review (OPR). A summary of the RMP is shown in Table 4.

Table 4. Summary of proposed Risk Management Plan

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>Outcomes study. Study format under assessment.</td>
<td>Routine. Additional: Communication measures directed to HCPs addressing appropriate patient selection and emphasizing aseptic insertion technique</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>Outcomes study. Study format under assessment.</td>
<td>Routine. Additional: The company will explore options to increase the accessibility of the patient information, e.g. via a company website depending on country regulations</td>
</tr>
<tr>
<td>Uterine perforation</td>
<td>European Active Surveillance Study for intrauterine device (EURAS-IUD) ongoing. Targeted follow-up questionnaire.</td>
<td>Routine. Additional: Communication measures directed to HCPs emphasizing correct insertion technique</td>
</tr>
<tr>
<td>Unintended pregnancy with LCS</td>
<td>Outcomes study. Study format under assessment.</td>
<td>Routine.</td>
</tr>
</tbody>
</table>
## Safety concern

<table>
<thead>
<tr>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine Pharmacovigilance including targeted follow-up of pregnancy outcomes. Cumulative presentation in PSURs.</td>
<td>Routine Pharmacovigilance.</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>Routine Pharmacovigilance.</td>
</tr>
<tr>
<td>Expulsion</td>
<td>Routine Pharmacovigilance.</td>
</tr>
<tr>
<td>Bleeding changes</td>
<td>Routine Pharmacovigilance.</td>
</tr>
</tbody>
</table>

### Important potential risks

<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential for medication error</td>
<td>Routine Pharmacovigilance with presentation of cases of medication error in the PSURs.</td>
<td>Routine. Additional: Communication measures to highlight differentiation of IUS via ultrasound; and Patient cards</td>
</tr>
<tr>
<td>Potential for off-label use in indications other than contraception</td>
<td>Database drug utilization study.</td>
<td>Routine.</td>
</tr>
<tr>
<td>Potential of use beyond approved duration of use</td>
<td>Database drug utilization study.</td>
<td>Routine:</td>
</tr>
</tbody>
</table>

### Important missing information

<table>
<thead>
<tr>
<th>Important missing information</th>
<th>Proposed pharmacovigilance activities (routine and additional)</th>
<th>Proposed risk minimization activities (routine and additional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric use/use in the adolescent population</td>
<td>Pediatric Investigational Plan: Adolescent study.</td>
<td>Routine</td>
</tr>
<tr>
<td>Return to fertility after removal of LCS</td>
<td>Data collection of study participants discontinuing the method for wish of pregnancy.</td>
<td>Routine</td>
</tr>
</tbody>
</table>

### Summary of first round recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received:
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these concerns include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

The sponsor should definitively state how the targeted follow-up of pregnancy outcomes is to be conducted.

The sponsor should state when the draft protocol for studies proposed to further monitor the important identified risks: 'Pelvic inflammatory disease', 'Ectopic pregnancy' & 'Unintended pregnancy with LCS' is expected to become available.

The sponsor should provide the final protocols of other post marketing studies to the TGA for review as they have become available.

An update on the progress/results/analysis of study/s, as outlined in the EU-RMP, will be expected in future PSURs and RMP updates.

The Australian sponsor has provided no detail about the additional risk minimisation activities (such as communication measures to HCPs, increasing patient accessibility to patient information, patient cards) to be undertaken in Australia in the ASA. Consequently the sponsor should definitively state what communication tools will be used in Australia and detail how these tools will be distributed to the target audience.

In regard to the final approved EU-RMP, the sponsor should advise the TGA if there are any material differences compared to Australian specific risk minimisation activities. In the event of there being such material differences, the sponsor should justify why any such material differences have not been adopted in Australia.

In regard to the proposed routine risk minimisation activities, the draft PI document is considered satisfactory.

In regard to the proposed routine risk minimisation activities, the draft CMI is considered satisfactory.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Second round evaluation

Sponsor responses to the above recommendations were acceptable except as noted below under Outstanding issues.


Outstanding issues

The sponsor should rework the Risk Minimisation Plan in the ASA to the satisfaction of the TGA, taking into account the significant changes to the Risk Minimisation Plan of the EU-RMP from Version: 1.1 to Version: 1.3, preferably before this application is approved.

Final recommendation

In the event of approval, the OPR recommended the following:
The EU Risk Management Plan (Version: 1.3, dated 28 November 2012) with an Australian Specific Annex (Version: 2, dated March 2013), to be revised as specified in the sponsor's correspondence dated 26 March 2013 with an amended Australian Risk Minimisation Plan agreed to by the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Background

This is a submission to register Jaydess, an IUS containing 13.5 mg levonorgestrel. Jaydess was designated ‘LCS12’ during development (indicating an expected release rate of 12 μg/day; ‘LCS16’ was a similar product with an expected release rate of 16 μg/day). Jaydess is a new strength (13.5 mg) compared to the registered product ‘Mirena’ which is an IUS containing 52 mg levonorgestrel.

The intrauterine delivery systems in Jaydess and Mirena also have distinct components, different construction of drug reservoir, with different PK characteristics and levonorgestrel release rates. The proposed duration of use is 3 years for Jaydess compared to the approved 5 years for Mirena. The T-body contains a silver ring in the upper part of the vertical stem ostensibly to facilitate differentiation of Jaydess from Mirena both at the time of insertion and by ultrasound detection in situ.

