# Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

# Levonorgestrel

# UK/W/0083/pdWS/001

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| **Rapporteur:** | UK |
| **Finalisation procedure (day 120):** | 18 January 2016 |

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**ADMINISTRATIVE INFORMATION**

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| Invented name of the medicinal products: | See section XII |
| INN (or common name) of the active substance: | Levonorgestrel |
| MAH(s): | See section XII |
| Pharmaco-therapeutic group (ATC Code): | Microlut: G02BA03<br>Jadelle: G03AC03<br>Mirena: G02BA03 |
| Pharmaceutical forms and strengths: | Microlut: Coated tablet; 30 µg<br>Jadelle: Implant; 75 mg<br>Mirena: Intrauterine delivery system (IUS); 52 mg |

# I. EXECUTIVE SUMMARY

This is a data submission for levonorgestrel in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. The UK is the rapporteur for this procedure.

One MAH has submitted data from company-sponsored clinical trials and published literature regarding the use of levonorgestrel in the form of progestogen-only pill (Microlut), progestogen-only implant (Jadelle) and levonorgestrel-releasing intrauterine system (Mirena) in the paediatric population.

As stated in the 'WHO Medical Eligibility criteria for contraceptive use – 2009', *in general, adolescents are eligible to use any method of contraception and must have access to a variety of contraceptive choices.*

The three methods of contraception discussed in this work-sharing procedure are amongst the armamentarium of contraceptive choices available to adolescents.

The MAH considers that the benefit-risk balance for levonorgestrel in the above forms remains unchanged in the paediatric population.

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit-risk balance of levonorgestrel in the form of progestogen-only pill (Microlut), progestogen-only implant (Jadelle) and levonorgestrel-releasing intrauterine system (Mirena) remains unchanged for the paediatric population.

# II. RECOMMENDATION

Based on the review of the submitted paediatric data, Summary of Product characteristics (SmPC) changes are proposed in sections 4.2 and Package leaflet (PL) changes are proposed in section 1.

**Summary of outcome**

- ☐ No change
- ☒ Change
  - ☐ New study data
  - ☐ New safety information
  - ☒ Paediatric information clarified: <section 4.2>
  - ☐ New indication

The final SmPC and PL recommendations are presented below:

**SUMMARY OF PRODUCT CHARACTERISTICS**

**Section 4.2 Posology and method of administration**

*[This section should be amended to include the below wording]*

*[…]*

*Paediatric population*
There is no relevant indication for the use of <product name> before menarche

**PACKAGE LEAFLET**

**1. What <product name> is and what it is used for**

*[This section should be amended to include the below wording]*

*[…]*

*Children and adolescents*
<Product name> is not indicated for use before the first menstrual bleeding (menarche).

# III. INTRODUCTION

On 23.04.2015, the MAH submitted paediatric data for levonorgestrel, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

The MAH submitted the following documentation as per procedural guidance:

- An expert overview for each of the following products containing levonorgestrel:
  (i) Microlut
  (ii) Jadelle
  (iii) Mirena

- Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) for Jadelle (Levonorgestrel implants) covering the period 24 December 2010 to 23 December 2014.

- PBRER/PSUR for Levonorgestrel intrauterine delivery system covering the period 28 September 2010 to 23 December 2014.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the clinical studies

The MAH provided the following information on the three products:

**Microlut**

Microlut is an oral progestogen-only pill for hormonal contraception. Microlut is provided in calendar-packs for four and five weeks with 28 and 35 tablets, respectively. Each tablet contains 30 µg levonorgestrel (LNG) as active ingredient. The dosage of Microlut is one tablet daily without any break, taken at the same time each day.

*Therapeutic indication:*
Contraception

*Mechanism of action:*
The continuous daily ingestion of 30 µg LNG prevents conception in several independent ways. Mainly, there are changes in the cervical mucus which make the migration and ascent of sperm difficult. Furthermore, changes in the endometrium throughout the cycle can be considered as having the effect of rendering nidation difficult. Ovulation is not inhibited in the majority of women, but continuous daily ingestion of 30 µg LNG can impair the mid-cycle gonadotropin peaks and the corpus luteum function which may contribute to the contraceptive action.

*Licensing status:*
Worldwide, Microlut® 35 is currently licensed in 19 countries and Microlut® 28 is currently licensed in 3 countries.

***Rapporteur's comments:***
The MAH has not provided information on the licensing position of Microlut in different EU member states. This information will be requested as part of the request for supplementary information (see section IX).

**Jadelle**

Jadelle consists of two implants to be inserted subdermally. The implants are either preloaded inside a disposable inserter (Jadelle 2 x 75 mg implants) or they can alternatively be inserted with the sterile disposable Jadelle trocar (Jadelle sine inserter 2 x 75 mg implants). The implants are about 43 mm in length and 2.5 mm in diameter. Each implant contains 75 mg of levonorgestrel. The release rate of levonorgestrel is about 100 µg/day at one month after insertion, declining to about 40 µg/day within one year, to about 30 µg/day within 3 years, and to about 25 µg/day within five years. Jadelle is a contraceptive method for long-term use (up to five years).

*Therapeutic indication:*
Contraception

*Mechanism of action:*
Levonorgestrel is a progestational steroid that suppresses Follicle-stimulating hormone, Luteinizing hormone and ovulation, and changes the cervical mucus so that sperm migration is inhibited.

*Licensing status:*
In EU, Jadelle 2 x 75 mg implants (preloaded) is registered in two countries (Finland, Portugal) and Jadelle sine inserter 2 x 75 mg implants is registered in Finland only.

**Mirena**

Mirena is a levonorgestrel intrauterine delivery system (LNG-IUS) containing 52 mg of levonorgestrel. Mirena consists of a white or almost white drug-elastomer core covered with an opaque drug release controlling membrane, which is mounted on the vertical stem of a T-body. The T-body has a loop at one end of the vertical stem and two horizontal arms at the other end. Removal threads are attached to the loop.

Mirena is placed in the uterus with a preloaded, ready-to-use inserter. The in vivo release rate of levonorgestrel in the uterine cavity is initially approximately 20 µg/24 hours and declines to 10 µg/24 hours after five years.

*Therapeutic indications:*
Contraception
Idiopathic menorrhagia

In addition, the indication 'Dysmenorrhea' is approved in the EU in Finland only.

*Mechanism of action:*
LNG-IUS has mainly local progestogenic effects within the uterine cavity. The levonorgestrel concentration achieved in the endometrium down-regulates endometrial estrogen and progesterone receptors, making the endometrium insensitive to the circulating estradiol and a strong anti-proliferative effect is seen. Morphological changes of the endometrium and a weak local foreign body reaction are observed during use of LNG-IUS. Thickening of the cervical mucus prevents passage of sperm through the cervical canal. The local milieu of the uterus and of the fallopian tubes inhibits sperm mobility and function, preventing fertilization. Ovulation is inhibited in some women using Mirena.

*Licensing status:*
Mirena is licensed in all EU countries.

***Rapporteur's comments:***
For this paediatric work-sharing procedure, the MAH has submitted data on three different methods of contraception containing levonorgestrel:

| | |
|---|---|
| 1. Progestogen-only pill | Product name: Microlut |
| 2. Progestogen-only implant | Product name: Jadelle |
| 3. Levonorgestrel-releasing intrauterine system | Product name: Mirena |

In the UK, there are contraceptive services available to young people and the Faculty of Sexual and Reproductive Healthcare has published guidance on 'Contraceptive choices for young people' (March 2010). The guidance is relevant to young people under 18 years of age and is intended for use by health professionals providing contraceptive services to young people. This guidance makes reference to the *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC) which provides recommendations on which contraceptive methods can be used safely in individuals based on age.

The table below lists the UKMEC categories for contraceptive methods in relation to age.

| Method | Age | UKMEC Category |
|---|---|---|
| Combined hormonal contraception (combined oral contraception, vaginal ring, patch) | Menarche to <40 years<br>≥40 years | 1<br>2 |
| Progestogen-only pill | Menarche onwards | 1 |
| Progestogen only implant | Menarche onwards | 1 |
| Progestogen-only injectable (DMPA or NET-EN) | Menarche to <18 years<br>18–45 years<br>>45 | 2<br>1<br>2 |
| Barrier methods (condoms, diaphragms, cervical caps) | Menarche onwards[a] | 1 |
| Copper-bearing intrauterine device | Menarche to <20 years<br>≥20 years | 2<br>1 |
| Levonorgestrel-releasing intrauterine system | Menarche to <20 years<br>≥20 years | 2<br>1 |

[a]The CEU recommends that condoms can be used before menarche if required.
DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enantate.

| | |
|---|---|
| UKMEC 1 | A condition for which there is no restriction for the use of the contraceptive method. |
| UKMEC 2 | A condition where the advantages of using the method generally outweigh the theoretical or proven risks. |

As per the UKMEC, there is no restriction for the use of the progestogen-only pill and progestogen-only implant from menarche onwards. The advantages of using the levonorgestrel-releasing intrauterine system generally outweigh the theoretical or proven risks from menarche to <20 years and there is no restriction for the use of this product in women older than 20 years.

The 'WHO Medical Eligibility criteria for contraceptive use – 2009' states that: *'In general, adolescents are eligible to use any method of contraception and must have access to a variety of contraceptive choices. Age alone does not constitute a medical reason for denying any method to adolescents. While some concerns have been expressed regarding the use of certain contraceptive methods in adolescents (e.g. the use of progestogen-only injectables by those below 18 years), these concerns must be balanced against the advantages of avoiding pregnancy. It is clear that many of the same eligibility criteria that apply to older clients apply to young people.'*

For the three contraceptive methods discussed in this work-sharing procedure, the WHO Medical Eligibility criteria for contraceptive use (2009) recommend the following categories for adolescents:

| Method | Age | Category |
|---|---|---|
| **Progestogen-only pill** | Menarche to < 18 years | 1 (Use method in any circumstances) |
| **Levonorgestrel implant** | Menarche to < 18 years | 1 (Use method in any circumstances) |
| **Levonorgestrel-releasing IUD (20 µg/24 hours)** | Menarche to < 20 years | 2 (Generally use the method) |

## IV.2 Non-clinical aspects

The MAH has reported that there are no non-clinical data relevant for the paediatric assessment of Microlut, Jadelle and Mirena.

