

Public Assessment Report

Scientific discussion

Jaydess
(levonorgestrel)

SE/H/1186/01/DC

This module reflects the scientific discussion for the approval of Jaydess. The procedure was finalised at 2012-12-04. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Bayer AG has applied for a marketing authorisation for Jaydess Intrauterine delivery system, 13.5 mg. The active substance is levonorgestrel. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Jaydess is presented in the form of an intrauterine delivery system containing 13.5 mg of levonorgestrel. The intrauterine delivery system consists of a whitish or pale yellow drug reservoir mounted on the vertical stem of a T-body. The drug reservoir consists of a core of 65 % levonorgestrel and 35 % poly(dimethylsiloxane) elastomer, covered with poly(dimethylsiloxane) membrane. A silver ring is attached to the upper end of the vertical stem. The T-body has a loop at one end and two arms at the other end and is made of polyethylene containing 20-24 wt% barium sulphate. Removal threads (made of polyethylene pigmented with black iron oxide) are attached to the loop. The product is administered with an integrated inserter. The drug product mounted on top of the inserter is packed in a thermoformed blister package made of polyethylene terephthalate film and a peelable lid of adhesive coated nonwoven material of polyethylene.

II.2 Drug Substance

Levonorgestrel has a monograph in the Ph Eur.

Levonorgestrel is a white to off-white, crystalline powder which is practically insoluble in water, sparingly soluble in methylene chloride and slightly soluble in alcohol. The structure of levonorgestrel has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism and chirality is described. The route of synthesis has been adequately confirmed.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Jaydess is formulated using excipients which are controlled according to acceptable in house specifications. No TSE-risk materials are used in the manufacture of Jaydess.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Levonorgestrel exerts potent progestin and anti-ovulatory activities in animals and humans. The mode of action of levonorgestrel in the product proposed for marketing is mainly by local progestogenic effects within the uterine cavity and cervix. The high levonorgestrel concentration in the endometrium down-regulates endometrial estrogen and progesterone receptors, making the endometrium relatively insensitive to circulating estradiol and a strong antiproliferative effect is seen. Thickening of the cervical mucus impedes the passage of sperm through the cervical canal. The local milieu of the uterus and fallopian tubes inhibits sperm mobility and function, thereby preventing fertilization.

Overall, the pharmacodynamic profile of levonorgestrel is considered well known. There is a large clinical experience of levonorgestrel in various gynecological treatment systems also in intrauterine device with a higher dose and longer duration of treatment (Mirena®). The product proposed for marketing contains half of the dose of levonorgestrel and is indicated for treatment duration of three years.

III.2 Pharmacokinetics

The pharmacokinetics of LNG in animals is considered well known.

No separate nonclinical pharmacokinetic studies have been performed with the intrauterine LNG-releasing system in animals which is accepted considering the extensive clinical experience with Mirena®. However, two local and systemic tolerance studies in monkeys systemic have been performed in which exposure to LNG was determined. These studies will be further described and assessed below but as expected, the local exposure in the monkey uterine tissue was distinctly higher than in serum. The average concentration of LNG which became systemically available after insertion of the IUS was 8 to 42 times higher than that achieved in serum of women in the clinical trials.

III.3 Toxicology

In support of the present application the Applicant has performed two 9-month non-clinical safety studies in the Cynomolgus monkey which are assessed below. Furthermore, a short review of published data with levonorgestrel is presented.

Published data demonstrates that all major findings noted in animal species after long-term treatment with levonorgestrel are well known pharmacodynamically mediated effects. Treatment with levonorgestrel in dogs caused induction of mammary hyperplasia considered to be related to a hypersecretion of growth hormone because this hormone, besides progestins, is the additional promoter needed to stimulate mammary tissue of dogs. Growth hormone has no

major mammary stimulatory role in other species studied. This effect in dogs is considered to represent a species-specific response and of no concern for human safety.