The intended target population for Jaydess specifically includes nulliparous women, according to the letter of application.

The proposed therapeutic indication is ‘Contraception’, identical to that for Mirena.

The Dosage and Administration instructions (abridged) include ‘Jaydess is inserted into the uterine cavity and is effective for up to three years.’ This section of the PI continues at length with a summary of the expected time course of in vivo release rate, failure rate, and limitations in subgroups.

Quality

The proposed product for marketing is stated to be the same as the Phase IIIb test product. The modified LCS12 device that included the silver ring profile was used from the Phase III trials onwards:

Figure 3. Jaydess device

The diameter of vertical stem is 1.55 mm. The ‘Silver profile’ is given as 6.5 mm, although the dimension thus specified is not described. The IUS is inserted into the uterus with a preloaded ready-to-use integrated inserter device.
Mirena IUS dimensions are 32 mm horizontal arms x 32 mm length of vertical stem. A shelf life of 24 months is supported. Two outstanding issues are:

- 'Protect from light' statement on PI and labels is recommended and was not agreed by the sponsor. The Delegate requested the sponsor addressed this in the response to this Overview.

- The IUS has varying release rates at different periods. The sponsor did not agree to include a single release rate on the carton label. The sponsor stated: "Mirena and Jaydess have a different construction of the drug reservoir. ... This leads to very different release rate profiles of the two products."

The in vivo release rate profiles of Jaydess and Mirena are shown in Figure 4.

Figure 4. In vivo release rate profiles of Jaydess (LCS12) and Mirena

The sponsor considers there are no TGA requirements for expressing the delivered dose as the strength of the product for intrauterine drug delivery systems, and that levonorgestrel 13.5 mg is the actual strength of Jaydess. However it is proposed to include the approximate intended release rate on the carton. This is considered acceptable to the clinical delegate. ACPM comment on this matter will be requested.

Device evaluation or referral to PSC was not required. The chemistry and quality evaluators have no objection to approval on any quality related issue.

Nonclinical
The nonclinical evaluator noted that the product had variations in composition from the higher strength registered product Mirena. The nonclinical evaluation report describes the average dose provided by Jaydess as 6 µg/day over 3 years, with a higher initial (burst) release of 25 µg/day.

The inclusion of a silver ring attached to an IUS (but of different polymer composition compared with the proposed commercial product) was not seen to affect local or systemic tolerance following intrauterine implantation in monkeys. Biocompatibility of the silver ring was further demonstrated in a set of tests for cytotoxicity, haemolysis, genotoxicity, acute toxicity, local tolerance (intramuscular and intracutaneous) and skin sensitisation potential.

Biocompatibility was also satisfactorily established for the modified drug reservoir used in Jaydess. The modified flange used in the Jaydess inserter device, containing a different colourant to that in Mirena, was shown to be biocompatible in tests for cytotoxicity, skin sensitisation and local (intracutaneous) tolerance.
There were no nonclinical objections to the registration of Jaydess. There were recommendations for revisions to nonclinical text in the PI. The sponsor responded with modifications and the TGA toxicology section has provided further comments.²

Clinical

Two clinical studies supporting the efficacy and safety of Jaydess were as follows:

Table 5. Clinical studies supporting the efficacy and safety of Jaydess

<table>
<thead>
<tr>
<th>Study no. (Protocol no.)</th>
<th>Design Duration</th>
<th>Study population</th>
<th>Number of women by treatment group</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A52238 (310442)</td>
<td>Multicenter, randomized, open-label, 2-arm, parallel group</td>
<td>Generally healthy, 18-35 year-old nulliparous or parous women in need of contraception</td>
<td>LCS12: 1432; LCS16: 1452</td>
<td>Pregnancy rate, bleeding pattern, safety</td>
</tr>
<tr>
<td>Phase 3</td>
<td>3 years (up to 5 years for LCS16 only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe, US, Canada, South America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A46796 b (388901)</td>
<td>Multicenter, randomized, open-label, controlled, 3-arm, parallel group</td>
<td>Generally healthy, 21-40 year-old nulliparous or parous women in need of contraception</td>
<td>LCS12: 240; LCS16: 245; Mirena: 256</td>
<td>Pregnancy rate, bleeding pattern, safety</td>
</tr>
<tr>
<td>Phase 2</td>
<td>3 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

² Details of PI revisions are beyond the scope of the AusPAR.

Pharmacokinetics

There was no short-term bioavailability study, due to the long duration of use of the product.

The in vitro dissolution testing showed a rapid decline in rate of release during the first 4 weeks, from approximately 55 μg/day after one day, 25 μg/day around day 2, to 14 μg/day for the sampling period days 5-11, and 12 μg/day for the sampling period days 19-25. Six months later the in vitro release rate was about 8 μg/day, declining to a level of 5 μg/day at the end of year 3.

The in vivo release rate was calculated from long-term in vitro dissolution data and analysis of the ex vivo residual content of levonorgestrel in Jaydess samples taken from women in clinical trials; about 100 ex vivo samples of Jaydess from the study A46796 and 800 from the study A52238. Model values for in vivo release rates based on these data are 14 μg/day on day 25, 9.6 μg/day after 60 days, 5.4 μg/day after 3 years, and an average release rate over 3 years of 6.4 μg/day.