## IV.3 Clinical aspects

**Introduction**

For each product, the MAH has provided an overview of efficacy data from available company-sponsored clinical trials and from the literature.

**Clinical studies**

**Microlut**

- **Efficacy Reported from MAH Clinical Trials**

The MAH identified one study which was performed in adult women but also included adolescents. The objective of this clinical study was to determine the contraceptive efficacy of Microlut® and to provide reliable data for a calculation of the Pearl Index. This clinical trial was carried out over the period of 18 months (Evaluation I), subsequently continued for the maximum period of 24 treatment cycles and evaluated again (Evaluation II).

**Clinical Study of SH 9.0999C (Microlut®) (Evaluation I), March 1971**

This clinical trial was carried out as an open, uncontrolled, multi-centre study (16 centres in seven countries - Columbia, Ecuador, Honduras, Mexico, Austria, Peru, Venezuela) in order to assess the contraceptive efficacy, cycle control and tolerability of Microlut®. The results for 1,969 women (total of 15,939 cycles) were available for evaluation purposes (Evaluation I). The treatment lasted a full 6 months for 1,459 women, a full 12 months for 740 women and a full 18 months for 132 women.

*Age distribution*

0.2% (n=3) were aged between 11 and 15 years. 7.5% (n=147) were aged between 16 and 20 years of age.

The majority of women, 80.4% (n=1,575), were aged between 21 and 35 years. 1% (n=19) were > 40 years of age and no age was given for 0.6% (n=11).

*Pregnancies*

There were 55 pregnancies reported over the first course (up to 18 months) of the trial. This corresponds to a rate of 4.14 pregnancies per 100 women-years (Pearl Index). However, 43 of the pregnancies were due to non-compliance. Based on the remaining 12 pregnancies, the actual drug failure index was 0.9, i.e. less than one pregnancy per 100 women-years. All born children were normally developed.

*Paediatric considerations*

No specific issues or concerns were reported for paediatric patients with regards to duration of menstrual bleeding, intensity of menstrual / withdrawal bleeding, spotting and intermenstrual bleeding, tolerability and acceptance of Microlut® use.

**Microlut® Clinical Trial Results (Evaluation II), March 1973**

The clinical trial described above was continued by some investigators after "Evaluation I" and after registration of Microlut® in Germany in order to assess the efficacy and tolerability of Microlut® over a prolonged treatment period.

Following a second recruitment phase after Evaluation I, the total number of women participating in the study amounted to 3,218. In total, Microlut® was used by 3,218 women over a maximum of 24 treatment cycles in order to record contraceptive efficacy and tolerability. The study population (n= 3,218) includes the subpopulation (n= 1,969) already included in the "Evaluation I" from March 1971. The treatment lasted a full 6 months for 2,430 women, a full 12 months for 1,640 women, a full 18 months for 832 women and a full 24 months for 346 women.

*Age distribution*

0.1% (n= 4) were aged between 11 and 15 years, 8.9% (n= 286) were aged between 16 and 20 years of age.

The majority of women, 79.3% (n= 2,542), were aged between 21 and 35 years. 1.6% (n= 49) were > 40 years of age and no age was given for 0.5 % (n= 16).

*Pregnancies*

In total, there were 90 pregnancies reported over the complete course (up to 24 months) of the trial. This results in the uncorrected Pearl Index of 4.19 with an upper limit of the two-sided confidence interval of 5.15. The calculation of the Pearl Index was based on 27,939 treatment cycles (1,640 women treated for 12 months), e.g. estimated number of women with reduced fertility such as older women or breast-feeding women were excluded from the sample size and the use of additional methods of non-hormonal contraception (e.g. condoms) were taken into account. The analysis of the study results showed that for the majority of pregnancies observed, poor patient compliance can be assumed and the pregnancy can be considered to be subject failures. In 31 of 90 cases, user error was not found. These pregnancies were attributed to failure of the medication. For method failure only, a corrected Pearl Index of 0.9 was found.

*Paediatric considerations*

No specific issues or concerns were reported for paediatric patients with regards to duration of menstrual bleeding, intensity of menstrual / withdrawal bleeding, spotting and intermenstrual bleeding, tolerability and acceptance of Microlut® use

*MAH conclusions from the above clinical trial*

In a sample of 3,218 fertile women including adolescent subjects, Microlut® proved to have an adequate contraceptive effect when taken as directed. The majority of treated women retained their customary menstrual bleeding patterns. Overall tolerance and acceptance was good.

When comparing adult versus adolescent women, no data was analysed according to specific age groups. Thus, no differentiating statement or conclusion with respect to these different age groups can be drawn. However, there is no indication for any differences between adolescent and adult women regarding the treatment with Microlut®.

- **Contraceptive Efficacy Information Reported in the Literature**

In February 2015, the MAH conducted a literature search in databases like Medline, Embase, Biosis, Current Contents, Derwent Drug File and the company's Product Literature Database to identify any articles mentioning the use of "progestogen-only pills" / "progestin-only pills" and

"levonorgestrel" and “Microlut” in children and adolescents (below age of 18 years), regardless of the indication.

A total of 13 published studies or reviews were analysed. Only one of the publications was considered to be meaningful for the purpose of the submitted clinical overview. In all other publications either no women below 18 years of age were included or data were not analysed according to specific age groups. The relevant publication is presented below:

> **Huber A (1974)** - In 1974, Huber published clinical data regarding his experiences with Microlut® in the use of adolescents. A group of 35 patients aged 14 – 18 years was treated with Microlut® over a period of 18 months (358 cycles). Overall, the preparation was well tolerated. In 7 cases, slight and mostly transient side effects such as nausea and headache were reported. However, 46% (n=16) of the patients expressly elected to discontinue treatment over the course of the study due to bleeding anomalies: oligomenorrhea (n=8), polymenorrhea (n=6), menorrhagia (n=2). The contraceptive efficacy was ensured as no pregnancy occurred during the trial.

- **MAH efficacy conclusions**

Historically, the safety and efficacy of oral progestin-only contraceptives including Microlut® have been established in women of reproductive age. Safety and efficacy are expected to be the same for adolescents under the age of 18 years and for users 18 years and older. In practice, oral progestin-only contraceptives including Microlut® are considered safe for girls younger than 18, as long as they are already menstruating.
In summary, the published data do consistently indicate that there is no evidence for potential impact in the benefit-risk assessment for Microlut® when used in women below 18 years of age in accordance with the recommendations and guidance given in the current Microlut® Company Core Data Sheet.

***Rapporteur’s comments:***
The submitted data do not provide new efficacy information for paediatric use and do not change the benefit-risk balance of Microlut.

**Jadelle**

- **Efficacy Reported from MAH Studies**

There were no MAH-sponsored clinical or post-marketing studies with Jadelle that included patients <18 years old.

- **Contraceptive Efficacy in Studies not Conducted by the MAH**

Even though the main focus of the submitted overview document is on Jadelle, the MAH has also included some published data concerning another levonorgestrel implant Norplant.

> Norplant consists of six flexible closed capsules containing levonorgestrel. Each of the six capsules contains 36 mg of levonorgestrel in dry, crystalline form. Norplant contraceptive implant was the first contraceptive implant developed by the Center for Biomedical research of the Population Council (US).

The MAH identified the following studies in PubMed search with key words Norplant OR Jadelle AND adolescent and presented them in alphabetical order:

1. **Berenson et al (1995)** conducted a case-control study in 94 adolescents using Norplant, comparing to age-matched adolescents using oral contraceptives during the same study period. Information on pregnancy status, satisfaction, continuation rate and condom practice was obtained. The study period was 6 months. None of the Norplant users and 6 of the oral contraceptive users became pregnant during the study period (p=0.03). This was despite only 15% of Norplant users but 40% of oral contraceptive users reported concomitant condom use. According to the authors, the study demonstrates the importance of the difference between the theoretical and the actual effectiveness of these contraceptive methods.

2. **Berenson et al (1997)** reported a follow-up study of the prospective case-control study mentioned above, with follow-up of 12 months. At 12 months, 56 Norplant users and 56 oral contraceptive (OC) users were compared with regards to pregnancy, continuation rate and satisfaction. By 12 months of follow-up, none of the Norplant users and 14 (25%) of OC users had become pregnant (p=0.01), despite a higher proportion (21%) of OC users reported always using concomitant condoms, compared to Norplant users (9%).

3. **Blumenthal et al (1994)** reported a follow-up study of 280 post-partum and post-abortal adolescents who chose either Norplant or some other method of contraception at the time of their procedure (abortion, delivery). They were interviewed between 6 and 18 months after the index procedure. A total of 92 adolescents used Norplant while 188 chose another method (combined oral contraceptives, condoms or no method). After 1 year, none of the Norplant users experienced a pregnancy, compared to 25% of combined oral contraceptive users, and 40% of condom users (p<0.01). The most frequent reason for discontinuation was side-effects (not significant between groups). In the combined oral contraceptives group, these were followed by failure to remember to take the pill, and contraceptive failure.

4. **Cardamakis et al (2002)** reported on a prospective study of 13 adolescents using Norplant. No pregnancies were observed during a follow-up of 24 months.

5. **Darney et al (1999)** conducted a prospective cohort study to determine whether teens initiating Norplant use condoms less frequently than teens using oral contraceptive pills or condoms alone and may therefore be at an increased risk of acquiring sexually transmitted infections. The study included 200 Norplant users, 100 OC users and 99 condom users. No teens using Norplant contraceptive implants became pregnant, 33% of condom users and 30% of oral contraceptive users became pregnant while using their method during the 2 years of the study. This was despite Norplant contraceptive implant users were less likely than oral contraceptive or condom users to report condom use at last sex or consistent condom use at 1- and 2-year follow-up.