Chronic toxicity studies in cynomolgus monkeys have been conducted with intrauterine systems modified for animal use to investigate local endometrial tolerance and systemic effects. Because the shape and size of the product proposed for marketing used in clinical trials is incompatible with the uteri of the cynomolgus monkey, the nonclinical studies have been performed using modified experimental intrauterine LNG-releasing systems composed of similar components and materials as used in LCS12 or Mirena®. Three concentrations of LNG has been evaluated; 2, 8 and 16 µg/day over a 9-month exposure period. 8 µg LNG/day is close to the proposed clinical concentrations which is 6 µg LNG/day.

The clinical signs (increased food consumption and increased body weight gain) observed in the highest dose group (16 µg/day) are caused by an exaggerated pharmacodynamic effect of levonorgestrel. The intrauterine systems revealed good local tolerance in the uterus; the findings observed are either due to the mechanical effect alone or to the local progestogenic action of the LNG-containing implant. No new or unexpected effects on the endometrium were found indicating that the material used is well tolerated locally. No systemic toxic or organ toxic effects were observed.

The mean serum LNG levels in the monkey study using intrauterine systems containing 2 and 8 µg LNG/day were 0.6-0.9 ng/mL for the low dose group and 1.9-3.3 ng/mL in the high dose group. These values were about 8-11 times and 24-42 times higher, for the low and high dose groups respectively, than the average LNG serum levels of 0.078 ng/mL (C_{av}) determined in humans in the Phase 2 study. In the monkey study using an intrauterine systems containing 16 µg LNG/day, a serum level of about 2-4 ng/mL was obtained indicating that overall the cynomolgus monkeys have been adequately exposed during the 9 month studies.

Levonorgestrel has no genotoxic potential. No indication of a carcinogenic potential was observed in carcinogenicity studies in mice, rats and monkeys. In dogs, following 7 years of treatment, mammary gland tumours have been noted. However, due to different reaction to progestins, the finding is considered a species-specific response to treatment with progestogens. Furthermore, there is an extensive clinical experience with levonorgestrel in oral contraception, where the systemic exposure to levonorgestrel is considerably higher than for the proposed product.

The Applicant has adequately summarized the reproductive effects of levonorgestrel. Levonorgestrel does not affect reproductive function adversely at dose levels relevant for clinical use achieved by the product proposed for marketing.

Biocompatibility studies with the device

The majority of materials used in Jaydess are used in Mirena® which has been on the market since 1992 and has been used by millions of women. In the product proposed for marketing, some components are new, including a silver ring in order to easily detect the IUS at clinical investigations. The components including the silver ring have been thoroughly investigated in biocompatibility testing with negative results. The silver ring has been tested in cytotoxicity assays demonstrating that the silver ion release will not result in cytotoxic concentrations. Moreover, the performed 39-week toxicity study in cynomolgus monkeys did not indicate any safety concerns for humans except those related to mechanical irritation in the uterine lumen. There was no sign of local intolerance, sensitization or genotoxicity induced by the product proposed for marketing.

Residual ethylene oxide in a product should according to the EMEA note for guidance CPMP/QWP/159/01 entitled "Limitations to the use of ethylene oxide in the manufacture of medicinal products" not exceed a limit of 1 ppm. However, a limit of 1 ppm ethylene oxide is according to the Applicant technically not feasible for LCS12 and therefore a limit of 2 ppm for the final product at release is proposed. This limit is assessed as being toxicologically qualified since this level was used in the 9-month cynomolgus studies. Furthermore, Mirena® has an ethylene oxide specification limit of 3 ppm and the clinical safety experience with this product is extensive. Therefore, there are no non-clinical concerns with using 2 ppm as limit for ethylene oxide for the proposed product.

There are from a non-clinical perspective no concerns for human safety at the proposed clinical use of Jaydess.