Systemic absorption

Subgroups of women (n = 12/13) in the Phase II dose-finding Study A46796 had serum levonorgestrel and Sex Hormone Binding Globulin (SHBG) determinations at baseline and day 1, 3, 7, and 2 weeks after insertion, and at each subsequent visit. Measurable levels of serum levonorgestrel were observed in all subjects one day after insertion. Results showed high variability. The mean (coefficient of variation (CV%)) Cmax (ng/L) for Jaydess (LCS12, n = 12) was 137 (28.6) at median time to achieve Cmax (Tmax) 14 days, (range 1-379 days), versus Mirena (n = 13) 360 (45.9) at day 7 (range 3-927 days).
Women from pivotal Phase III Study A52238 had serum levonorgestrel determinations after LCS12 insertion (n = 7) that provided the following mean PK parameters.

Table 6. Mean (CV) pharmacokinetic parameters of levonorgestrel after insertion of LCS12

<table>
<thead>
<tr>
<th>Subgroup 3</th>
<th>AUC (ng·d/L)</th>
<th>Cmax (ng/L)</th>
<th>Tmax (day)</th>
<th>Cav (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaydess: LCS12</td>
<td>76461 (41.6%)</td>
<td>171 (52.1%)</td>
<td>2.00 (1.00-16.0)</td>
<td>70.0 (42.3%)</td>
</tr>
</tbody>
</table>

AUC: area under the concentration-time curve; Cav = average concentration.

Using sparse blood sampling from women in both studies, a population PK model was established with typical serum concentrations of levonorgestrel as follows:

Table 7. Geometric mean and the 5th and 95th percentile of levonorgestrel serum concentrations after insertion of LCS12 (data in ng/mL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 day</th>
<th>7 days</th>
<th>30 days</th>
<th>3 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric Mean</td>
<td>116</td>
<td>162</td>
<td>131</td>
<td>99.8</td>
<td>71.0</td>
<td>64.3</td>
<td>51.8</td>
</tr>
<tr>
<td>5th percentile</td>
<td>85.8</td>
<td>102</td>
<td>83.0</td>
<td>68.2</td>
<td>44.4</td>
<td>40.6</td>
<td>36.2</td>
</tr>
<tr>
<td>95th percentile</td>
<td>154</td>
<td>249</td>
<td>198</td>
<td>153</td>
<td>109</td>
<td>95.5</td>
<td>91.9</td>
</tr>
</tbody>
</table>

In comparison, data from Study 229, for a single oral dose of levonorgestrel 30 µg (Microlut) (n = 18), the arithmetic mean for serum levonorgestrel Cmax was 760 ng/L (CV 35.2%).

Pharmacodynamics

In A46796 available progesterone levels (n = 53) suggested ovulation for all women treated with LCS12 (Jaydess, n = 21), compared to no evidence of ovulation for 2 women treated with LCS 16 (n = 15) in year 1. For Mirena (n = 17), levels suggested no ovulation for 4 women in year 1, 2 during year 2, and 1 during year 3. From the pivotal Study A52238, the tabulation of ovulation assessment by progesterone levels in each year for the Jaydess subset showed 13/14 had levels consistent with ovulation in year 1, 10/11 in year 2 and 11/11 in year 3.

Effects on the cervix were determined by cervical scores in subsets of women both studies, n = 53 in A46796 (mean total score 3.6 LCS12 versus 3.5 Mirena) and n = 39 in A52238 (mean total score 3.1 LCS12 versus 2.9 LCS16). Low scores indicated thickening of cervical mucus for all treatments. Endometrial biopsies were taken on a yearly basis up to the end of the 3 year period in subsets of 30 per treatment arm in both studies. A strong progestin effect and secretory endometrium was observed in the majority of cases indicating a high degree of endometrial suppression during treatment (see Clinical safety below).

Individual values for available serum oestradiol concentrations (taken twice a week each week for 6 weeks each year, in a subset of approximately 20 women per treatment arm in each study) were stated to fall into the range for normal menstrual cycles; Cav values were between 98.8 and 126.6 pg/mL.

In A52238 in a subset of 205 subjects (LCS12 n = 102, LCS16 n = 103) there was no decrease in mean BMD; see under Clinical Safety.

In A52238 a subset (n = 12) had serum silver concentrations determined prior to and during treatment; no increases were detected with all concentrations except one pre-dose measurement below LLOQ of the bioanalytical method, 1 µg/mL; this LLOQ is within the range measured in populations not exposed to occupational silver, 0.072 to 1.4 µg/mL.
Clinical efficacy

Dose finding study A46796

This was a Phase II dose-finding multicentre randomised study in 5 European countries comparing LCS12 (n = 239), LCS16 (n = 245) and Mirena (n = 254) in parous and nulliparous women aged 21-40 years for 3 years. The mean age was about 32 years; the demographic and baseline characteristics of treatment groups were comparable. Of the 738 women, 159 were nulliparous (21.5%). A total of 208 women (28%, treatment groups comparable) discontinued study medication prematurely. Correct position of IUS in uterine cavity was seen in > 96% of women in all groups, and no difference in correct position of the IUS was seen between parous and nulliparous women. Total exposure was comparable; LCS12: 601.68 WY; LCS16: 611.48 WY; Mirena: 627.94 WY. The test IUS did not include the silver ring.