6. **Dinerman et al (1995)** performed a prospective comparative study on 54 Norplant, 64 OC, and 48 other method using adolescents for 6 months. Despite similar reports of sexual activity, one subject who used the implant (2%) vs 13 subjects who used oral contraceptives (20%), and eight subjects who used other methods (17%) became pregnant.

7. **Glantz et al (1995)** performed a prospective study in 122 adolescents using Norplant for 12 months. No conceptions occurred during Norplant use, but 3 subjects were later diagnosed having been pregnant already at the time of Norplant insertion.

8. **Levine et al (1996)** performed a prospective 50-month study on adolescent and adult women using Norplant (n=1800). Follow-up data were available for 93.8% (n=1688) of these patients which included adolescents (n=674) and adults (n=1014). Over a 50-month period, two pregnancies occurred in the whole population resulting in a failure rate of 0.11%.

However, in one case, the patient was probably pregnant at the time of insertion (6 weeks postpartum). The second patient was found to be pregnant 37 months after device placement.

9. **Rosenthal et al (1995)** performed a retrospective chart review of 72 adolescents using Norplant. The mean follow-up time was 18 months (range 12 to 29 months). The study did not report pregnancies.

➢ **Guidelines:**

In addition to the publications described above, the MAH reported that there are several recent guidelines that support the use of subdermal contraceptive implants in adolescents:

- The American College of Obstetricians and Gynecologists (ACOG) states in the committee opinion number 539 from 2012 the following: "adolescents should be encouraged to consider long-acting reversible contraception (LARC) methods. The LARC methods include intrauterine devices and the contraceptive implant."

- The American Academy of Pediatrics state in their policy statement on contraception for adolescents (2014) that the top tier methods of contraception, including intrauterine devices (IUDs) and implants, should be considered as first-line choices for adolescents, regardless of parity.

- The WHO medical eligibility for contraceptive use (2009) recommend use of implants for women <18 years as category "1 – no restrictions".

➢ **MAH efficacy conclusions**

In summary, the MAH considers that currently available evidence suggests that the contraceptive efficacy of Jadelle is comparable to that seen in adult women. While the MAH acknowledges that this evidence is based on observational prospective or retrospective studies with the 6-rod LNG-releasing implant Norplant, the MAH considers that there is no reason to suspect that the efficacy profile would be different between Norplant and Jadelle in adolescents. Use of subdermal implant as a first-line method of contraception in adolescents is also supported by international guidelines, without any current restrictions for use.

***Rapporteur's comments:***

The rapporteur notes that the presented evidence from the literature refers to the LNG-releasing implant Norplant. The submitted data do not provide new efficacy information regarding the use of Jadelle in paediatrics.

It is noted that international guidelines indicate that the LNG-releasing implant is a long-active reversible contraception method that can be considered for use in adolescents.

**Mirena**

➢ **Overview of clinical pharmacology**

No MAH-sponsored clinical pharmacology studies with Mirena have been conducted to investigate pharmacodynamics and pharmacokinetics in patients < 18 years of age.

During the development of another levonorgestrel-releasing intrauterine system Jaydess, the MAH has reported that a paediatric clinical trial was conducted in post-menarcheal female adolescents (CSR PH-37272). Jaydess is a low dose levonorgestrel contraceptive system for intrauterine contraception with an initial *in vitro* release rate of 12µg/day. The mechanism of

action of Jaydess and Mirena is the same: Levonorgestrel (LNG) has a local progestogenic effect on the endometrium leading to endometrial suppression and a progestogenic effect on the cervical mucus leading to its thickening which inhibits sperm mobility and function. In addition, the device has a weak foreign body effect supporting contraceptive efficacy. Systemic concentrations of LNG are low and related to the intrauterine release from the intrauterine device.

The paediatric clinical trial CSR PH-37272 was completed in June 2013. It was a 1-year, multi-centre, single arm study to assess the safety, efficacy and discontinuation rate of Jaydess in post-menarcheal female adolescents under 18 years of age. The mean age of included subjects (n=304) was 16.2 years (range 12 to 18 years, with a majority of subjects being between 15 and 18 years. One subject was 12 years old, 1 subject 13 and 23 subjects were 14 years old. In this study, a population pharmacokinetic (PK) evaluation was performed based on sparse blood sampling (n=283). The mean serum concentrations of total LNG decreased from average concentrations of 145ng/L at 1 month to 90.9ng/L at 6 months. Thereafter, the decrease was slightly slower until 77ng/L at 12 months after insertion. The included covariate analysis revealed no age-related differences in the LNG PK. However, an effect of body weight on the clearance parameter (LNG clearance increases linearly by 1.5% per kg body weight) has been estimated, but no additional independent effect of age. The residual LNG content was determined in the used Jaydess devices collected from subjects who prematurely discontinued the study treatment in order to determine the performance of Jaydess. These data were well in accordance with previous residual content measurements in adults, showing that the amount of LNG released over time in adolescents is equivalent to the amount of LNG released in adults.

The estimated mean serum concentration values in post-menarcheal female adolescents were compared to adult concentration data and were found to be slightly higher. The higher mean is explained by, on average, a lower body weight of adolescents and the covariate effect of body weight on the LNG clearance. A 10% lower median body weight (60 kg in adolescents versus 66 kg in adults) leads on average to a 9.6% lower apparent clearance in adolescents. The lower body weight associated with lower clearance results in higher systemic exposure. Compared to serum concentrations in adults, the estimated mean serum concentrations in adolescents were 10.7% higher at 1 month, 10.2% higher at 3 months and 9.6% higher at 12 months. Despite these slightly higher mean serum concentrations in adolescents, the estimated ranges lie completely within the ranges estimated for adults. The minor differences were not seen to result in any significant impact on safety or efficacy of Jaydess. Dose adjustment was therefore not deemed to be necessary.

In summary, the MAH concludes that the same *in vivo* release from Jaydess has been shown in adults and adolescents and this is expected for Mirena as well. Due to the same local mechanism of action of Jaydess and Mirena, which is independent of the age, the MAH considers that there are no expected differences with regards to efficacy between adults and adolescents. In addition, it has been shown for Jaydess that the PK in adolescents is similar to the PK in adults, which is also anticipated for Mirena.

- **Efficacy reported from MAH Studies**

There were no MAH-sponsored clinical or post-marketing studies with Mirena that included patients <18 years old

- **Efficacy in Contraception and Idiopathic Menorrhagia in studies not conducted by the MAH**

The MAH performed a literature search in PubMed database (up to 9th March 2015) with key words Mirena, levonorgestrel-releasing, LNG-IUS, or LNG-IUD (levonorgestrel intrauterine device) combined with adolescent or teen. The search was limited to English language articles and excluded case reports. The abstracts of the identified articles were reviewed to identify studies reporting either efficacy/effectiveness and/or safety outcomes. Studies reporting on products which have not been granted marketing authorisation were excluded.

No studies on efficacy of Mirena use in adolescents for off-label indications were identified. However, one survey (*Paterson et al* 2009) reporting on continuation rate and safety parameters with Mirena in adolescents included also a subset of adolescents using Mirena for off-label indications (e.g. dysmenorrhea, endometriosis, "menstrual management").

The following 17 studies were identified in literature search describing efficacy of Mirena in contraception and treatment of idiopathic menorrhagia in adolescents. These included prospective, randomized and single group studies, as well as retrospective studies, and are summarised below in alphabetical order:

1. **Adams Hillard 2012:** a retrospective study on 21 women (mean age 16.8 years, range 11-26) with developmental delay using Mirena for menstrual suppression, with mean follow-up of 11 months. Primary efficacy measure: Satisfaction with menstrual suppression. Families were satisfied with the menstrual suppression from Mirena. There was one request for removal. The patient had been amenorrheic for 5 years on depot medroxyprogesterone acetate (DMPA), and with the LNG-IUS she experienced monthly bleeding which she disliked.

2. **Alton et al 2012:** a retrospective cohort study of women (n=233) from menarche to 21 years, with separate analysis of adolescents (n=69) and young women aged 18-21 years (n=164) in a study period covering 8 years. 222 patients used Mirena and 11 patients used the copper intrauterine device. No pregnancies occurred during the follow-up with the intrauterine device in place.

3. **Aoun et al (2014)** reported a retrospective chart review on the discontinuation reasons of intrauterine contraceptives (IUCs). 82% of IUC users were using Mirena, including adolescents (n=249). Contraceptive failure was reported by 0.4% within 12 months and 1.0% within the whole study period (mean follow-up 37 months) in the overall cohort, with similar rates in different age groups.

4. **Aslam et al (2010)** reported a cohort study of 48 adolescents (mean age 15 years) who were using Mirena for treatment of menorrhagia and/or dysmenorrhea, with follow-up between 3 and 18 months, with a study period covering 8 years. An improvement of the menstrual symptoms was observed in 93% of subjects.

5. **Bayer et al 2013:** A review summarizing the evidence on the use of Mirena in adolescents for different medical indications, including menorrhagia, dysmenorrhea (primary or secondary to endometriosis), menstrual suppression, treatment of anovulatory bleeding disturbances and endometrial hyperplasia. The authors conclude: Although studies specific to adolescents using the LNG-IUS are limited, the available evidence suggests benefits that are at least comparable to those seen in adult women.

6. **Bayer et al 2012:** A retrospective cohort study in adolescents (n=307, up to 19 years) on insertion of Mirena (88% of IUDs), 12% received the Copper IUD ParaGard and

continuation up to 12 months, comparing nulliparous vs parous adolescents. There were no pregnancies reported in those subjects with documented IUD continuation. There were 14.3% (6/42) reported subsequent unintended pregnancies in subjects who had requested and undergone IUD removal.

7. **Behringer et al 2011:** a retrospective cohort study in women using Mirena was conducted to quantify rates of, and reasons for, discontinuation of use of IUS in adolescents (n=131) and nulliparous women compared to older and parous women (N=694). No pregnancies were detected among adolescents, while 0.4% of the adult women experienced contraceptive failure.