III.4 Ecotoxicity/environmental risk assessment

An environmental risk assessment in accordance with CPMP/SWP/4447/00 focusing on the active substance levonorgestrel was provided. In the Phase 1 assessment the $PEC_{\text{surfacewater}}$ was lower than 0.01 µg/L but the PD characteristics of levonorgestrel suggest that it may affect the reproduction of environmental animals. Therefore a Phase 2 assessment was provided. The log Kow was determined to 3.55 and further PBT testing is not warranted.

The tailored testing strategy is suitable for this progestin and the substitution of the ELS fish test with a short-term reproduction test is accepted. It is also accepted to perform the OECD 308 aerobic part instead of the full OECD 308 study since significant shifting to sediment was observed and a toxicity study in sediment dwelling organisms was provided in Tier B. A Tier B bioaccumulation study was also provided. The obtained BCFs of 250 to 119 indicated that levonorgestrel is moderately bioaccumulative.

The Tier A risk assessment indicated that a risk is expected from the introduction of levonorgestrel from LCS12 into the aquatic environment. No risk is expected for the groundwater or for the waste water treatment plant. The Tier B $PEC_{\text{surfacewater}}$ of 0.007 ng/L and $PEC/PNEC$ quotient of 0.7 are accepted.

It can be concluded that the use of levonorgestrel in LCS12 is not expected to pose a risk to the surface water environment.

The Tier B sediment risk assessment is accepted and it can be concluded that the use of levonorgestrel in LCS12 is not expected to pose a risk for the sediment environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is an application according to Article 8(3), known active substance, for an intrauterine delivery system (IUS) containing levonorgestrel. Levonorgestrel is a progestagen previously used in other products for contraception, both in an intrauterine delivery system (Mirena®) and in oral contraceptives.

IV.2 Pharmacokinetics

In an IUS, the effect of levonorgestrel is mainly local, although some of the active substance is absorbed and can be detected systemically. Jaydess is claimed to be effective for up to 3 years. The IUS Mirena has been on the market for approximately 20 years and this product has a

labelled release rate of 20 micrograms/24 hours and is effective and can remain in place for up to 5 years.

The declaration of the strength for Jaydess states the total amount of levonorgestrel present in the IUD (13.5 mg) and not the release rate. In section 5.2 of the SmPC, *in vivo* release rates are described based on observed *ex vivo* residual content data, since the true *in vivo* release rate into the uterine cavity cannot be measured. Jaydess and Mirena have somewhat different release profiles, with Jaydess having a polyphasic profile (higher release rate initially) whereas Mirena has a monophasic profile.

Pharmacokinetic data can be of use mainly to assess the systemic concentrations of levonorgestrel achieved with this new IUS with a lower release rate in comparison with Mirena. The LNG release rate is lower compared with Mirena and the systemic levonorgestrel concentrations achieved are lower in comparison with Mirena and much lower when compared with orally administered levonorgestrel, e.g. in combined OCs. The mean $C_{\max}$ of levonorgestrel obtained with Jaydess was 137 ng/l in the phase 2 study and 171 ng/l in the phase 3 study. This should be compared with a $C_{\max}$ of 360 ng/l for Mirena in the phase 2 study and with a $C_{\max}$ of 760 ng/l after a single oral 30 microgram dose of levonorgestrel.

There are no plasma levonorgestrel concentration data available for Jaydess immediately following insertion; however, data are available with Mirena showing measurable concentrations 1 hour after insertion. This is likely the case also for Jaydess. Since Jaydess has open and not closed ends of the drug-containing core, unlike Mirena, this may affect the initial concentrations achieved. However, based on simulations of a worst-case scenario with a higher release rate, the $C_{\max}$ obtained would still be below or in a similar range as LNG levels normally obtained with a combined oral contraceptive. This high concentration would also occur only momentarily and is not deemed a safety problem.