Primary variable: unintended pregnancy

There was one pregnancy in the LCS12 group, an ectopic pregnancy in the second year of treatment, compared to 5 in the LCS16 group (2 were ectopic) and nil in the Mirena group.

Thus the 3-year Pearl Indices (UL of 95% CI) were: LCS12: 0.17 (0.93), LCS16: 0.82 (1.92), Mirena: 0 (0.59) as shown below:

Table 8. Study A46796. Unadjusted Pearl Indices

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total exposure (WY)</th>
<th>Relevant exposure (WY)</th>
<th>Number of pregnancies</th>
<th>Pearl index</th>
<th>Lower 95% CIL</th>
<th>Upper 95% CIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCS12</td>
<td>Overall</td>
<td>601.68</td>
<td>597.17</td>
<td>1</td>
<td>0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>LCS16</td>
<td>Overall</td>
<td>611.48</td>
<td>606.66</td>
<td>5</td>
<td>0.82</td>
<td>0.27</td>
</tr>
<tr>
<td>LCS12&amp;16</td>
<td>Overall</td>
<td>1213.16</td>
<td>1203.83</td>
<td>6</td>
<td>0.50</td>
<td>0.18</td>
</tr>
<tr>
<td>Mirena</td>
<td>Overall</td>
<td>627.94</td>
<td>621.98</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>LCS12</td>
<td>2 years</td>
<td>422.55</td>
<td>420.90</td>
<td>1</td>
<td>0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>LCS16</td>
<td>2 years</td>
<td>431.22</td>
<td>429.81</td>
<td>4</td>
<td>0.93</td>
<td>0.25</td>
</tr>
<tr>
<td>LCS12&amp;16</td>
<td>2 years</td>
<td>853.77</td>
<td>850.71</td>
<td>5</td>
<td>0.59</td>
<td>0.19</td>
</tr>
<tr>
<td>Mirena</td>
<td>2 years</td>
<td>440.41</td>
<td>437.67</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>LCS12</td>
<td>3 years</td>
<td>598.79</td>
<td>595.07</td>
<td>1</td>
<td>0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>LCS16</td>
<td>3 years</td>
<td>608.47</td>
<td>604.53</td>
<td>5</td>
<td>0.83</td>
<td>0.27</td>
</tr>
<tr>
<td>LCS12&amp;16</td>
<td>3 years</td>
<td>1207.27</td>
<td>1199.60</td>
<td>6</td>
<td>0.50</td>
<td>0.18</td>
</tr>
<tr>
<td>Mirena</td>
<td>3 years</td>
<td>625.16</td>
<td>619.71</td>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

WY: women years; CIL: confidence interval limit

The cumulative failure rate (Kaplan-Meier analysis) over 3 years was 0.005 for LCS12 versus 0.0 in the Mirena group:

Table 9. Cumulative failure rates by year of treatment for all women and over 3 years of treatment, unadjusted – FAS, Study A46796

<table>
<thead>
<tr>
<th>N</th>
<th>Number of pregnancies</th>
<th>Total exposure time (WY)</th>
<th>Cumulative failure rate *</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCS12 Year 1</td>
<td>240</td>
<td>0</td>
<td>225.13</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>LCS12 Year 2</td>
<td>210</td>
<td>1</td>
<td>196.77</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>LCS12 Year 3</td>
<td>187</td>
<td>0</td>
<td>172.17</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Cumulative, 3-year failure rate for all women * and by subgroup</td>
<td>All women *</td>
<td>240</td>
<td>1</td>
<td>595.07</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>10-35 years</td>
<td>154</td>
<td>1</td>
<td>308.86</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>16-45 years</td>
<td>58</td>
<td>0</td>
<td>79.65</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>&gt;35 years</td>
<td>110</td>
<td>0</td>
<td>289.23</td>
<td>0.010</td>
</tr>
<tr>
<td>Parity</td>
<td>Nulliparous</td>
<td>52</td>
<td>0</td>
<td>107.85</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Parous</td>
<td>198</td>
<td>1</td>
<td>487.22</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Secondary variables

Bleeding and spotting days decreased gradually after the first 90-day reference period over the 3 year study. This is summarised in the following table; numbers 1 and 12 in the 2nd column refer to the sequential numbering of 90 day reference periods, that is, period 12 is the last in the 3 year study duration:

Table 10. Bleeding and spotting episodes in Study A46796

<table>
<thead>
<tr>
<th>Treatment</th>
<th>90-day reference period</th>
<th>No. of subjects</th>
<th>Mean length</th>
<th>SD</th>
<th>Mean maximum length</th>
<th>SD</th>
<th>Mean range of length</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCS12</td>
<td>1</td>
<td>227</td>
<td>9.89</td>
<td>0.96</td>
<td>16.3</td>
<td>1.15</td>
<td>11.4</td>
<td>1.14</td>
</tr>
<tr>
<td>LCS16</td>
<td>12</td>
<td>235</td>
<td>5.41</td>
<td>0.53</td>
<td>16.1</td>
<td>1.01</td>
<td>12.0</td>
<td>1.09</td>
</tr>
<tr>
<td>Mirena</td>
<td>12</td>
<td>235</td>
<td>4.21</td>
<td>0.20</td>
<td>5.3</td>
<td>0.97</td>
<td>2.2</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Amenorrhea was observed in 2.7%, 6.1% and 5.9% of subjects in the LCS12, LCS16 and Mirena groups respectively during the second 90 day reference period, increasing to 12.7%, 18.9% and 23.6% during the final 90 day reference period. From Month 7, 25% of women in all groups had 4 or more days bleeding in any one month.