8. **Berenson et al 2013:** a large retrospective health insurance database study on adolescents aged 15-19 years, compared to women aged 20-24 and 25-44 years who received IUDs (78% Mirena, 22% ParaGard). A claim for contraceptive failure (normal or abnormal pregnancy) was identified in 1.8% of women aged 14-19 years, in 1.7% of women aged 20-24 years, and in 1.0% of women aged 25-44 years in the Mirena cohort, compared to 4.4%, 2.9% and 1.6% in the Copper IUD cohort. Contraceptive failure was more common among Copper IUD users, compared to Mirena users. Comparison of different age groups for Copper IUD or Mirena users showed that failure was more common among women aged 14-19 years compared to women aged 25-44 years. The authors state that this difference might be due to chance as a low number of pregnancies was detected, or due to difference in natural fertility between younger and older groups. The authors also mention that it is possible that some of the pregnancies were the result of luteal phase placements or spontaneous expulsions that were not coded.

9. **Godfrey et al 2010:** a prospective randomized study on use of Mirena (n=12) and Copper IUD (n=11) among adolescents followed up for 6 months. No pregnancies occurred during the study. One pregnancy occurred 37 days after removal of Copper IUD due to prolonged bleeding.

10. **Howard et al 2013:** A prospective cohort study on use of Mirena (n=37) or DMPA (n=29) in post-partum adolescents. One pregnancy occurred during the study but the publication did not specify in which group this occurred or whether it occurred during use of either product.

11. **Mantrala et al 2013:** Retrospective cohort study on adolescents (n= 52, aged 10-20 years) with developmental disabilities. Due to the developmental disability, most insertions were performed under anaesthesia. No pregnancies occurred.

12. **Pasternack et al 2012:** Retrospective cohort study on reasons of removal of IUDs in adolescents (n=172) vs adult women (n=183). The study did not report pregnancies.

13. **Pillai et al (2010)** reported experience with Mirena for treatment of menstrual problems in adolescents with a range of medical problems or with severe learning disability. Mirena provided significant therapeutic benefit for 12 of 14 participants, with the majority opting to continue for the 5-year duration of the device.

14. **Savasi et al 2013:** Retrospective cohort study in adolescents (n=56, aged 10-21 years) with developmental delay using Mirena. Indications for Mirena use included: complete menstrual suppression (82%), management of menorrhagia (20%) or dysmenorrhea (9%), reduced burden of menstrual hygiene (24%), and contraception (22%). No pregnancies were reported, only four removals occurred due to menstrual symptom (bleeding and/or pain).

15. **Tang et al 2012:** A review on randomized comparative trials of hormonal and intrauterine contraceptives in women aged <25 years. Based on a search in Feb 2012, 4 trials were included, whereof 2 included Mirena (vs oral contraceptive and vs Copper IUD respectively). The review concluded: Current evidence is insufficient to compare contraceptive efficacy and continuation rates for hormonal and intrauterine methods in women aged 25 years and younger. Limited data suggest that the levonorgestrel intrauterine system may be an acceptable alternative to the combined oral contraceptive in this population.

16. **Teal et al 2012:** a prospective observational cohort study on the feasibility of IUD insertion in adolescents (n=1182, aged 13-24 years). First-attempt insertion success rate was 95% in both nulliparous and parous subjects, and the majority (78%) of second attempts were successful.

17. **Teal and Sheeder 2012:** a prospective observational cohort study on adolescent mothers (n= 136, aged 14-23 years) who received Mirena (n=77) or Copper IUD (n=66) as part of their post-partum healthcare. Pregnancy was reported among 4.7% of subjects during the follow-up. However, it should be considered that the cohort represents a selected population at highest risk of unintended pregnancy.

- **Guidelines:**

In addition to the publications described above, the MAH reports that there are several recent guidelines that support use of intrauterine devices in adolescents:

- American College of Obstetricians and Gynecologists (ACOG) state in the committee opinion number 539 from 2012 the following: “adolescents should be encouraged to consider long-acting reversible contraception (LARC) methods” The LARC methods include intrauterine devices and the contraceptive implant.

- The American Academy of Pediatrics consider their policy statement on contraception for adolescents (2014) that the top tier methods of contraception, including intra-uterine devices and implants, should be considered as first-line choices for adolescents, regardless of parity.

- The WHO medical eligibility criteria for contraceptive use (2009) recommend use of intrauterine devices for women under 20 years as category “2 – generally use the method”.

- **MAH efficacy conclusions**

In summary, the MAH considers that the currently available evidence suggest that the efficacy, including contraceptive efficacy and treatment of idiopathic menorrhagia, are comparable to those seen in adult women. While the MAH acknowledges that this evidence is mainly based on observational prospective or retrospective studies, the amount of data gathered in these post-marketing studies represents a large amount of data reflecting “real-life use” of the product in this population, and must therefore be taken into account. Use of intrauterine contraception for adolescents as first-line method of contraception is also supported by international guidelines.

***Rapporteur’s comments:***
The submitted data do not provide new efficacy information for paediatric use and do not change

the benefit-risk balance of Mirena.
It is noted that international guidelines indicate that the LNG-intrauterine delivery system is a long-active reversible contraception method that can be considered for use in adolescents.

# V. SAFETY

**Microlut**

- **Safety Reported from MAH Clinical Trials**

Clinical Study of SH 9.0999C (Microlut®) (Evaluations I and II)
Adverse events such as headaches, dizziness, dysmenorrhoea, nervousness, nausea and vomiting, changes in libido, breast tenderness, depression and adverse events such as acne, chloasma, oedema, varicose veins, thrombophlebitis, hepatopathy) were documented in each cycle before the start of the medication for the next cycle. Spontaneously reported adverse events during treatment were documented after each treatment cycle. Overall, the study results demonstrated good tolerance of Microlut®. The spectrum and extent of the documented undesirable effects was comparable to the side effects reported in connection with other POPs.

- **Safety Information Reported in the Literature**

The retrieved publications revealed one case reporting hyperglycaemic episodes in a 13 year-old girl. The first episode occurred after use of Microlut® and the second after use of LNG-containing emergency contraceptive pill (0.05mg ethinylestradiol + 250µg LNG). She recommenced on Microlut® after she had recovered from the second hyperglycaemic episode with no further ill effects after 2 months. Additionally, data presented in this case report imply that complaints such as nausea, vomiting, polyuria and polydipsia started approximately 2 weeks prior to the use of Microlut®. These observations do not suggest that the event is solely attributable to the use of Microlut®. This case report was described in more detail in the Periodic Safety Update Report covering the period between 1990 and 1995.

No specific issues or concerns were reported for paediatric patients in the publication by **Huber 1974** regarding his experiences with Microlut® in adolescents.

Overall, literature research did not reveal any evidence of particular safety issues relating to the use of Microlut® in adolescent women.

- **MAH Safety Conclusions**

Based on the limited available clinical data, the safety profile of Microlut® in adolescent patients appears in line with that of the adult population. Taking into account the safety data from the clinical trial and the literature research, there was no evidence of any particular safety issues relating to the use of Microlut® in adolescent women.

**MAH Overall Conclusion**

Based on the available evidence, the MAH considers that there appears to be no difference in efficacy with the use of Microlut® between adolescent and adult women. The dose administered in adolescents was the same as for adults and there was no indication of a different mode of action of Microlut® between these two groups.

The safety profile of Microlut® in adolescent users seems to be in line with that of the adult population.

There was no evidence of any particular safety and efficacy issues relating to the use of Microlut® in the paediatric population.

***Rapporteur's comments:***
Based on the submitted data, the rapporteur considers that the benefit-risk balance of Microlut in the paediatric population remains unchanged.

**Jadelle**

- **Safety Reported from MAH Studies**

There were no MAH-sponsored clinical or post-marketing studies with Jadelle that included patients <18 years old.

- **Safety in Studies not Conducted by the MAH**

The MAH identified the following studies in PubMed search with key words Norplant OR Jadelle AND adolescent and presented them in alphabetical order:

1. **Berenson et al (1995)** conducted a prospective case-control study in 94 adolescents (up to 18 years of age) using Norplant, comparing to age-matched adolescents using oral contraceptives during the same study period. Information on pregnancy status, satisfaction, continuation rate and condom practice was obtained. The Norplant users had more often experienced a pregnancy before starting the method, compared to oral contraceptive users. After 6 months, all Norplant users were still using the method. In contrast, 43% of oral contraceptive users had discontinued. During use, at least one side-effect was reported by 98% of Norplant users and by 71% of oral contraceptive (OC) users. The most common side-effect reported by Norplant users was menstrual irregularity (70%) and for OC users the most common side-effect reported was weight gain (43%). Norplant users reported significantly more often menstrual irregularity, increase in appetite, and hirsutism/hair loss, than OC users. When weighed, the mean weight gain was higher in Norplant users compared to OC users. The authors concluded that the side effects observed with Norplant use in this study were similar to those previously reported in the literature.

2. **Berenson et al (1997)** reported a follow-up study in a subset (56 adolescents) of the prospective case-control study mentioned above, with follow-up of 12 months. At 12 months, the continuation rate with Norplant was 91%, while it was only 34% among OC users (p=0.01). The side-effects reported more often by Norplant users at 12 months, compared to OC users, were menstrual irregularity and emotional problems. Norplant implant users gained an average of 8.7 pounds over the study period in comparison with 4.2 pounds gained by oral contraceptive users.

3. **Blumenthal et al (1994)** reported a follow-up study of 280 post-partum and post-abortal adolescents who chose either Norplant or some other method of contraception at the time of their procedure (abortion, delivery). They were interviewed between 6 and 18 months after the index procedure. A total of 92 adolescents used Norplant while 188

chose another method (combined oral contraceptives, condoms or no method). The discontinuation rate was significantly lower in the Norplant group (16%), compared to the combined oral contraceptives group (47%). The main side effect responsible for discontinuation among both combined oral contraceptives and Norplant users was bleeding.