No specific data on plasma protein binding or tissue distribution have been provided in the dossier for Jaydess, which is acceptable in view of the mainly local effect and since the use of an intra-uterine levonorgestrel device is not a new concept for contraception. For another IUS referred to, which releases 30 µg LNG per day, a concentration gradient between endometrial tissues and plasma is observed and this is to be expected also for Jaydess, although the absolute concentrations are likely lower with Jaydess compared with a 30 µg/day IUS and with Mirena with a release rate of 20 µg/day.

No specific *in vivo* studies related to the elimination of levonorgestrel have been conducted in support of this application. After intravenous administration, the clearance of levonorgestrel is 1.0 ml/min/kg and the mean terminal half-life of levonorgestrel in plasma is approximately 20 hours. Published studies have shown an extensive metabolism of levonorgestrel, both by reduction, hydroxylation and conjugation. An *in vitro* study submitted by the applicant showed that CYP3A4 appears to be the main isoenzyme catalysing the oxidative metabolism of levonorgestrel.

No studies in special populations have been performed with Jaydess and none are required for this application. Due to the relatively low systemic levonorgestrel concentrations, no safety concerns are foreseen for women with renal or hepatic impairment. As for other hormonal contraceptive products, a standard contraindication is included for acute liver disease or liver tumours.

Body weight can influence plasma steroid concentrations and may thereby affect the contraceptive efficacy of some systemically acting hormonal contraceptive methods. However,

since the effect of Jaydess is local, no major concerns related to body weight are foreseen from a pharmacokinetic perspective. There are no clinical efficacy, safety or pharmacokinetic data in females aged below 18 years.

No *in vivo* interaction studies have been performed with Jaydess. In an *in vitro* study, levonorgestrel inhibited CYP3A4 but there was no influence on other CYP isoenzymes. Maximum therapeutic serum levels of levonorgestrel are several-fold lower than the IC₅₀ values for CYP3A4 inhibition and an interaction seems unlikely. There are no concerns related to interactions for this product.

The T-body of Jaydess contains a silver ring in the upper part of the vertical stem. The silver ring is visible on ultrasound and aids in differentiation of Jaydess *in situ* from Mirena, which lacks the silver ring. The Jaydess application contains information from silver concentration measurements in human serum and a literature assessment of environmental exposure to silver. The results from a limited number of females showed no indications of elevated silver ion concentrations in serum due to Jaydess use. Based on theoretical considerations on the amount of silver included in Jaydess compared with normal, environmental exposure, there are no safety concerns. The risk for intrauterine exposure to silver in case of contraceptive failure was briefly discussed and the effect of silver *per se* was not deemed different from what is currently known and labelled for intrauterine LNG systems if the woman becomes pregnant (abortion, premature labour).

IV.3 Pharmacodynamics

The active ingredient contained in Jaydess is a progestogen, levonorgestrel (LNG), which is released directly into the uterine cavity. The local endometrial effect is considered to be the primary contraceptive effect with Jaydess. Effects on the cervical mucus prevent passage of sperm through the cervical canal.

The ovulation seems to be maintained with Jaydess dose in most women, even during the first year of use. Higher incidence of anovulation was observed in women with Mirena.

IV.4 Clinical efficacy

One phase 3 study (A52238) and one phase 2 study (A46796) were performed in support of efficacy of LCS12 in the revised indication “Contraception for up to 3 years”. In both studies the low dose levonorgestrel contraceptive intrauterine systems (LCS) were studied with two different release rates (LCS12 and LCS16, release rate 12 and 16 µg/24 hrs, respectively) and, in study A 46796, the LCS-systems were compared to Mirena (release rate 20 µg/24 hrs) as well.

The studies evaluated contraceptive efficacy, measured as number of unintended pregnancies, PI, and cumulative failure rates using the Kaplan-Meier method. Moreover, bleeding pattern and pharmacodynamic parameters were assessed.