Pivotal efficacy study A52238

This was as a multi-centre, open label, randomised, two-arm, parallel-group study in 11 countries in Europe and North and South America, in healthy women aged 18-35 years, nulliparous or parous, in need of contraception. The study was uncontrolled, that is, both arms were test products; women were randomised to one of two doses of the low dose levonorgestrel IUS, described by intended in vitro release rates 12 µg/24 h (LCS12, ‘Jaydess’) and 16 µg/24 h (LCS16). In this study the base intrauterine device had the silver profile added, as proposed for registration. The clinical evaluator noted there was no difference in correct position of the IUS between parous and nulliparous women. Women were not aware of which IUS had been inserted until the end of the 3 year period, when those with LCS16 could be included in the extension phase up to 5 years.

The full analysis set included 2884 participants in total; LCS12 n = 1432, LCS16 n = 1452. Total exposure times (women years (WY)) were LCS12 1217.78 versus LCS16 1252.78 over the first year, and 3058.62 versus 3211.36 over 3 years.

Primary efficacy was measured by the pregnancy rate, calculated as the Pearl Index (pregnancies per 100 WY) and by life table analysis. There were 10 pregnancies over 3 years in each group.

The 3 year unadjusted Pearl Index (UL of 95% CI) was 0.33 (0.60) for LCS12 and 0.31 (0.57) for LCS16:
Table 11. Pearl Indices by year of treatment for women 18 to 35 years of age, 3-year and Year 1 Pearl Indices by subgroup and treatment, unadjusted – FAS, Study A52238

<table>
<thead>
<tr>
<th>Pl by year of treatment and over 3 years, women 18 to 35 years of age a</th>
<th>LCS12</th>
<th>LCS16</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women / no. of pregnancies</td>
<td>Relevant exposure time (wy)</td>
<td>Pearl Index (unadj)</td>
</tr>
<tr>
<td>Year 1 Pl</td>
<td>1432 / 10</td>
<td>3058.62</td>
</tr>
<tr>
<td>Year 2 Pl</td>
<td>1162 / 9</td>
<td>1015.87</td>
</tr>
<tr>
<td>Year 3 Pl</td>
<td>960 / 2</td>
<td>825.17</td>
</tr>
<tr>
<td>3-year Pl</td>
<td>1432 / 10</td>
<td>3058.62</td>
</tr>
</tbody>
</table>

For nulliparous women, the 3-year Pearl Index was 0.36 (0.92) compared to 0.31 (0.67) for parous women in the LCS12 group:

Table 12. 3-year Pearl Index, women 18 to 35 years of age and by subgroup

<table>
<thead>
<tr>
<th>Age</th>
<th>LCS12</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35 years a</td>
<td>1432 / 10</td>
</tr>
<tr>
<td>18-25 years</td>
<td>556 / 4</td>
</tr>
<tr>
<td>26-35 years</td>
<td>866 / 6</td>
</tr>
</tbody>
</table>

The cumulative 3-year failure rate for all women (18-35 years) with LCS12 was 0.009 (95% CI 0.005, 0.017):

Table 13. Cumulative, 3-year failure rate by subgroup and treatment and by year of treatment for women 18 to 35 years of age, unadjusted – FAS, Study A52238

<table>
<thead>
<tr>
<th>LCS12</th>
<th>N</th>
<th>Number of pregnancies</th>
<th>Relevant exposure time (wy)</th>
<th>Cumulative failure rate</th>
<th>Lower 95% CL</th>
<th>Upper 95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>1432</td>
<td>5</td>
<td>1217.76</td>
<td>0.004 b</td>
<td>0.002</td>
<td>0.010</td>
</tr>
<tr>
<td>Year 2</td>
<td>1162</td>
<td>3</td>
<td>1015.87</td>
<td>0.003</td>
<td>0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Year 3</td>
<td>960</td>
<td>2</td>
<td>825.17</td>
<td>0.002</td>
<td>0.0001</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Cumulative, 3-year failure rate for women 18 to 35 years b of age and by subgroup

<table>
<thead>
<tr>
<th>Age</th>
<th>LCS12</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35 years a</td>
<td>1432</td>
</tr>
<tr>
<td>18-25 years</td>
<td>556</td>
</tr>
<tr>
<td>26-35 years</td>
<td>866</td>
</tr>
</tbody>
</table>

Table 14 (from Study A52238) shows women with clinically important bleeding:
Other efficacy parameters included menstrual bleeding, return to fertility and user satisfaction. Pooled trial results were also presented. The clinical evaluator concluded the study efficacy data supported the contraception indication in that the results were consistent with the EMA CHMP guidelines for Pearl Index criteria.