4. **Cardamakis et al (2002)** reported on a prospective study of 13 adolescents using Norplant. The follow-up period was 24 months with a continuation rate of 100% (13/13) for the first 6 months, 92.5% (12/13) for 12 months and 53.8% (7/13) for the whole period. No infections at the implant site or expulsions were observed. Menorrhagia was observed in 4/13 (30.76%) adolescents in the third month. No new unexpected side effects were reported.

5. **Cromer et al (1994)** performed a prospective study in adolescents (11 to 20 years) choosing Norplant (n = 58), Depo-Provera (n = 66), or oral contraceptive pill [OCP] (n = 75) for contraception. At baseline and follow-up visits over 6 months, patients were interviewed regarding gynaecologic history, side effect symptoms, and satisfaction. A total of 105 and 40 adolescents were assessed at 3 and 6 months, respectively. At follow-up, more than 80% of OCP users maintained regular menstrual cycles, whereas over 80% of those choosing Norplant or Depo-Provera had disrupted cycles. Complaints of nausea and dizziness among Norplant users and fatigue among Depo-Provera and OCP users increased significantly between the baseline and follow-up visits. Reports of local reactions to the Norplant device were common but not clinically significant. Blood pressure readings, facial acne, and body mass index did not change over time in any treatment group.

6. A publication from the same group **(Cromer et al, 1996)** reports the results of a prospective comparison of bone mineral density (measured by dual-energy X-ray absorptiometry) in adolescents receiving contraceptive injectable depot medroxyprogesterone acetate (Depo-Provera, n=15), Norplant (n= 7) or oral contraceptives (n=9), compared to girls receiving no hormonal treatment (n=17). After 1 year, bone density decreased 1.5% in Depo-Provera users, compared with increases of 2.5% in Norplant users, 1.5% in oral contraceptive users, and 2.9% control subjects ($p < 0.02$). After 2 years, bone density increased a total of 9.3% in Norplant users and 9.5% in control subjects but decreased a total of 3.1% in Depo-Provera users ($p<0.0001$). The authors conclude that their data suggest that Depo-Provera may, at least temporarily, suppress the expected skeletal bone mineralization in adolescents, whereas Norplant and oral contraceptives are associated with the expected increase in bone density in this population.

7. A retrospective chart review of the women that were recruited in the above studies published by *Cromer et al* was performed by **Zibners et al (1999)**. In total, 494 patient charts were analysed, including the women who initially chose Norplant. The mean age for the entire sample was 15.5 years (+ 1.6 SD). Over 4 years of follow-up, continuation rates were significantly higher for implant users than for the other hormonal groups ($P < 0.001$). At 1 year, continuation rates were 82% for implants, 45% for depot medroxyprogesterone acetate (DMPA), and 12% for oral contraceptive pills (OCPs). Combining these rates with those of the subsample who switched without interruption to another hormonal method, “continued protection” rates were much higher after 1 year: 96% implants, 83% DMPA, and 49% OCPs.

8. **Cullins et al (1994)** performed an 18-month observational study of 136 adolescents (aged 13 to 18 years) and 542 adults (aged 19 to 46 years) who received Norplant.

Fifteen adolescents (11%) and 60 adults (11%) had Norplant removed during the study period. Life table analysis indicated high continuation rates with 90% for adults and 92% for adolescents at 12 months. The most common reasons for removal included irregular bleeding, weight gain, headaches, and desire for pregnancy. The authors conclude that implant acceptability, continuation, and tolerance of side effects were high and comparable among adolescent and adult Norplant users.

9. **Darney et al (1999)** conducted a prospective cohort study to determine whether teens initiating Norplant use condoms less frequently than teens using oral contraceptive pills or condoms alone and may therefore be at an increased risk of acquiring sexually transmitted infections. The study included 200 Norplant users, 100 OC users and 99 condom users. Norplant contraceptive implant users were less likely than oral contraceptive or condom users to report condom use at last sex or consistent condom use at 1- and 2-year follow-up. The implant group showed a significant decrease in condom use from admission to 2 years after method initiation. The proportion of implant users self-reporting new sexually transmitted infections at 2-year follow-up, however, was not significantly greater than that of oral contraceptive or condom users. The authors concluded that teens who choose oral contraceptives and condoms do not use them consistently enough to avoid pregnancies or sexually transmitted infections.

10. **Dinerman et al (1995)** performed a prospective comparative study on 54 Norplant, 64 OC, and 48 other method using adolescents (up to 18 years of age) followed up for 6 months. Implant users were more likely than oral contraceptive users to continue their method (87% vs 50%; $P < 0.001$) despite similar satisfaction scores (one-way analysis of variance, $P = 0.52$). Implant users were more likely to experience irregular menses, mood swings, acne, and hair loss ($P< 0.05$). Condom use, and number of newly diagnosed Sexually Transmitted Diseases (STDs) during the study did not differ between study cohorts.

11. **Glantz et al (1995)** performed a prospective study in 122 adolescent Norplant users (between ages of 13-19 years) for 12 months. The continuation rates were 71% and 62% at 1 and 2 years, respectively. The most common reasons for discontinuation were menstrual problems as well as hair loss, headache, fatigue, nausea, weight change, breast symptoms and appetite changes.

12. **Levine et al (1996)** performed a prospective 50-month study on adolescent (< 20 years) and adult (≥ 20 years) women using Norplant (N=1800). Follow-up data were available for 93.8% of these patients (n = 1688, 45,576 women-months of use), adolescents (N=674) and adults (N=1014). Over the 50-month study period, the cumulative continuation rate did not differ significantly between adolescents and adults (93.6 versus 91.1%). Continuation rates were no different between cohorts at 1, 2, 3 or 4-year time points. The primary reason for device removal included: irregular menses (28%), headaches (20%), local arm irritation or pain (16%), desiring pregnancy (12%), and hair loss, rash, or patient request (8%). There was no difference in the primary reason for device removal between adolescents and adults.

13. **Rosenthal et al (1995)** performed a retrospective chart review of 72 adolescents using Norplant. The mean follow-up time was 18 months (range 12 to 29 months). The study did not report pregnancies. Continuation rate was 97% at 12 months and 86% at 24 months. There was no trend in condom use, or difference in incidence of sexually transmitted diseases before and during Norplant use.

14. **Stevens-Simon and Kelly (1998)** performed a study to determine if adolescent mothers who request early removal of Norplant differ from those who do not in ways that might predispose them to repeated conceptions, and in their concerns about adverse effects. The study followed up a total of 181 teenage mothers (aged 13 to 18 years) who received Norplant and who were divided to "removers" (N=66, who had their implants removed by 20months) and "continuers" (N=115, who continued beyond 20 months). The investigators hypothesized that "removers" would have more risk factors for repeated conception than the "continuers". The study showed this hypothesis to be true. Concerns regarding adverse effects rose in tandem with risk factors for repeat pregnancy. Most of the women reported some adverse effects related to (levonorgestrel) LNG implant use. The most common adverse effect was moodiness (70%) followed by irregular vaginal bleeding (65%), headaches (61%), depression (46%), and weight gain (44%). Irregular vaginal bleeding was the most commonly cited reason for removal, and the desire for repeated conception was the second most commonly cited reason for removal.

15. **Suman et al (1988)** reported on continuation rates among 144 young women aged 14-21 years using Norplant. Of the 130 women who could be contacted after insertion, approximately 60% reported a Norplant-related problem, such as breakthrough bleeding, headaches, and depression or mood swings. The continuation rates were 83% at 12 months and 63% at 24 months. Main reasons for requesting removal were irregular bleeding, followed by desire for pregnancy. Discontinuation probability was not found to be associated with age.

- **MAH Safety Conclusions**

Data on the safety of levonorgestrel implant use in adolescents derive mostly from published studies with Norplant. More than 1800 adolescent users were included in prospective studies or analysed in retrospective chart reviews identified by the literature search. All authors report high continuation rates. Reasons for discontinuation (mainly irregular bleeding) and observed side effects did not differ from what is known from LNG implant use in adults. Studies on impact of LNG implant on condom use gave inconsistent results, but none of the studies showed an increase in STD incidence after initiation of the implant (Darney 1999, Dinerman 1995, Rosenthal 1995). One study on LNG implant impact on bone mineral density (BMD) in adolescents was identified, showing no negative impact on BMD (Cromer 1996).
In summary, no new safety concerns can be identified from the published data on LNG implant use in adolescents.

- **Benefits and Risks Conclusions**
  - Benefit-risk balance of Jadelle in the adult population (from the 17th PBRER/PSUR for Jadelle covering the period 24 Dec 2010 to 23 Dec 2014):

Jadelle has a very high contraceptive efficacy which is less dependent on user-compliance and compares favourably to other contraceptive methods including barrier methods, COC, Progestogen-only pill (POP), injectables, and intra-uterine contraceptives. Further non-contraceptive benefits include possibility of alleviation of dysmenorrhea. Jadelle can be inserted immediately after medical or surgical abortion, including second trimester abortion, with immediate effect of contraceptive efficacy. Jadelle does not interfere with lactation. Jadelle can be used by women in whom oestrogen-containing combined hormonal contraceptives are contraindicated.

The great majority of Jadelle users experience changes in their menstrual pattern. However, in controlled trials in adult Jadelle users, serious bleeding problems were not more frequent than in controls. Bleeding disturbances however constitute a main reason for discontinuation of the method. Serious complications related to insertion (e.g. infection) or removal (e.g. nerve

damage, complications due to deeply inserted implant or device breakage) are rare. In case of contraceptive failure, a pregnancy occurring under Jadelle is more likely to be ectopic than pregnancies conceived without contraceptives. However, due to the high contraceptive efficacy of Jadelle the absolute rate of ectopic pregnancies in Jadelle users is very low. As with other progestin-only contraceptives, ovarian cyst formation may occur with Jadelle but is non-serious and transient in the vast majority of cases. The evidence for an association of Jadelle use with other significant health problems (hepatobiliary problems, idiopathic intracranial hypertension) is weak.