The full analysis set (FAS) included all women with successful insertions or for whom the insertion of an IUS was attempted. In the pivotal study A52238, totally 2884 women were included in the FAS, with mean treatment duration of 821 days or 2.25 wy for the LCS12 group. In the study A46796 only women with successful IUS insertion were included in the FAS, in total 741 women with mean treatment duration of 915 days, or 2.51 wy in the LCS12 group.

For the pooled analysis altogether 1672 women were included in the FAS of LCS12, vs 1697 for LCS16 and 256 for Mirena. The mean treatment duration for all women with LCS12 was

834 days or 2.29 wy, with LCS16 853 days or 2.34 wy and for Mirena 895 days or 2.45 wy. Based on the pooled analysis of studies A52238 and A46796, the LCS12 and LCS16 were comparable with regard to their total exposure by year and overall. Overall compliance, defined as position of the IUS in the uterine cavity with ultrasound was high.

The majority of participants were Caucasian. The mean age was in general younger in the pivotal study, with no relevant differences regarding body weight or height. A greater proportion of women had BMI > 30 kg/m² in study A52238 and study A52238 had a higher proportion of nulliparous women. In the pivotal study A52238, the proportion of nulliparous women were 39% and 40% were younger than 25 years.

The treatment groups were comparable with regard to gynecological history. A higher proportion of women discontinued in study A52238 (40%) vs study A46796 (30%) most often due to AEs. The percentage of women lost to follow up was highest in North-America.

Pregnancy outcome

In the dose-response study A46796, a total of 6 pregnancies were observed during treatment. There were one pregnancy in the LCS12 group (an ectopic pregnancy) and 5 in the LCS16 group (of which 2 were ectopic). Of the remaining 3 pregnancies in users of LCS16, 2 ended in spontaneous abortion and 1 pregnancy was normal and carried to term (the result of an unnoticed expulsion). No pregnancy was observed with Mirena.

In the pivotal study A52238 there were 10 pregnancies in each group. Of these, 3/10 in the LCS12 group and 7/10 in the LCS16 group were ectopic. Of the remaining 7 pregnancies in the LCS12 group, 3 pregnancies ended in spontaneous abortion and one in induced abortion, 2 pregnancies were normal and carried to term, and 1 pregnancy was delivered prematurely by cesarean section due to preeclampsia, with a normal fetal outcome. Of the 3 remaining pregnancies in the LCS16 group, one was a blighted ovum that ended in spontaneous abortion, 1 was a spontaneous abortion, and 1 pregnancy was normal and carried to term. When a normal pregnancy was diagnosed due to partial expulsion, the IUS was in all cases removed.

Contraceptive efficacy

In study A46796, the unadjusted and adjusted Kaplan-Meier estimates were similar regarding the probability of getting pregnant. The cumulative failure rate over 3 years was 0.005 per 100 woman-years in the LCS12 group, 0.025 in the LCS16 group, and 0.000 in the Mirena group. In pivotal study A52238, contraceptive efficacy was calculated for women 18 to 35 years using PI and life table analysis. Unadjusted and adjusted PIs were calculated. The resulting differences were very small with almost identical values. For women 18 to 35 years old, the unadjusted PI for LCS12 year 1 was 0.41 and 0.33 year 3 for LCS12 in study A52238. No pattern in the pregnancy rates over time was observed. No clear dose-response relationship was observed with 10 pregnancies in each treatment group.

Life table analysis with Kaplan-Meier estimate was performed for 18- to 35-year old women. The cumulative failure rate at year 1 was 0.4% and 0.9% for 3 years with no relevant differences between subgroups by age, parity or BMI within LCS12 treatment.

Ectopic pregnancies

Totally, ten of 20 pregnancies observed under treatment were ectopic (LCS12: 3, LCS16: 7). The relevant 3-year exposure was similar in the two treatment groups: 3058.62 WY in the LCS12 group and 3211.36 WY in the LCS16 group. Exposure by single year was also similar. The relative risk of ectopic pregnancy appears around 50%. The subgroup analyses regarding risk of ectopic pregnancy for age, parity or BMI did not reveal any difference between the subgroups.