**Clinical safety**

Summaries of pooled safety data and examination of adverse events in each study are detailed in the clinical evaluation report (see Attachment 2 of this AusPAR). Exposure for LCS12 was 1488 women years for year 1 and 3779 women years at three years of treatment.

**Adverse events**

A higher proportion of nulliparous women (552/608, 90.8%) compared to parous women (850/1064, 79.9%) reported AEs overall for LCS12; for Mirena from the single study available the corresponding figures were 57/59 (96.6%) and 176/197 (89.3%). Among the most frequent AE reports in the pooled summary was the system organ class (SOC) ‘Reproductive and breast disorders’, reported by 359/608 (59%) nulliparous and 445/1064 (41.8%) of parous women who received LCS12, compared to 30/59 (50.8%) nulliparous and 114/197 (57%) parous women who received Mirena, the latter all from Study A46796.

For LCS12, the integrated statistical analysis indicates that in nulliparous (n = 608) and parous (n = 1064) women, occurrences of PID were 0 and 5 (0.5%) respectively, and for endometritis 3 (0.5%) and 11 (1.0%) respectively. For LCS12, pelvic pain was reported by 9% of nulliparous versus 4.1% of parous women.
The most common drug related AEs were acne and ovarian cyst. The most frequently reported serious drug-related AEs in pivotal Study A52238 for LCS12 as assessed by investigators were: appendicitis 6 (0.4%), ectopic pregnancy 3 (0.2%), ovarian cyst 4 (0.3%), spontaneous abortion 3 (0.2%), and PID 2 (0.1%).

The available data comparing SAEs for LCS12 (the non-market version of the device, without the silver ring attached) with the registered IUS Mirena are from Study A46796. Overall SAE rates in this study were n = 12 (5%) for LCS12 and n = 16 (6.3%) for Mirena; numbers in different event categories are small, as per Table 15.

**Table 15. Most frequent serious adverse events –FAS, Studies A52238 and A46796**

<table>
<thead>
<tr>
<th>Event</th>
<th>LCS12 n (%)</th>
<th>LCS16 n (%)</th>
<th>A46796 LCS12 n (%)</th>
<th>A46796 LCS16 n (%)</th>
<th>A46796 Mirena n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1432 (100)</td>
<td>1452 (100)</td>
<td>240 (100)</td>
<td>245 (100)</td>
<td>256 (100)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>66 (4.6)</td>
<td>71 (4.9)</td>
<td>12 (5.0)</td>
<td>12 (4.9)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>6 (0.4)</td>
<td>7 (0.5)</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>3 (0.2)</td>
<td>7 (0.5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Ovarian cyst</td>
<td>4 (0.3)</td>
<td>3 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (0.3)</td>
<td>4 (0.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td>2 (0.1)</td>
<td>4 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>3 (0.2)</td>
<td>2 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>2 (0.1)</td>
<td>4 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
</tbody>
</table>

There were no concerns arising from laboratory testing. The clinical evaluator noted there was no information for women with hepatic impairment.

**Events of special interest**

Expulsion rates were reported to be low (about 4%), with a trend to more in parous women and women ≤ 25 years. One perforation prior to insertion was reported. Insertion was successful in 99% of women.

From pooled data, 86/608 (14.1%) nulliparous women received anaesthesia at LCS12 insertion versus 48/1064 (4.5%) of parous women.

Insertion and removal was assessed by the investigator as ‘easy’ in about 90% and ‘very difficult’ in 2% of all women across the studies. In A46796 easier insertion of the LCS12 was reported versus Mirena in nulliparous women (Table 16):

**Table 16. IUS ease of insertion. Study A46796**

<table>
<thead>
<tr>
<th>IUS insertion</th>
<th>LCS12</th>
<th>LCS16</th>
<th>Mirena</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy</td>
<td>44 (84.6%)</td>
<td>43 (87.8%)</td>
<td>44 (75.9%)</td>
<td>131 (82.4%)</td>
</tr>
<tr>
<td>Very difficult</td>
<td>2 (3.8%)</td>
<td>1 (2.0%)</td>
<td>1 (1.7%)</td>
<td>4 (2.5%)</td>
</tr>
</tbody>
</table>

From pooled data for LCS12 (1672 insertions) pain reports in nulliparous women were: none 7.6%, mild 31.1%, moderate 44.7%, severe 16.6%, versus reports parous women: none 30.2%, mild 50.8%, moderate 16.1%, severe 2.7%. For Mirena (256 insertions) the corresponding frequencies were nulliparous women: 5.1%, mild 15.3%, moderate 57.6%, severe 20.3%, versus parous women: none 20.8%, mild 47.7%, moderate 28.4%, severe...
2.5%. Thus, even for ‘easy’ insertions, many nulliparous women would experience significant pain.

The data from Study A46796 suggest a trend for less pain on insertion for LCS groups than Mirena, but more than a quarter of nulliparous women receiving LCS12 experienced moderate to severe pain in this study (Table 17, below), and 10% nulliparous versus 3% parous had severe pain on removal.