- **MAH benefit-risk considerations in the paediatric population:**

No MAH-sponsored clinical studies with Jadelle or Norplant included patients <18 years old.
A total of 15 trials describing efficacy and safety of Norplant in contraception in adolescents were identified in the literature. These included both prospective cohort studies, as well as retrospective studies. In addition, international guidelines regarding adolescent contraceptive use were reviewed. The assessment of the paediatric use of Jadelle is based on the published studies and guidelines.

The available published data on Norplant in the adolescent population suggests similar high contraceptive efficacy comparing favourably with other contraceptive methods in this population and reports high continuation rates. No new risks have been identified in this population from this review. Reasons for discontinuation (mainly irregular bleeding) and observed side effects did not differ from what is known from LNG implant use in adults. Use of subdermal implant contraception for adolescents as first-line method of contraception is also supported by international guidelines, without any restrictions for use.

In summary, the currently available evidence suggests that the efficacy and safety of Jadelle appears to be comparable to that seen in adult women.

***Rapporteur's comments:***
The Faculty of Sexual and Reproductive Healthcare Clinical guidance on 'Progestogen-only implants (February 2014)' provides information on the risks associated with the insertion or removal procedure of progestogen-only implants. The guidance states that '*non-insertion of the implant, deep insertion, and nerve injury are three types of harm cited in litigation cases involving the contraceptive implant.'* The rapporteur notes that complications related to the insertion or removal of Jadelle are monitored on an ongoing basis in the PBRER/PSUR procedure.
Overall, the data provided on safety of Jadelle in paediatrics does not give rise to new safety concerns and the benefit-risk balance of Jadelle in the paediatric population remains unchanged.

**Mirena**

- **Safety Reported from MAH Studies**

There were no MAH-sponsored clinical or post-marketing studies with Mirena that included patients <18 years old.

The previously cited paediatric clinical trial with another levonorgestrel-releasing intrauterine system, Jaydess, was conducted in 304 post-menarcheal female adolescents (CSR PH-37272) and showed a safety profile over 1 year of observation consistent with that in the adult population. The 2 most common adverse events that led to discontinuation were: pelvic pain (12 subjects, 3.9%), and device expulsion (10 subjects, 3.3%). Two (0.7%) subjects

discontinued due to serious events (endometritis and pelvic pain). There were no subjects with pelvic inflammatory disease (PID). A total of 3 cases with endometritis were reported, which were confirmed not to be PIDs according to the protocol defined criteria. Eighteen (5.9%) subjects had ovarian cysts reported as an AE, and 10 (3.3%) subjects experienced expulsions. There were no subjects with perforations. In conclusion, Jaydess was generally safe, well tolerated, and easy to use in the adolescent population. No new or unexpected safety concerns were identified in the adolescent population of this study.

- **Published Data on Safety (Studies not Conducted by the MAH)**

From a literature search, the MAH identified the following 20 studies describing safety of Mirena in contraception and/or treatment of idiopathic menorrhagia in adolescents. These included prospective, randomized and single group studies, as well as retrospective studies, and are summarised below in alphabetical order:

1. **Adams Hillard 2012:** retrospective study on 21 women (mean age 16.8 years, range 11-26) with developmental delay using Mirena for menstrual suppression, with mean follow-up of 11 months. 20 insertions were performed under anaesthesia (9 cases had additional procedures). No unsuccessful insertions or major complications occurred. One subject (patient who had been amenorrheic during DMPA use but began to experience monthly bleedings during Mirena use) requested device removal during the study.

2. **Aoun et al (2014)** reported a retrospective chart review on the discontinuation reasons of 2138 intrauterine contraceptive (IUC) users. 82% of IUC users were using Mirena including 249 adolescents. There was no difference in discontinuation at 12 months between adolescents and older women, but by end of study period (37 months), adolescents had a higher discontinuation rate (49%) compared to women aged 20-24 (45%) and women aged 25-35 (37%) , mainly due to pain. No significant differences were found in expulsion rates among the three age groups. No perforations were reported in the adolescent group and pelvic inflammatory disease (PID) rate was similar in the different age categories.

3. **Alton et al 2012:** retrospective cohort study of women (n=233) from menarche to 21 years, with separate analysis of adolescents (n=69) and young women aged 18-21 years (n= 164) using mostly Mirena (only 11 of 233 were using copper IUD), study period covering 8 years. Indications for use included contraception, idiopathic menorrhagia and menstrual suppression. Insertion difficulties were recorded in 1.3%. No perforations occurred. The depth of uterine sound was recorded on 60% (140/233) of patients with a mean uterine length of 7 cm. The shortest uterine length recorded was 5.5cm (2 patients) and the largest was 10 cm. The continuation rate was 50% in the adolescent group vs 71.5% in the young women´s group at 5 years. Under-18-year-olds were at greater risk of expulsion, though not statistically significant. Nulliparity, but not age was significantly associated with higher expulsion risk. No significant difference in infection rate was observed. The authors concluded that the rate of continuation was found to be lower in adolescents under 18 as compared to 18 – 21 year-old users, but was still higher than what is found with other hormonal contraceptives and that IUDs appear to be a safe option for the adolescent population.

4. **Amies Oelschlager et al 2014:** a retrospective chart review of 30 adolescents (age range 12-22 years) with congenital and acquired cardiovascular conditions using LARCs. There were 27 levonorgestrel-releasing intrauterine devices (IUD), 1 copper IUD, and 3 etonogestrel implants placed. Common primary and secondary indications were desired contraception (22 patients, 73%), desired menstrual suppression (15 subjects, 50%) and treatment of heavy menstrual bleeding (8 subjects, 27%). There were 2 confirmed IUD

expulsions (both LNG-IUS). This includes one patient who experienced a spontaneous expulsion 1 month after placement and subsequently became pregnant. In addition, there was 1 removal due to persistent irregular bleeding and cramping (IUD not specified). There were no cases of pelvic inflammatory disease or pregnancies with LARC methods in place.

5. **Aslam et al (2010)** reported a cohort study of 48 adolescents (mean age 15 years) who were using Mirena for treatment of menorrhagia and/or dysmenorrhea, with follow-up between 3 and 18 months. There were no cases of perforation, expulsion or infections at 3 months follow-up. The Mirena was removed in one patient due to severe pain 10 days after insertion, and 4 months later in another patient due to persistent bleeding, giving a 4.2% removal rate in the first year. No continuation rates beyond 1 year were reported in the publication.

6. **Bayer et al 2013:** A review summarizing the evidence on the use of Mirena in adolescents for different medical indications, including menorrhagia, dysmenorrhea (primary or secondary to endometriosis), menstrual suppression for women with mental disabilities, treatment of anovulatory bleeding disturbances and endometrial hyperplasia. No specific safety concerns were identified regarding women with dysmenorrhea or endometrial hyperplasia. The potential safety concerns regarding Mirena use for women with mental disabilities include the need for anaesthesia for insertion, difficulty that patients with mental disabilities have in providing feedback regarding pain, and potential problems with monitoring for expulsion.

7. **Bayer et al 2012:** A retrospective cohort study in adolescents (n=307, up to 19 years of age) on insertion of Mirena (88% of IUDs, 12% received the Copper IUD ParaGard) and continuation up to 12 months, comparing nulliparous vs parous adolescents. 96.4% (296/307) had a successful IUD insertion upon first attempt; all of the 11 unsuccessful IUD insertion attempts were among nulliparous teens. The majority of these (7/11) subsequently underwent repeat insertions attempts which were successful. Mean uterine depth in those subjects not undergoing IUD insertions post-abortion was greater in parous (mean ± SD: 7.3 ± 1 cm) compared with nulliparous (mean ± SD: 7 ± 0.7 cm) adolescents. One nulligravid subject underwent a successful IUD insertion with a uterine sound depth measured at <6 cm (reported as 5 cm); this subject had documented IUD continuation at 2 months without any reported problems. No perforations were documented. Follow-up data were available for 56% (172/307) of subjects. The median time from IUD insertion to follow-up documenting IUD outcome was 5 months (range 2 days–23.5 months). During the first 12 months of use, there were 2.9% IUD expulsions and 24.4% removals for any reason, with no differences between nulliparous and parous teens, however, nulliparous teens more often discontinued due to pain and bleeding complaints. IUD continuation at 6 months was 83.3%. Pelvic inflammatory disease was diagnosed in 4.6% (8/172) of post-IUD insertions, the majority of these were treated with IUD left in situ. The authors concluded: Overall, adolescents experience minimal complications with IUD use, with similar rates of successful insertion as adults. IUD discontinuation rates were not significantly different between nulliparous and parous teens. While discontinuation in teens was higher than reported in adults, it was lower than reported among teens using other forms of contraception.

8. **Behringer et al 2011:** a retrospective cohort study in women using Mirena was conducted to quantify rates of, and reasons for, discontinuation of use of Mirena in 828 women, including 131 adolescents (as defined as≤20 years of age). Adolescent women were not more likely to have their Mirena removed within 2 years than adult women. Among those women who had their Mirena removed by a clinician, there was no

difference in duration of use for adolescents versus adult women. When looking at reasons for removal, adolescent women were also not more likely than adult women to have had their IUS removed because of desiring pregnancy, treatment of PID, or dissatisfaction. Adolescents were more likely to experience expulsion than adult women (9.9% vs 5.2%), although this difference did not reach statistical significance.