For women 18 to 35 years old, the unadjusted PI for ectopic pregnancy LCS12 year 1 was 0.16 and 0.10 year 3 for LCS12 in study A52238.

Life table analysis with Kaplan-Meier estimate was performed for 18- to 35-year old women. The cumulative probability for ectopic pregnancy by year 1 was 0.2% and 0.2% for 3 years with no relevant differences between subgroups by age, parity or BMI within LCS12 treatment.

Bleeding pattern

In both studies, menstrual bleeding patterns were recorded using diary cards and evaluated by category and intensity according to the sponsor's bleeding intensity codes and WHO definitions. Bleeding patterns were analyzed by 90-day and 30-day reference periods, in days and in episodes. For each 90-day reference period also by the WHO clinically important bleeding categories, there was a clear trend for an increase in the number of women with amenorrhea and infrequent bleeding over the course of the study.

Overall, the greatest decrease in the mean number of bleeding and spotting days occurred between the first and second 90-day reference period in all treatment groups. The bleeding and spotting showed initially a similar pattern and not before the end of the second 90-day reference period, a more dose-dependent trend was observed with more infrequent bleeding in the Mirena group (study A46796).

The greatest reduction of menstrual bleeding was noticed in the Mirena group. After 3 years, the percentage of amenorrhea in the LCS groups was about half of that in the Mirena group. Almost every fourth woman with the Mirena IUS had no bleeding after 3 years of treatment.

The treatment arms in study A52238 were comparable regarding user satisfaction. Three out of four women were satisfied with the treatment and almost 80% would like to continue with LCS.

IV.5 Clinical safety

Safety data were analyzed based on pooled data across the two studies and for each individual study. The studies evaluated contraceptive safety, measured as number of AEs, dysmenorrhea, vital signs and weight, physical and gynaecological examination, insertion - and removal procedure. In a subset of patients, ovarian and cervical function, endometrial histology and BMD were assessed.

In general, there were no clinically relevant differences between treatment groups in the rate and severity of AEs, drug-related AEs or discontinuation due to AEs. The proportion of women reporting any AE was highest during year 1 and decreased by each year thereafter. Adverse events were analyzed for subgroups (18 to 25 years, 26 to 35 years, and over 35 years), ethnic subgroup, parity, and BMI. In general, there were no overall trends that were not reflected by the study population taken as a whole. More AEs overall were reported in the 18 to 25 year age group, and in nulliparous women.

Slightly more women in study A46796 experienced drug-related AEs (67 to 72%) than women in study A52238 (50 to 52%). In studies A52238 and A46796, AEs in the SOC *Infections and infestations* and *Reproductive system and breast disorders* were most frequently reported (approximately 50% in each group and study).

A higher frequency of certain AEs in study A46796 as compared to study A52238 (including acne, headache, breast pain and discomfort, mood changes and weight gain) can be explained by the fact that in study A46796, certain events were classified as progestogen-related and assessed at every visit.

Common AEs in pivotal study A52238 displayed here as those occurring in $\geq 3.0\%$ of women in either treatment group are provided in table below.

Number (%) of subjects with common (in $\geq 3\%$ patients overall) AEs by preferred term and descending frequency of occurrence overall – FAS study A52238