Table 17. IUS insertion pain. Study A46796

<table>
<thead>
<tr>
<th>IUS insertion, pain</th>
<th>LCS 12 (100.0%)</th>
<th>LCS 16 (100.0%)</th>
<th>Mirena (100.0%)</th>
<th>Total (100.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>239 (100.0%)</td>
<td>245 (100.0%)</td>
<td>254 (100.0%)</td>
<td>738 (100.0%)</td>
</tr>
<tr>
<td>mild</td>
<td>101 (42.3%)</td>
<td>112 (45.7%)</td>
<td>103 (40.6%)</td>
<td>316 (42.8%)</td>
</tr>
<tr>
<td>moderate</td>
<td>55 (22.2%)</td>
<td>59 (24.1%)</td>
<td>90 (35.4%)</td>
<td>202 (27.4%)</td>
</tr>
<tr>
<td>severe</td>
<td>12 (5.0%)</td>
<td>9 (3.7%)</td>
<td>17 (6.7%)</td>
<td>38 (5.1%)</td>
</tr>
<tr>
<td>missing</td>
<td>1 (0.4%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
</tr>
</tbody>
</table>

The overall ectopic pregnancy rate from the pooled trial data was 0.11 per 100 women years for LCS12 and 0.24 per 100 women years for LCS16. However, no ectopic pregnancy was reported for Mirena from study A46796. While the ectopic pregnancy rate for Jaydess is low, lack of comparison with Mirena in the pivotal study raises concern that there may be an undetected clinically significant difference in risk of pregnancy, and specifically ectopic pregnancy.

There were no concerns raised from gynaecological findings. Ultrasound of endometrium showed comparable low levels (< 1%) of abnormal findings in all groups after 36 months.

There was no decrease in mean bone mineral density (BMD) in subgroup testing from Study A52238:

Table 18. Bone mineral density measurements. Study A52238

<table>
<thead>
<tr>
<th>No. of subjects (BL)</th>
<th>Mean BMD (BL)</th>
<th>SD</th>
<th>No. of subjects (ES/M36)</th>
<th>Mean BMD at ES/M36</th>
<th>SD</th>
<th>Change from BL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCS 12</td>
<td>102</td>
<td>1.1829</td>
<td>0.1313</td>
<td>68</td>
<td>1.2118</td>
<td>0.1283</td>
</tr>
<tr>
<td>LCS 16</td>
<td>102</td>
<td>1.1793</td>
<td>0.1254</td>
<td>71</td>
<td>1.2132</td>
<td>0.1309</td>
</tr>
<tr>
<td>Total hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCS 12</td>
<td>102</td>
<td>1.0404</td>
<td>0.1299</td>
<td>80</td>
<td>1.0466</td>
<td>0.1291</td>
</tr>
</tbody>
</table>

In A46796, endometrial histology evaluation was normal for all women tested at years 1, 2, and 3 (n = 90) with marked progesterone effect in all three treatment groups; 1 woman each in LCS12 and LCS16 groups had abnormalities at baseline. In A52238 a subset of n = 60 women, (LCS12 n =31) had endometrial histology studied; again one woman in each LCS group had abnormalities at baseline. At month 12 and 24 endometrium was secretory in all classified; at month 36 it was secretory in 46/48 women and proliferative in one for whom previous biopsies were secretory, and unclassified in another.

Clinical evaluator’s recommendation

Overall, the clinical evaluator found there were no new safety concerns compared to Mirena, but recommended ongoing monitoring for ectopic pregnancies, PID and expulsions, as well as outcomes in women with BMI > 35.

The clinical evaluator considered the benefit-risk balance was favourable on a population basis, provided pharmacovigilance and education (including selection of suitable patients) was ensured. There was concern about risk to future fertility particularly in nulliparous
women due to ectopic pregnancies and PID. The evaluator recommended the Indication should be 'Contraception for 3 years', as this is different to Mirena.

### Risk management plan

The RMP evaluator made recommendations with respect to risk minimisation activities for ectopic pregnancy and the currency of education for insertion. Most aspects of the RMP were acceptable. The sponsor provided assurance that the printed materials would be provided to the TGA when available.

### Risk-benefit analysis

#### Delegate considerations

1. The drug delivery rate for Jaydess is not steady. The construction of the drug reservoir is different to Mirena. There is apparently an initial 'burst effect', with high early release rates and a different profile compared to Mirena, based on the available data.

   *In vitro* rates of release were approximately 30 µg/24 h in the first few days, or possibly up to 55 µg/24 h on the first day. The average *in vitro* release rates are given during weeks 3-4 (sampling from days 19-25) because this is when the plateau describing membrane-controlled release is reached. The estimated *in vivo* release rate is approximately 14 µg/24 h after 24 days, 10 µg/24 h after 60 days, and 5 µg/24 h after 3 years; thus the 'average' is 6 µg/24 h over the period of 3 years.

2. Jaydess is proposed for contraceptive protection over a period of up to 3 years, compared to 5 years for the currently approved Mirena.

   The base IUD for Jaydess is somewhat smaller than Mirena; it is stated in the sponsor’s letter of application that this was designed ‘to aid successful insertion, particularly in young and nulliparous women’. Of note, the additional approved indications for Mirena of *menorrhagia* and *use with oestrogen replacement therapy* are not proposed for Jaydess.

   Clinical use was compared to Mirena only in the Phase II dose-finding trial A46796; this trial did not use the final commercial Jaydess product with silver ring.

   The pivotal Study A52238 used the modified IUS proposed for registration, but did not compare efficacy and safety with the Mirena. Therefore there are no directly comparable data, in particular for important SAEs such as ectopic pregnancy and PID.