9. **Berenson et al 2013:** a large retrospective study in a private health insurance database on adolescents aged 15-19 years, compared to women aged 20-24 and 25-44 years who received IUDs (78% Mirena, 22% ParaGard). In total, 1,528 LNG-IUS users and 307 Copper IUD users were identified that were between 15 and 19 years at time of insertion. Serious complications, including ectopic pregnancy and pelvic inflammatory disease, occurred in less than 1% of patients regardless of age or IUD type. Women aged 15–19 years were more likely than those aged 25–44 years to have a claim for dysmenorrhea [odds ratio (OR) =1.4, confidence interval (CI) =1.1, 1.6] and amenorrhea (OR=1.3, CI=1.1, 1.5). Overall, early discontinuation did not differ between teenagers and women aged 25–44 years (13% vs. 11%, p>0.05) among Mirena users – however among Copper IUD users the discontinuation rate was markedly higher among teens compared to older women. Mirena users had reduced odds of having claims related to diagnoses of bleeding disturbances/ dysmenorrhea and infection, as well as reduced odds of abnormal pregnancy and normal pregnancy compared to the copper IUD. The authors concluded that Mirena may be a better choice for most women than the copper IUD, when available, as it may result in fewer side effects and lower discontinuation rates.

10. **Friedman (2014)** reported the results of a satisfaction survey (questionnaire 3 and 6 months post-insertion) including 79 women aged 15-24 years (73.4% LNG-IUS, 26.6% Copper IUDs). Satisfaction with the IUD was high. Five of 60 participants who were available at 6 months post-insertion no longer had the IUD in place, and 5 other participants had discontinued the IUD prior to the 3-month assessment. Reason for discontinuation for LNG-IUS included: pain/cramping, bleeding/amenorrhoea, expulsion (n=2), wish to be an egg donor, partner not wishing contraception. No pregnancies, perforations or diagnosis of pelvic inflammatory disease are mentioned in the article.

11. **Godfrey et al 2010:** a prospective randomized study on use of Mirena (n=12) and copper IUD (n=11) among adolescents (aged 14 to 18 years) followed up for 6 months. At 6 months, the continuation rates were 75% for the Levonorgestrel Intrauterine System users and 45% for the Copper T 380A users (p=0.15). Two Copper T 380A users experienced partial expulsion. Increased bleeding and pelvic pain were the most commonly reported side effects for both the Mirena and CuT380A users.

12. **Howard et al 2013:** A prospective cohort study on use of Mirena (n=37) or DMPA (n=29) in post-partum adolescents (aged 20 and younger). The continuation rate was 77% vs 43% for Mirena vs DMPA after one year. More women reported unacceptable or unpredictable bleeding during the study in the DMPA group, compared to the Mirena group.

13. **Madden et al (2014)** reported on the cumulative expulsion rate at 36 months from the contraceptive CHOICE project in the US. The project included a total of 4,219 Mirena users (thereof 439 aged 14 to 19) and 1,184 copper IUD users (90 adolescents aged 14 to 19 years). There were 432 expulsions reported. The 36-month cumulative expulsion rate was 10.2 per 100 IUD users. The expulsion rate was significantly higher among adolescents, compared to older women in both IUC groups, the hazards ratio (HR) was 2.26 in the Mirena group and 3.06 in the Copper IUD group.

14. **Mantrala et al 2013:** Retrospective cohort study on adolescents (n= 52, aged 10-20 years) with developmental disabilities. Due to the developmental disability, most insertions were performed under anaesthesia. No PIDs occurred, 5.8% of patients had Mirena removed due to persistent bleeding. Over 90% of patients were continuing with Mirena at the last follow up.

15. **Pasternack et al 2012:** Retrospective cohort study on reasons of removal of IUDs in adolescents (n=172) vs adult women (n=183). The most common reasons for removal in adolescents were bleeding and/or cramping, desired pregnancy and incorrect location. The percentage of adolescents who had an IUD removed for bleeding and/or cramping was not different from that of adults, regardless of the type of device (Mirena or Copper IUD).

16. **Paterson et al (2009)** reported the results of a nationwide survey on Mirena use in 179 adolescents (age: 11 to 19 years). The most common indication for use was menorrhagia (17%), followed by contraception (14%). 29% of adolescents had an “off-label” primary indication other than contraception or menorrhagia (e.g. dysmenorrhea, endometriosis, but also "menstrual management" and "intellectual disability" were classified as "other"). There was a 1-year continuation rate of 85%. The mean time to withdrawal of the LNG-IUD in the study population was 855 days (range=1–2561 days). No cases of perforation and 11 cases of expulsion were identified. The cumulative incidence of expulsion was 8%.

17. **Pillai et al 2010** reported experience with Mirena for treatment of menstrual problems in adolescents (age: 11 to 21 years) with a range of medical problems or with severe learning disability. Out of 14 patients, two discontinued before 5 years, one for continuing menstrual problems and one for expulsion of the system.

18. **Savasi et al 2014:** Retrospective cohort study in adolescents (n= 56, aged 10-21 years) with developmental delay using Mirena. Recorded uterine length from intra-operative sounding ranged from 4 to 10 cm (mean 7.4 cm). Five cases had measured uterine lengths of less than 6 cm. Four of these cases had successful LNG IUS insertion and 1 insertion was abandoned after the cavity was sounded at 4 cm. Removal rate was 7.4%, and expulsion rate 1.9%.

19. **Teal et al 2012:** a prospective observational cohort study on the feasibility of IUD insertion in adolescents (n= 1182, aged 13-24 years). 77% received an LNG-IUS and 23% a Copper-T. First-attempt insertion success rate was 95% in both nulliparous and parous subjects, and the majority (78%) of second attempts were successful. Mean uterine depth was 7.0±0.7 cm for nulliparas and 7.4±0.8 cm for parous women. Sixty-one percent returned for routine follow-up between 4 and 12 weeks. There were no perforations and 20 (1.7%) expulsions. The authors concluded: IUD insertion in adolescents is generally successful and uncomplicated, with neither nulliparity nor youth predicting failure.

20. **Teal and Sheeder 2012:** a prospective observational cohort study on adolescent mothers (n= 136, aged 14-23 years) who received Mirena (n=77) or Copper IUD (n=66) as part of their post-partum healthcare. The IUDs were inserted between 0.2 and 59.1 months after delivery (mean 8 months). The continuation rate after one year was 55%. During the complete observation period, the most common reasons for removal were expulsion (for LNG IUS 13.3%), pain (14.7%), bleeding (8.0%), pregnancy desire (8.0%) and pregnancy (2.7%). Expulsion rates and pregnancy rates are higher than reported in

the general population. However, it should be considered that the cohort represents a selected population at highest risk of unintended pregnancy.

- **MAH Safety Conclusions**

Evidence for safety of Mirena use among adolescents is mainly based on observational research, including a considerable number (>4000) of patients, reflecting “real-life use” of the product in this population from various aspects [insertion procedure, complications, general safety, continuation rate, treatment of menorrhagia etc.].
In summary, the data indicate that insertion of Mirena does not appear to be associated with increased risk of complications (e.g. insertion failure, PID, perforation) among adolescents compared to adult women.
Observations on uterine size are in line with studies showing that uterine cavity size remains relatively stable and the uterine length and width increase with parity rather than with age (Hasson 1982, Kurz 1984). This is also illustrated by the observations in the adolescent study with Jaydess.
Studies are inconsistent with regards to expulsion risk among adolescents vs adult women, some studies reporting increased expulsion risk (Madden et al 2014, Alton et al 2012, Behringer et al 2011), and some no difference (Aoun et al 2014) between groups.
In general, rates of discontinuation of any contraceptive method are elevated among adolescents compared to adult women. Continuation rates as low as 50% at 3 months and 12% at 12 months have been reported by adolescent users of oral contraceptives (Zibners et al 1999, Balassone 1989), and rates <50% at 6 months for adolescents using injectable contraceptives (Polaneczky et al 1989). The continuation rates reported in the studies with Mirena in adolescents ranged between 55 and 85% at 12 months. Therefore, they compare favourably to those reported for other adolescent contraceptive method users.

- **MAH Benefits and Risks Conclusions**
  - Benefit-risk profile of Mirena in the adult population (indications: contraception, idiopathic menorrhagia) [31st PBRER/PSUR covering the period of 28 Sep 2010 to 23 Dec 2014]:

Mirena has a very high contraceptive efficacy which is less dependent on user-compliance and compares favourably to other contraceptive methods including barrier methods, COC, POP, injectables, copper IUDs. Its efficacy is not influenced by hepatic enzyme-inducing drugs (in contrast to other hormonal methods). Further non-contraceptive benefits include decreased menstrual blood loss and alleviation of dysmenorrhea. Some studies have also suggested that Mirena may have beneficial effects on pelvic pain related to endometriosis or adenomyosis. Due to its mainly local mechanism of action and the fact that it does not contain estrogens, Mirena is suitable for many women to whom combined contraceptive methods are contraindicated or not desirable. Mirena can be inserted immediately after surgical abortion, with immediate effect of contraceptive efficacy. Mirena does not interfere with lactation.

Among the pharmaceutical treatment options that can be used long-term, Mirena is generally recognized as the most efficacious method in the treatment of idiopathic menorrhagia/heavy menstrual bleeding. The National Institute for Health and Care Excellence (NICE) guideline for heavy menstrual bleeding recommends the levonorgestrel-releasing intrauterine system as first line treatment, if history and investigations indicate that pharmaceutical treatment is appropriate and hormonal treatment is acceptable.

The majority of Mirena users experience bleeding changes. Other adverse drug reactions observed at a "very common" frequency in clinical trials include headache, and abdominal/pelvic pain. Ovarian cysts are observed under Mirena use but are in the vast majority transient and asymptomatic. Hormonal side effects of the levonorgestrel are less frequently observed.

Identified safety risks are device related complications (such as expulsions), and side effects caused by levonorgestrel. Important safety risks/serious events (PID, uterine perforation) are rare and can be managed with adequate medical or surgical treatment. Clinical trials and observational studies have established that the risk of PID associated with insertion of intrauterine contraceptives is confined to the first weeks after insertion. The risk of uterine perforation is increased in women who are breastfeeding at time of insertion, or have given birth up to 36 weeks before insertion. However, the need for reliable contraception is high in this population, but contraceptive options in this population are restricted to methods not interfering with lactation.