MedDRA preferred term	LCS12 N = 1432 (100%)	LCS16 N = 1452 (100%)	Total N = 2884 (100%)
Ovarian cyst	186 (13.0%)	304 (20.9%)	490 (17.0%)
Acne	163 (11.4%)	169 (11.6%)	332 (11.5%)
Urinary tract infection	158 (11.0%)	145 (10.0%)	303 (10.5%)
Headache	133 (9.3%)	137 (9.4%)	270 (9.4%)
Dysmenorrhea	130 (9.1%)	108 (7.4%)	238 (8.3%)
Cervical dysplasia	107 (7.5%)	115 (7.9%)	222 (7.7%)
Vaginitis bacterial	105 (7.3%)	127 (8.7%)	232 (8.0%)
Nasopharyngitis	103 (7.2%)	109 (7.5%)	212 (7.4%)
Abdominal pain	100 (7.0%)	101 (7.0%)	201 (7.0%)
Vulvovaginal mycotic infection	99 (6.9%)	110 (7.6%)	209 (7.2%)
Pelvic pain	96 (6.7%)	123 (8.5%)	219 (7.6%)
Sinusitis	90 (6.3%)	96 (6.6%)	186 (6.4%)
Nausea	74 (5.2%)	58 (4.0%)	132 (4.6%)
Influenza	72 (5.0%)	94 (6.5%)	166 (5.8%)
Vulvovaginal candidiasis	72 (5.0%)	72 (5.0%)	144 (5.0%)
Abdominal pain lower	67 (4.7%)	61 (4.2%)	128 (4.4%)
Vaginal hemorrhage	66 (4.6%)	73 (5.0%)	139 (4.8%)
Back pain	59 (4.1%)	65 (4.5%)	124 (4.3%)
Bronchitis	58 (4.1%)	38 (2.6%)	96 (3.3%)
Procedural pain	58 (4.1%)	54 (3.7%)	112 (3.9%)
Weight increased	56 (3.9%)	68 (4.7%)	124 (4.3%)
Vaginal discharge	55 (3.8%)	58 (4.0%)	113 (3.9%)
Depression	51 (3.6%)	49 (3.4%)	100 (3.5%)
Upper respiratory tract infection	51 (3.6%)	57 (3.9%)	108 (3.7%)
Vaginal infection	48 (3.4%)	60 (4.1%)	108 (3.7%)

Sorted by frequency in LCS12 group

MedDRA = Medical Dictionary for Regulatory Activities, Version 14.0

In the pivotal study, no relevant difference was noticed between the LCS12 and LCS16 regarding withdrawal of study treatment due to an adverse event. Vaginal haemorrhage was the most frequent AEs leading to withdrawal of study medication during LCS treatment (3.3%). There was a trend towards lower number of AEs from reproductive system and breast disorders in the LCS12 group compared to LCS16 group.

The most common AEs in $\geq 10\%$ of subjects overall were ovarian cysts. In study A46796, an ovarian cyst was diagnosed in 22.0% in the Mirena group, compared to 5.9% in the LCS12 group. Ovarian cyst occurred slightly more often in LCS16 group, 201 women (13.8%) vs 110 women (7.7%) in the LCS12 group. No difference in the number or types ovarian cysts was noticed during LCS12 treatment

Urinary tract infection was the most common infection in both individual studies and in the pooled LCS treatment group data. SAEs in the SOC *Infections and infestations* were reported for 54 total women (1.5%).

One death during treatment was reported during study A52238 assessed by the investigator as unrelated to study drug.

In the pooled analysis, SAEs were reported for 4.7% of women in the LCS12 treatment group, 4.9% of women in the LCS16 group, and 6.3% of women in the Mirena group.

Overall, PIDs (as diagnosed by the investigator, not always confirmed by laparoscopy) were reported in approximately 0.4% of the women in the LCS treatment groups (FAS, pooled LCS12 and LCS16 data across studies A52238 and A46796). Most of the PIDs reported were serious or moderate to severe in intensity, related to study drug, occurred in parous women, and occurred during year 1 of the study. There was no increased risk in the LCS12 group. No increased risk of PID was observed in women ≤ 25 years of age.