   For the Jaydess PI the sponsor proposes to delete several precautionary statements that are found in the Mirena PI, including the following: *(Jaydess)*..‘is not the method of first choice for young nulligravid women. Previous studies indicate that women with many sexual partners are more susceptible to infections (see Pelvic Infections).’ In addition, it was proposed to include under *Paediatrics* the following extrapolation: ‘Safety and efficacy has been studied in women aged 18 and over. Efficacy and safety is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older.’

   This implies that the sponsor considers that the data support Jaydess as a method of first choice for young nulligravid women, by comparison with Mirena. The clinical data included significant numbers of nulliparous women, as for the original registration of Mirena. However there appears to be no statistically supported evidence for easier insertion, or for decreased rates of AEs compared to Mirena, to justify such a change. For example, the ectopic pregnancy rate for LCS12/Jaydess was
0.11 per 100 women years, versus the cited rate of 0.06/100 women years for Mirena, but in this dossier there were no pregnancies, ectopic or otherwise, reported for Mirena, whereas with LCS12 there were 4 ectopic pregnancies, and 11 pregnancies overall, reported in pooled data. It was also noted that for unsuccessful insertions of LCS12, ‘malfunction of the inserter’ was frequently given as the reason.

The Delegate has concerns that the new IUS Jaydess is to be promoted for use in nulliparous women, without specific data to support increased safety compared to the currently registered Mirena.

The Delegate requested that the sponsor’s response to the Delegate’s Overview provide justification for the claim of improved efficacy and safety for nulliparous women for Jaydess compared to Mirena. Clarification regarding the inserter proposed for registration was also required; it was not clear if it is identical to the new Mirena inserter, or whether it has a slightly smaller diameter as described in the letter of application and the dossier?

3. A specific issue is that extrapolation from ‘non-clinical testing’ has been cited to support safety of magnetic resonance imaging (MRI) under specified conditions, for women with Jaydess IUS with silver ring profile in situ. There appears to have been no information provided for TGA evaluation to support the proposed PI statement under the sub-heading Magnetic Resonance Imaging (MRI).

4. The Jaydess PI is based on the currently approved Mirena PI; however there are many proposed changes to the text, and several versions have been provided during the evaluation process. The sponsor was requested to provide updated draft PI incorporating all changes recommended by various evaluation areas of the TGA and in the Delegate’s Overview.

Overall, the PK modelling suggested more variable levonorgestrel plasma levels over the first year compared to relatively steady levels over the next two years. The pharmacodynamic data showed lower frequency of amenorrhea and low frequency of suppression of ovulation with Jaydess compared to Mirena. Lower rates of amenorrhea may have bearing on acceptance or discontinuation rates. Lack of ovulation suppression is not considered to impact on the preventative efficacy which is principally a local effect on the uterine endometrium and cervical mucous. The observed efficacy of Jaydess was consistent with the adopted guidelines and comparable but nevertheless lower than Mirena, which may be an issue at individual user level. However, consistently lesser suppression of ovulation may have an unspecified relation with ectopic pregnancy. The data indicated higher relative risk of ectopic pregnancy (1.8 fold) with Jaydess compared to Mirena. The sponsor was requested to comment on these issues in its response to the Overview.

Proposed action

A recommendation was not proposed at this stage. The decision regarding registration was to be made once the sponsor’s response to the Delegate’s Overview was reviewed by TGA and the advice from ACPM became available.

Request for advice from ACPM

The Delegate proposed to seek general advice on this application from the ACPM in addition to requesting the committee address matters raised in the Overview (above).

3 Details of recommendations and revisions regarding the PI are beyond the scope of the AusPAR.
Response from sponsor

The sponsor's response to matters raised in the Delegate's Overview has not been included in this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM) having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Jaydess intrauterine drug delivery system containing 13.5 mg of levonorgestrel to have an overall positive benefit–risk profile for the amended indication:

Contraception for three years

Proposed conditions of registration:

The ACPM advised that the conditions of registration should include the following:

- Subject to satisfactory negotiation of the RMP most recently approved by the TGA, including provision of physician and consumer educational materials to the TGA. The need for notifying imaging staff concerning the silver collar before MRI procedures should be reflected in these documents.

- Negotiation of PI and CMI to the satisfaction of the TGA. The committee supported the Delegate's view that all safety information and precautions currently in the Mirena PI should be included in the Jaydess PI.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- A statement in the relevant sections of the PI and the CMI to ensure procedures are known and understood in the case of an unplanned pregnancy

- A statement in the CMI to ensure correct disposal procedures in case of expulsion in a domestic situation.

- A statement in the CMI that accurately reflects the information on the silver collar for MRI purposes.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Jaydess levonorgestrel 13.5 mg intrauterine drug delivery system, indicated for:

Contraception for up to 3 years.

Specific conditions applying to these therapeutic goods

March 2013), in associated with submission PM-2012-01933-3-5, and any subsequent revisions, as agreed with the TGA must be implemented in Australia.

**Attachment 1. Product Information**

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at [http://www.tga.gov.au/hp/information-medicines-pi.htm](http://www.tga.gov.au/hp/information-medicines-pi.htm).

**Attachment 2. Extract from the Clinical Evaluation Report**