Although the absolute rate of ectopic pregnancies with Mirena is lower than in patients without any contraceptive method, the relative risk of ectopic pregnancy in women becoming pregnant under Mirena is increased. Intrauterine pregnancy, when occurring during use of Mirena, is associated with a higher risk for spontaneous abortion and premature delivery. The more common risks of bleeding changes, ovarian cysts and expulsions are non-serious.

- **MAH benefit-risk considerations in the paediatric population:**

No MAH-sponsored clinical or post-marketing studies with Mirena included patients <18 years old. A clinical trial in 304 adolescents using another levonorgestrel-IUS, Jaydess, showed a safety profile over 1 year of observation which was consistent with that in the adult population.

A total of 20 trials describing efficacy and/or safety of Mirena in contraception and/or treatment of idiopathic menorrhagia in adolescents were identified in the literature. These included prospective, randomized and single group studies, as well as retrospective studies. In addition, international guidelines regarding adolescent contraceptive use were reviewed. The assessment of the paediatric use of Mirena is based on the published studies and guidelines.

In summary, while the MAH acknowledges that the evidence for efficacy and safety of Mirena use among adolescents is mainly based on observational research, there is a large amount of data reflecting “real-life use” of the product in this population from various aspects (insertion procedure, complications, general safety, continuation rate, contraceptive efficacy, efficacy in treatment of menorrhagia etc.).

The currently available evidence suggests that the efficacy of Mirena in adolescents, including contraceptive efficacy and efficacy in treatment of idiopathic menorrhagia, is comparable to that seen in adult women. The continuation rates reported in the studies with Mirena in adolescents ranged between 55 and 85% at 12 months, which compare favourably to those reported for other adolescent contraceptive method users. Similar to the adult population, the most frequently reported reason for discontinuation are bleeding pattern changes and pain.

No new safety risks were identified in the adolescent population. In particular, no difference in insertion-related complications (PID, perforation) has been identified. The safety profile of Mirena in adolescents was consistent with what has been observed in adults.

In summary, the MAH considers that the currently available evidence suggests that the efficacy and safety of Mirena are comparable to those seen in adult women.

***Rapporteur’s comments:***
Based on the submitted data, the benefit-risk balance of Mirena in the paediatric population remains unchanged.

# VI. PROPOSED CHANGES TO PRODUCT INFORMATION

## ➢ MAH's proposed changes

**Microlut**

The MAH proposes the addition of ***text*** in the SmPC:

**4.2 Posology and method of administration**

***Special populations***
***Children and adolescents***
***Microlut® is only indicated after menarche.***

***Rapporteur's comments:***
In order to conform to 'A guideline on Summary of Product Characteristics - September 2009', the rapporteur recommends that information relevant to the paediatric population is presented under the sub-heading 'Paediatric population' instead of sub-headings 'Special populations' and 'Children and adolescents'.

Additionally, the rapporteur recommends that the statement *'Microlut® is only indicated after menarche'* is amended to *'There is no relevant indication for the use of Microlut® before menarche.*' so as to maintain consistency with the text proposed for Jadelle and Mirena.

**Jadelle**

The MAH proposes the following changes in the SmPC (~~deleted text~~, ***new text***):

**4.1 Therapeutic indications**
Contraception.
~~Clinical efficacy and safety have been established in women aged 18 to 40 years.~~

**4.2 Posology and method of administration**
***Special populations***
***Children and adolescents***
***Safety and efficacy of Jadelle have been established in women of reproductive age. There is no relevant indication for the use of Jadelle before menarche.***

***Rapporteur's comments:***
The rapporteur does not endorse the deletion of the text *'Clinical efficacy and safety have been established in women aged 18 to 40 years'* as this concerns the adult population and is therefore outside the remit of this European Paediatric work-sharing procedure under Article 45.

Furthermore, the rapporteur does not agree with the addition of text *'Safety and efficacy of Jadelle have been established in women of reproductive age'*. This statement affirms that the assessment of all safety and efficacy data in post-menarcheal female adolescents and adults has been concluded. Although the submitted data during this work-sharing procedure provide some information on the use of Jadelle in adolescents, the data is not considered sufficient to

assert that safety and efficacy have been established in post-menarcheal female adolescents and adults. Therefore, the addition of this text is not supported.

In summary, the rapporteur only endorses the addition of text '*There is no relevant indication for the use of Jadelle before menarche.'* in section 4.2 of SmPC.

**Mirena**

The MAH reported that Mirena is registered nationally, except for a mini-mutual recognition procedure (MRP) with PT, PL and ES. The proposed text below reflects the currently MRP-approved text. This text is approved in EU countries with the exception of AT, BG, CY, DE, EL, FR, HR, LT, MT and UK.

**4.2 Posology and method of administration**

**Special populations**
Children and adolescents
Safety and efficacy of Mirena have been established in women of reproductive age. There is no relevant indication for the use of Mirena before menarche.

***Rapporteur's comments:***
As mentioned in the preceding comments, the rapporteur does not agree with the addition of the text *'Safety and efficacy of Mirena have been established in women of reproductive age.'* as part of this European Paediatric work-sharing procedure under Article 45.

The rapporteur only endorses the addition of text '*There is no relevant indication for the use of Mirena before menarche.'* in section 4.2 of SmPC.

- **Rapporteur's proposed SmPC changes**

In summary, the rapporteur recommends an update in section 4.2 of Microlut, Jadelle and Mirena as follows:

**Section 4.2 Posology and method of administration**

*[This section should be amended to include the below wording]*

*[…]*

Paediatric population
There is no relevant indication for the use of <product name> before menarche.

# VII. RAPPORTEUR'S CONCLUSION AND RECOMMENDATION AT DAY 89

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit-risk balance of levonorgestrel in the form of

progestogen-only pill (Microlut), progestogen-only implant (Jadelle) and levonorgestrel-releasing intrauterine system (Mirena) remains unchanged for the paediatric population.

The MAH has proposed updates to the Summary of Product Characteristics (SmPC) of Microlut, Jadelle and Mirena. The rapporteur is recommending changes to the proposed wording and thereof, the MAH is requested to provide additional clarification and information, as detailed in Section IX Request for supplementary information.

# VIII. COMMENTS FROM MSS

Following the circulation of the Day 70 PPdAR, the rapporteur received comments from two member states who agreed with the rapporteur's overall conclusions.

# IX. REQUEST FOR SUPPLEMENTARY INFORMATION

The MAH is requested to submit the following information:

- The licensing position of Microlut in different EU member states.
- The MAH is requested to comment on the SmPC updates as proposed by the rapporteur (see Section VI).
- In accordance with the SmPC updates, the MAH is requested to provide a proposal for Package Leaflet (PL) wording.

# X. MAH RESPONSES TO THE PRELIMINARY PDAR DAY 89

**Question 1:**
The MAH is requested to submit information on the licensing position of Microlut in different EU member states.

**MAH response:**
Microlut was first registered in the EU in 1971 in Germany as a purely national license. It is currently registered and marketed in 5 countries in the EU (Germany, Belgium, Finland, Luxembourg, and United Kingdom).

***Rapporteur's comments:***
The MAH provided information on the licensing position of Microlut in the EU. Issue resolved.

**Question 2:**
The MAH is requested to comment on the SmPC updates as proposed by the rapporteur (see Section VI).

**MAH response:**

- Microlut

The MAH agrees to the suggested insertion under the proposed sub-heading in section 4.2 of the SmPC: '*There is no relevant indication for the use of Microlut before menarche.*'

- Jadelle

The MAH agrees to the suggested insertion in section 4.2 of the SmPC of '*There is no relevant indication for the use of Jadelle before menarche.*'

- Mirena

The MAH agrees to the proposal by the rapporteur to include '*There is no relevant indication for the use of Mirena before menarche.*' in section 4.2 of the SmPC, if not already part of the approved local label of Mirena.

***Rapporteur's comments:***
The MAH responses are acceptable. Issue resolved.

**Question 3:**
In accordance with the SmPC updates, the MAH is requested to provide a proposal for Package Leaflet (PL) wording.

**MAH response:**
Following the request above, the MAH would like to provide a proposal for the wording in the Package Leaflets as follows:

> *Children and adolescents*
> <Product> is for use in women of childbearing age. <Product> is not indicated for use before the first menstrual bleeding (menarche).

***Rapporteur's comments:***
The statement '<Product> is for use in women of childbearing age.' is not accepted as this is considered similar to aforementioned statement referring to 'women of reproductive age.' (see comments in section VI.)
The rapporteur only endorses the wording '<Product> is not indicated for use before the first menstrual bleeding (menarche).' and recommends that this is added to Section 1 of the Package Leaflet: What <product name> is and what it is used for

# XI. RAPPORTEUR'S FINAL CONCLUSION AND RECOMMENDATION

The rapporteur concludes that based on the data provided as part of this European paediatric work-sharing procedure under Article 45, the benefit-risk balance of levonorgestrel levonorgestrel in the form of progestogen-only pill (Microlut), progestogen-only implant (Jadelle) and levonorgestrel-releasing intrauterine system (Mirena) remains unchanged.
Based on the review of the submitted paediatric data, the rapporteur recommends the following updates in SmPC and PL for levonorgestrel in the above forms:

**SUMMARY OF PRODUCT CHARACTERISTICS**

**Section 4.2 Posology and method of administration**

*[This section should be amended to include the below wording]*

*[…]*

*Paediatric population*
There is no relevant indication for the use of <product name> before menarche

**PACKAGE LEAFLET**

**1. What <product name> is and what it is used for**

*[This section should be amended to include the below wording]*

*[…]*

*Children and adolescents*
<Product name> is not indicated for use before the first menstrual bleeding (menarche).

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The applicant is therefore requested to submit a Type IB variation to update the SmPCs and PLs of levonorgestrel in the form of progestogen-only pill (Microlut), progestogen-only implant (Jadelle) and levonorgestrel-releasing intrauterine system (Mirena) in line with the above work-sharing recommendations within 60 days of this report.

# XII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

| MAHs | MEDICINAL PRODUCTS |
|---|---|
| Bayer | Microlut |
| Bayer | Jadelle |
| Bayer | Mirena |