A total of 0.8% of women in the LCS12 and LCS16 arms in study A52238, and 0.5% of the women in study A46796 were diagnosed with endometritis. Study drug was mostly not discontinued and most events were considered non-serious, and occurred most frequently in parous women and during the first year of the study in both studies. Due to this AE, a total of four of the 26 women (15%) with endometritis were withdrawn from the studies. No differences were noted among the treatment groups or over time in the number or types of fibroids during LCS12 treatment.

Totally 10 cases of ectopic pregnancy occurred. All but one were considered related to the study drug, so that the most frequent study drug-related SAEs were ectopic pregnancy/ruptured ectopic pregnancy in 9 women. The rate of drug-related ectopic pregnancy was for LCS12 0.1% vs LCS16 0.4%. An issue for concern is the risk for ectopic pregnancies with LCS 12. However, in the studies, the rate of ectopic pregnancy was similar in parous and nulliparous women.

In the pivotal study the proportion of high grade SIL was 6.8% at screening for cervical dysplasia. During treatment the frequency of high grade SIL increased to 18.1%. The total number of device expulsions/dislocations (3.7% in the LCS12 group, and 3.2% in the LCS16 group), and procedural pain was low and comparable in the two study arms. The frequency of expulsions in both studies A52238 study A46796 is within the range previously reported for Mirena. Pooled data showed more that partial and total expulsions occurred in parous than in nulliparous women in both study A52238 and study A46796. More expulsions occurred in women age ≤ 25 than in women age $> 25 < 35$.

In study A46796 a dilatation was performed twice as often in the Mirena group as in the LCS12 group at insertion. The insertion procedure was by the investigator assessed as easy in 95% in LCS12 group and in 86% in Mirena group.

Based on the pooled data across studies A52238 and A46796, uterine perforations occurred in 1 / 3625 (0.027%) of the women. Due to the limited number of uterine perforations occurring in the studies with LCS12, no conclusions on risk factors are possible.

The insertion procedures were assessed by the subjects as painless or with mild pain in 72% in the LCS group vs 58% in the Mirena group. The removal procedures were assessed both by the investigators and subjects as painless or with mild pain in more than 60%. Insertion was easier in parous women in all treatment groups, while, in nulliparous women, there was a trend towards easier insertion of an LCS than a Mirena.

No relevant difference regarding pregnancy follow up and return to fertility was observed after end of treatment with LCS12 compared to Mirena. A majority of women ovulated during treatment with LCS12 even during year 1 and 2. The changes in cervical mucus and serum

hormone levels during treatment with LCS12 are expected and related to the effects of the intrauterine delivery system with LNG.

No adverse effects regarding haematology, serum chemistry, liver enzymes, lipid profile and HbA1c was observed during LGS treatment. No treatment related adverse effects were observed in any LCS groups for any urinalysis parameter or hemostasis. No difference in bone mineral density was observed during LCS12 treatment. Moderate or severe dysmenorrhea decreased since the bleeding decreased during LCS12 treatment.

IV.6 Discussion on the clinical aspects

The Applicant wanted to target Jaydess to nulliparous women, but given the limited data, in particular with regard to pregnancy risk and the risk of ectopic pregnancy, this targeting has been removed from the indication. The applicant has further strengthened the ectopic pregnancy warning in section 4.4 of the SmPC. A statement in section 4.4 that Jaydess is not first contraceptive choice in young nulliparous women is also included.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Jaydess Intrauterine delivery system, 13,5 mg is recommended for approval.

The applicant has justified a PASS for 26 000 women and committed to further evaluate any difficulties associated with insertion, which also are important for the frequency of unintended pregnancy and ectopic pregnancy, need for analgesia/dilatation, and failed insertion for women receiving Jaydess, Mirena or copper IUD.

The applicant commits to investigate treatments for dysplasia as an outcome of interest in the proposed EURAS-LCS12 study in the treatment groups under study (Jaydess, Mirena, Copper IUD).

VI. APPROVAL

The Decentralised procedure for Jaydess Intrauterine delivery system, 13,5 mg was successfully finalised on 2012-12-04.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)